NDA 20762

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-762

OCT 1 1997

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Attention: Joseph Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your new drug application dated September 30, 1996, received October 1, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nasonex (mometasone furoate) Nasal Spray.

We acknowledge receipt of your submissions dated October 4, 18, and 24, December 2, 1996, and January 31, February 3, 7, and 28, March 20 and 24, April 4, May 8, 9, 14, and 21, June 17, July 2, 11, and 21, August 6, 14, 20, and 22, and September 4, 12, 15, 16, 18, 19, 26, and 29, 1997. The user fee goal date for this application is October 1, 1997.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the prophylaxis and treatment of the nasal symptoms of seasonal allergic rhinitis and the treatment of the nasal symptoms of perennial allergic rhinitis, in adults and children 12 years of age and older. Accordingly, the application is approved effective on the date of this letter. The expiry for all packaging configurations is 15 months. We remind you of your decision to withdraw the from the application.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft physician labeling, patient's instructions for use, and container and carton labeling. Marketing the product with FPL that is not identical to this marked-up draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-762." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated September 29, 1997. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to this NDA. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising
and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Denise Toyer, Project Manager, at (301) 827-5584.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, (HFD-530)
Corporate Building, Room N461

FROM: Division of Pulmonary Drug Products HFD-570
Attention: Craig M. Bertha, Ph.D. Phone: 827-1095

DATE: November 12, 1996

SUBJECT: Request for assessment of the proposed name

Proposed Trademark: NASONEX Nasal Spray **NDA/ANDA #** N 20-762

Established name, including dosage form: mometasone furoate monohydrate nasal spray

Other trademarks by the same firm for comparison products:
VANCENASE AQ Nasal Spray

Indications for use (may be a summary if proposed statement is lengthy):
Prophylaxis and treatment of seasonal allergic rhinitis (SAR), and treatment of perrennial rhinitis (PR)

Initial comments from the submitter: (concerns, observations, etc.) The strength of the product is 50 µg (anhydrous basis)/actuation and the route of administration is intranasal. Each container provides 120 actuations and the daily dose is two actuations in each nostril once daily for adults and adolescents 12 years and older.

NOTE: **Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.**

Rev Dec. 1990

U.S. patents pertaining to the drug mometasone furoate monohydrate: None; however, mometasone furoate monohydrate is being manufactured from an intermediate compound, mometasone furoate, which is claimed in U.S. Patent 4,472,393, having an expiration date of September 18, 2001 and being owned by Schering Corporation.

U.S. patents pertaining to the composition and formulation of NASONEX brand of mometasone furoate monohydrate nasal spray: None.

U.S. patents pertaining to methods of use of NASONEX brand of mometasone furoate monohydrate nasal spray: None.

The person signing this application on behalf of the applicant declares: (1) that U.S. Patent 4,472,393 of Schering Corporation claims mometasone furoate; and (2) that mometasone furoate is used to manufacture mometasone furoate monohydrate, the active ingredient in NASONEX brand of mometasone furoate monohydrate nasal spray; and (3) that with respect to U.S. Patent 4,472,393 a claim of patent infringement could reasonable be asserted against a person, not licensed thereunder by Schering Corporation, who engages in the use of mometasone furoate to manufacture the active ingredient in NASONEX brand of mometasone furoate monohydrate nasal spray.

EXCLUSIVITY SUMMARY for NDA # 20-762 SUPPL #_____

Trade Name NASONEX Nasal Spray Generic Name mometasone furoate

Applicant Name Schering-Corporation HFD-570

Approval Date, if known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /_x_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_x_/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_x_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d Did the applicant request exclusivity?

YES /_x__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

__Three_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 .

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /_X__/ OTC Switch /___/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-625 Mometasone furoate topical cream

NDA# 19-796 Mometasone furoate topical lotion

NDA# 19-543 Mometasone furoate topical ointment

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

C93-013 C93-215 C92-280

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not

redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

C93-013 C92-280

C93-215 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # YES /_X_/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # YES /_X_/	NO /___/ Explain: _____
Investigation #3	
IND YES /_X_/	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

Denise P. Toyer
Signature

Project Manager
Title:

26 September 1997
Date

Signature of Division Director

10/1/97
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

Claim for Exclusivity

1. Pursuant to the provisions of Sections 505 (c) (3) (D) (iv) and 505 (j) (4) (D) (iv) of the Food, Drug and Cosmetic Act (FDCA) and 21 CFR 314.108 (b) (5), the applicant claims three (3) years of exclusivity for its NASONEX™ (mometasone furoate monohydrate) NASAL SPRAY, for use in the prophylaxis and treatment of symptoms of seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis, in adults and adolescents 12 years of age and older.

2. The applicant certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108 (a).

3. A list of all published studies or publicly available reports of clinical investigations known to the applicant through a computer-assisted literature search that are relevant to the conditions for which the applicant is seeking approval is provided as **Attachment 1.**

4. The applicant certifies that it has thoroughly searched the scientific literature through a computer-assisted search of the Scholar database, and Dialog database encompassing the subfiles MEDLINE, BIOSIS Previews, EMBASE and SciSearch, for English and non-English literature relating to mometasone furoate nasal spray in humans, covering the period from 1985 to 8/28/96.

5. To the best of the applicant's knowledge, the list of scientific literature pertaining to mometasone furoate nasal spray is complete and accurate, and in the opinion of the applicant, such published studies or publicly available information do not provide a sufficient basis for the approval of the use of mometasone furoate monohydrate nasal spray for the prophylaxis and treatment of symptoms of seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis, without reference to the new information contained in the clinical trials in the application. The applicant's opinion that the studies or reports are insufficient is based on the following:

   - The literature does not contain adequate characterization of the efficacy and safety profile of mometasone furoate in the management of prophylaxis and treatment of symptoms of seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis, which is established by the data from the new

clinical studies conducted by the applicant under IND and included in this application.

- The overall clinical program requirements of this application, and the design of the studies were discussed with the Food and Drug Administration's Pilot Drug Evaluation Staff (Dr. Patricia Love) prior to study initiation. These studies were also review by the Division of Pulmonary/Oncology Drug Products in a July 31, 1995 pre–NDA meeting. Such studies are not available in the published literature without reference to the sponsor's new clinical investigations.

6. The applicant was the sponsor named in the Form FDA-1571 for IND under which the new clinical investigations were conducted

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-762 Trade (generic) names Nasonex Nasal Spray (mometasone furoate)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

X 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:
Nasonex Nasal Spray (mometasone furoate) is indicated for the treatment of seasonal allergic rhinitis and perennial allergic rhinitis nasal symptoms and prophylaxis of nasal symptoms of seasonal allergic rhinitis in adults and in pediatric patients between the ages of 12 and 17.

Schering is currently conducting clinical studies in the pediatric population (ages 3 and above). They anticipate submitting the data during the 3rd quarter of 1998.

Denise P. Toyer
Signature of Preparer

26 September 1997
Date

cc: Orig NDA
HFD-570 Div File
NDA Action Package

Memorandum

To: NDA 20-762, Nasonex Nasal Spray
From: Hilary V. Sheevers - Pharm./Tox. Team Leader Hilary V Sheevers 9/26/97
Re: Team Leader NDA Summary, HFD 570
Date: September 26, 1997

Nasonex Nasal Spray is an intranasal formulation of the glucocorticosteroid mometasone furoate monohydrate. Nasonex is a potent corticosteroid with anti-inflammatory properties, and in animal models inhibited allergen-induced eosinophil infiltration and Th cell accumulation. The proposed indication for Nasonex Nasal Spray is the prophylaxis and treatment of seasonal and perennial allergic rhinitis. Patients are expected to be greater than 12 years old, and the maximum dose is 200 µg/day. The active ingredient has previously been approved and marketed as a topical dermal product.

Outstanding Issues:

- There are no outstanding pharmacology/toxicology issues to delay approval or this drug product.

- A future concern will be dose comparisons in carcinogenicity studies for nasal products. Recent nasal drug product labels (e.g. Vancenase, Flonase) include dose comparisons between humans and animals based on surface area. The sponsor was asked to do label Nasonex in a similar manner as well, because the human AUC was not quantifiable. However, when (if) the inhalation mometasone products come in as NDAs, the dose comparisons will appear more favorable for the inhalation products than the intranasal products. That is, the carcinogenicity studies will appear to have been performed at a higher dose multiple in animals compared to humans for the inhalation products than for the intranasal product. Thus, although we remain consistent among steroid nasal products, this issue eventually will need to be revisited to decide just what is the best factor for comparison for intranasal products.

Summary of Significant Preclinical Studies:

In general, mometasone furoate **chronic toxicity studies** revealed a pattern of classic glucocorticosteroid toxicity effects. Mometasone was evaluated fully in acute, subchronic, and chronic studies in rats and dogs for 6 months by inhalation. Common changes in rats (the more sensitive species) included HPA axis suppression; adrenal, spleen, thymus and lymph node atrophy; and opportunistic infections probably related to the immunosuppressive properties of the drug. In the 6-month inhalation dog study, changes were noted primarily in the adrenals. In a 12-month intranasal dog study, effects related to steroid treatment decreased, and consisted of absence of nasal lymphoid aggregates, and changes in the adrenals, thymus, and skin were noted. Although no NOAEL doses were identified, the changes were as expected for this drug class and as is generally the case, should be clinically monitorable by following ACTH levels.

Reproduction studies were performed in rats, mice, and rabbits. In rodents (SC), which are quite sensitive to corticosteroid effects, malformations and reduced survival were noted in doses overlapping the clinical dose (based on body surface area comparisons). In rabbits (oral), malformations and effects on fetal growth were noted at doses well above the clinical dose. As with other glucorticosteroids, Nasonex is recommended as pregnancy category C. In general, and particularly for nasal products, results seen in the SC and oral animal studies are far more serious than that experienced in the human population. No changes in fertility were noted in an oral rat multigenerational study, although changes of importance included prolonged gestation and labor and, reduced body weight gain at doses slightly below the clinical dose (on a body surface area basis)

Two inhalation **carcinogenicity studies** were performed. No statistically significant increases in tumors were noted in Sprague Dawley rats in doses up to 3 times the clinical dose and in Swiss CD-1 mice up to 4 times the clinical dose on a surface area basis. Mometosone furoate was a weak positive in a single chromosome aberration in vitro study. However, the drug tested negative in a mouse lymphoma assay, a bacterial reverse mutation assay, a Chinese hamster lung cell assay, an in vivo mouse bone-marrow assay, and rat bone-marrow clastogenicity assay, a mouse male germ-cell clastogenicity assay, and it did not induce unscheduled NA synthesis in vivo in rat hepatocytes. Thus, mometasone is not considered to a genotoxic compound.

Labeling changes were discussed with the sponsor and are accurately represented in the final proposed label. Based on preclinical data, the submission is recommended to be approvable.

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

APPLICATION #:	20-762	APPLICATION TYPE:	NDA
SPONSOR:	Schering-Plough, Inc.	PRODUCT/PROPRIETARY NAME:	Nasonex
		USAN / Established Name:	Mometasone furoate
CATEGORY OF DRUG:	Corticosteroid	ROUTE OF ADMINISTRATION:	Intranasal
MEDICAL REVIEWER:	Alexandra S. Worobec, M.D.	REVIEW DATE:	October 1, 1996

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
September 30, 1996	October 1, 1996	NDA 20-762	Filing Date for NDA 20-762
January 31, 1997	February 4, 1997	NDA 20-762	4 Month Safety Update
February 10, 1997	February 11, 1997	IND 35-932	Annual Report
May 21, 1997	May 22, 1997	NDA 20-762	Response to FDA Request-Prophylaxis Studies
July 11, 1997	July 14, 1997	NDA 20-762	Response to FDA Request-HPA Study Data Listings
August 5, 1997	August 6, 1997	NDA 20-762	Response to FDA Request-Additional HPA Study Data Listings
August 19, 1997	Not Applicable	NDA 20-762	FAX from Schering Plough, Inc.: Information regarding NASONEX batches used in clinical trials.
August 28, 1997	Not Applicable	NDA 20-762	FAX from Schering Plough, Inc.: Information regarding Study C94-052: 24 Hour Urinary Free Cortisol Analysis.

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
April 30, 1987	NDA 19-543	Elocon (Mometasone Furoate) Ointment
May 6, 1987	NDA 19-625	Elocon (Mometasone Furoate) Emulsion
March 3, 1989	NDA 19-796	Elocon (Mometasone Furoate) Lotion

Overview of Application/Review: This is an NDA for mometasone furoate aqueous nasal spray (NASONEX™ Aqueous Nasal Spray, 50 µg) administered at a dose of 200 µg qd for the treatment of SAR and PAR nasal symptoms, and prophylaxis of nasal symptoms of SAR in adult and pediatric subjects age 12 years and older. A total of 20 studies (controlled and uncontrolled) were reviewed to assess efficacy and safety of mometasone furoate nasal spray in adult and pediatric subjects ≥ 12 years of age. Three pivotal studies (C93-013, C93-215, and C92-280) demonstrated statistically significant efficacy of mometasone treatment at 200 µg qd in decreasing total nasal symptoms of SAR, as compared with placebo treatment for the 3 clinical indications listed above. The 200 µg qd dose of mometasone nasal spray demonstrated a greater numerical decrease in total nasal symptoms, as compared with mometasone 50 µg qd and mometasone 100 µg qd, administered intranasally. Statistically significant and consistent decrease in total nasal symptoms with mometasone treatment was demonstrable by 2.0-2.5 days of treatment, as compared with placebo. Statistically significant decrease in total nasal symptoms was seen by 1 week of treatment with mometasone 200 µg qd, but a numerical decrease in total nasal symptoms continued to occur by week 2 of treatment. No significant demographic differences in response (based on age, gender, or race) were seen with mometasone treatment at 200 µg qd. No outstanding safety concerns were seen with mometasone treatment, and the incidence of adverse events was similar to the placebo treatment group. A slightly greater number of mometasone treated subjects developed nasal ulcers, as compared with placebo treated subjects and this AE generally occurred after > 4 weeks of treatment with mometasone nasal spray. Four HPA axis suppression studies, and 2 clinical studies which evaluated cataract and glaucoma formation failed to reveal a greater incidence of abnormal adrenal response, cataract or glaucoma formation in mometasone treated subjects, as compared to placebo group subjects. Based on review of the data presented in the submission for NDA 20-762, the medical reviewer recommends approval of mometasone furoate nasal spray in adult and pediatric subjects age 12 years and older for the treatment of nasal symptoms of SAR, prophylaxis of the nasal symptoms of SAR, and the treatment of nasal symptoms of PAR.

Outstanding Issues: No outstanding clinical issues.

Recommended Regulatory Action: Approvable	N drive location:
New Clinical Studies: N/A Clinical Hold	N/A Study May Proceed
NDAs:	
Efficacy / Label Supp.: N/A Approvable	N/A Not Approvable
Signed: Medical Reviewer: Alexandra A. Hartlee M.D. (see secondary reviewer memo)	Date: 09/04/97
Medical Team Leader: M Almond	Date: 9/12/97

Medical Officer's Review

NDA #:	20-762	Submission Date: October 1, 1997
Medical Officer Review #:	20-762	Review Completed: September 3, 1997

1.2. Drug Name

1.2.1. Generic Name: Mometasone furoate monohydrate

1.2.2. Proposed Trade Name: NASONEX™ Nasal Spray

1.2.3. Chemical Name: 9, 21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione Monohydrate

1.3. Sponsor: Schering Plough Research Institute, Inc.

1.4. Pharmacologic Category: Corticosteroid

1.5. Proposed Indication: Treatment of symptoms due to seasonal allergic rhinitis, prophylaxis of symptoms due to seasonal allergic rhinitis, treatment of symptoms due to perennial allergic rhinitis in adult and pediatric subjects ≥ 12 years of age.

1.6. Dosage form and route of administration: 50 mcg (µg), administered as 2 sprays intranasally via nasal spray to a final dose of 200 mcg (µg) qd.

1.7. NDA Drug Classification: S

1.8. Related Drugs:

NDA 19-543	Elocon (Mometasone Furoate) Ointment (Schering, Inc., approved 30-Apr-87)*
NDA 19-625	Elocon (Mometasone Furoate) Emulsion, Cream (Schering, Inc., approved 06-May-87)*
NDA 19-796	Elocon (Mometasone Furoate) Lotion (Schering, Inc., approved 30-Mar-89)*

*NOTE: These products are for topical application.

1.9.	Related Reviews:	Chemistry review #1 dated:	02/13/97
		Chemistry review #2 dated:	07/09/97
		Chemistry review #3 dated:	08/01/97
		Chemistry review #4 dated:	08/28/97
		Pharmacology/Toxicology review dated:	09/15/97
		Pharmacology/Toxicology supplement review dated:	08/19/97
		Biopharmaceutics review dated:	09/11/97
		Statistical review dated:	07/14/97

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3.0. Conduct of the Review

The clinical review of NDA 20-762 was conducted using volumes 164-313 of the NDA submission, along with volumes 7.1-7.5 of the Four Month (120 Day) Safety Update, and additional volumes provided by the sponsor which address specific FDA clinical safety and efficacy concerns regarding mometasone furoate nasal spray.

Clinical studies were reviewed by category of indication, starting with seasonal allergic rhinitis (SAR), then prophylaxis of SAR, and finally perennial allergic rhinitis (PAR). In each indication category, the pivotal clinical trial was reviewed first, followed by each supporting study for that indication. Line listings were reviewed for all efficacy endpoints, demographic subgroups, and the efficacy results for the intent-to-treat population were compared to the efficacy evaluable population in order to evaluate any potential discrepancies. The safety review also consisted of a review of all adverse events by summary tables and line listings, along with review of the physical examination line listings with special attention paid to the incidence of nasal ulcer/perforation, nasal or oral candidiasis, herpes simplex, zoster, cataract and glaucoma formation. ECG abnormalities and vital signs were reviewed by line listings to rule out any untoward predisposition to hypertension or arrhythmia with mometasone use. Laboratory tests were likewise reviewed, with special attention to trends in mean values post-treatment with mometasone compared with the placebo subjects and subject outlier values for liver function tests (LFTs), white blood cell counts, and HPA-axis suppression tests of plasma or urine cortisol. 'Clinically significant' liver function elevations or white blood cell count changes were defined as falling outside the 'normal' range values for the clinical parameter. Specifically with regard to liver function test abnormalities, elevations in the active control and placebo group subjects were not noted or described in the clinical study reviews although rare subjects in these 2 groups also manifested abnormalities in SGOT, SGPT, bilirubin, and alkaline phosphatase. Cases of LFT elevation due to documented 'viral' hepatitis for all treatment groups were not noted in the clinical review. Safety findings were reviewed by demographic subgroups in order to define any potential populations at higher risk for developing adverse events or laboratory abnormalities with mometasone nasal spray use.

Pertinent positive and negative safety and efficacy findings are discussed in each clinical study review, with the appropriate volumes indexed from the NDA in brackets [Volume of NDA: pages]. An integrated summary of efficacy and of safety follow analysis of the individual studies, and efficacy and safety results of the entire NDA, along with recommendations for approval are summarized in the Conclusion- 'Executive summary of efficacy and safety' section (section 11.0).

4.0. Chemistry, Manufacturing, and Controls

Mometasone furoate monohydrate, the active component of NASONEX Nasal Spray, is a corticosteroid having the chemical name 9, 21-Dichloro-17-[(2-

furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione Monohydrate. Mometasone furoate monohydrate is a white to light yellow powder, with an empirical formula of $C_{27}H_{30}Cl_2O_6 \cdot H_2O$, and a molecular weight of 539.45. Mometasone is practically insoluble in water, slightly soluble in methanol, ethanol and isopropanol; soluble in acetone and chloroform; and freely soluble in tetrahydrofuran. Its partition coefficient between octanol and water is greater than 5000.

NASONEX Nasal Spray is a metered-dose, manual pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mometasone furoate calculated on an anhydrous basis, in an aqueous medium containing glycerin, microcrystalline cellulose, and carboxymethylcellulose sodium, sodium citrate, 0.25% w/w phenylethyl alcohol, citric acid, benzalkonium chloride, and polysorbate 80. A listing of ingredients in NASONEX Nasal Spray is summarized as follows:

Ingredient	mg/g in drug product
Mometasone furoate monohydrate micronized (Inhalation Grade) Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF 65 cps Glycerin USP Citric Acid USP Monohydrate Sodium Citrate USP Dihydrate Polysorbate 80 NF Benzalkonium Chloride Solution NF (17% without alcohol) Phenylethyl Alcohol USP Purified Water USP qs ad	a

[a]Equivalent to 0.515 mg/g of mometasone furoate anhydrous. A 3% manufacturing overcharge is included for mometasone furoate monohydrate.
[b]Equivalent to 0.204 mg/g Benzalkonium Chloride. A 2% manufacturing overcharge is included for Benzalkonium chloride.

NASONEX Nasal Spray is available in one dosage strength, 50 µg. This dose represents the dose delivered to the nose following each actuation. After initial priming (10 actuations), each actuation of the pump delivers a metered spray containing 100 mg suspension of mometasone furoate, monohydrate; equivalent to 50 µg of mometasone furoate calculated on the anhydrous basis. Each bottle of NASONEX Nasal Spray contains 120 metered sprays [1.1:Label Review:1].

The to-be marketed device will be slightly different from the device used in the clinical trials in NDA 20-762 in that the closure system for the to-be-marketed product will consist of an indwelling spray pump which will be crimped onto a HDPE container rather than the 'threaded' closure design utilized in the clinical trials [CMC Review # 1, Dr. Craig Bertha, HFD-570, 02/13/97, p. 75]. Thus the 'to-be-marketed' version of NASONEX Nasal Spray has the same pump system as the threaded closure device that was used in the clinical trials for NASONEX (and is the existing commercial package used for the Vancenase AQ Nasal suspensions

(both 0.042 and 0.084) [1.5; 234]) but has a redesigned bottle shape, actuator, and method of attachment of the pump to the bottle (crimped closure) [CMC Review #1, Dr. Craig Bertha, 02/13/97, p. 75]. The product contact materials for these 2 packaging configurations remains unchanged.

The formulation for all clinical batches was 2450, the same as the proposed 'to-be-marketed' formulation [Chemistry Review, Dr. Craig Bertha, HFD-570, 02/12/97, p. 97 and Attachment 3].

5.0. Animal Pharmacology/Toxicology

Pre-clinical pharmacology/toxicology studies indicate that mometasone furoate has greater local pharmacological activity as compared with systemic activity. After a single intranasal dose, animal studies showed that the highest drug levels were seen in the esophagus, trachea, nasal passage, and mouth, but not in the lungs. Plasma drug concentrations were not affected by gender or treatment duration. In vitro studies demonstrated that mometasone was highly bound to human and animal plasma proteins. Mometasone furoate was mainly eliminated through the feces.

Toxicity of mometasone furoate was evaluated in rats and dogs by intranasal and inhalation routes of administration. Testing duration lasted up to one year. Similar to other corticosteroids, the major target organs of toxicity of mometasone furoate were the liver, thymus, lymph tissues, lungs, skin, spleen, mammary, and adrenal glands. Changes included increases in liver weight, atrophy of the thymus and adrenal glands, and suppression of the HPA axis. Nonetheless, experimental data from the intranasal and inhalation studies show that the tolerated dose with mild glucocorticoid effects was much higher in animals than the proposed human dose. Following a 6 month inhalation study, the NOAEL level in dogs was 21 µg/kg/day, which was approximately 5 and 3.4 times the proposed human intranasal dose on the basis of body weight and body surface area, respectively. In terms of glucocorticoid effects, a tolerated daily dose with mild glucocorticoid effects in dogs was defined as 15 µg/kg body weight or 300 µg/m^2 body surface area--an approximately 4 and 2.4 times greater dose than the proposed human dose on the basis of body weight and body surface area. In the 3-month rat study (D-22797), the NOAEL was 48 µg/kg/day, approximately 12 and 2.3 times the proposed human intranasal dose on the basis of body weight and body surface area, respectively.

Reproductive toxicities were not induced in animals treated intranasally at a tolerated dose with mild glucocorticoid effects. Negative studies were seen in 8 out of 10 genetic toxicology studies. Although mometasone furoate produced chromosomal aberrations in CHO cells at cytotoxic concentrations, this finding may not be drug-related. Results from two, 2-year carcinogenicity studies showed that mometasone furoate has none or a very limited cancer risk to humans. In summary, the preclinical data are sufficient to support the proposed human clinical use at the recommended dose.

6.0 Clinical Background

The relevant human experience which served as the basis for this review consisted of the clinical studies section of NDA 20-762 [Vol. 165-301], along with review of human pharmacokinetics studies for NDA 20-762 [Vol. 164]. Mometasone furoate nasal spray is not currently approved for marketing in any country. Three other dosage forms of mometasone furoate (cream, lotion, and ointment) are currently marketed in the U.S. and internationally in numerous countries [1.1, 3.C:1-13].

Regarding human pharmacology, pharmacokinetics, and pharmacodynamics, a total of two (2) human pharmacokinetic trials were reviewed. The mass balance study demonstrated that when administered as an intranasal suspension, mometasone absorption is minimal (approximately 2% of the administered radioactivity is recovered in the urine). When given as intravenous and oral solutions, mometasone is extensively metabolized and excreted mainly in the feces. When given as an intranasal suspension, most of the administered dose is recovered in the feces, probably as unabsorbed drug. Mometasone furoate which is swallowed and absorbed appears to undergo rapid and extensive first-pass hepatic metabolism. The multiple metabolites are more polar than mometasone furoate, and because of their polarity, are not considered to have pharmacological activity. No major metabolite is formed.

Plasma mometasone concentrations after intranasal administration of this product were inadequate to assess its bioavailability. After administration of a 1.0 mg single dose of intravenous solution of mometasone furoate, the mometasone mean $AUC_{0-\infty}$ for males and females were: 17557 pg/hr/ml (CV-30%) and 18742 pg/hr/ml (CV-19%), respectively. The elimination half lives for males and females were 7.73 (CV-48%) and 16.6 (CV-78%) hours, respectively. Part of the observed difference is probably due to differences in subject volume of distribution of males vs. females, but the remaining difference is not entirely explained by the data presented. This possibility of increased bioavailability in females was thus closely examined when evaluating the safety of mometasone furoate nasal spray. After intravenous administration, the total body clearance of mometasone furoate is 96 mL/min., confirming extensive metabolism.

The pivotal clinical efficacy and safety batches were of full production scale and represent the final, 'to-be-marketed' product. The batch used for the bioavailability study was of one-half production scale and used a packaging system different from the 'to-be-marketed' product. These minor differences were not felt to have an important effect on bioavailability [Clinical Pharmacology and Biopharmaceutics Review, Dr. Bradley Gillespie, p. ..

NASONEX's proposed indication is for the prophylaxis and treatment of symptoms of seasonal allergic rhinitis and the treatment of symptoms of perennial allergic rhinitis in adults and children 12 years of age and older. The proposed recommended dose is 2 sprays (50 µg of mometasone furoate/spray) in each nostril once daily for a total daily dose of 200 µg qd.

7.0 Description of Clinical Data Sources

The clinical data sources for this review consisted of the 21 clinical studies submitted to NDA 20-762 (20 of these were submitted at the time of NDA filing 10/01/96). Eight (8) of these 21 studies were for the SAR indication, 2 were for the prophylaxis of SAR indication, and 11 were for the PAR indication. Most of the studies were double-blinded, active comparator and placebo controlled, parallel group design multi-center studies. Greater than 3000 subjects comprised the intent-to-treat (ITT) population for both safety and efficacy in NDA 20-762.

While post-marketing experience is not available with mometasone furoate nasal spray, as this formulation is not currently approved in any country, mometasone furoate has been marketed as a topical lotion, ointment, and cream since the late 1980's and has been shown to be well-tolerated and effective in its intended use. During review of this NDA, a number of clinical efficacy studies for mometasone furoate nasal spray were published (*Dose ranging study of mometasone furoate (Nasonex) in seasonal allergic rhinitis, Bronsky, E.A., Aaronson, D.W., Berkowitz, R. B., et al., Ann Allergy Asthma Immunol. 1997. 79: 51-6, Once-daily mometasone furoate nasal spray: efficacy and safety of a new intranasal glucocorticoid for allergic rhinitis, Davies, R. J. and Nelson, H. S., Clin Ther. 1997. 19: 27-38; discussion 2-3, Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study, Hebert, J. R., Nolop, K., and Lutsky, B. N., Allergy. 1996. 51:569-576, A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray, Graft, D., Aaronson, D., Chervinsky, P., et al., JACI. 1996. 98:724-73, Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients, Drouin, M., Yang, W. H., Bertrand, B., et al., Ann Allergy Asthma Immunol. 1996. 77:153-160*). As these publications represent synopses of clinical studies already submitted to NDA 20-762, they were not individually reviewed in the medical officer's efficacy evaluation of mometasone nasal spray.

7.1 Nomenclature Committee Recommendations

The proposed trademark for mometasone furoate monohydrate nasal spray by the sponsor, Schering Plough, Inc. is NASONEX Nasal Spray which was found to be acceptable by the nomenclature committee [Consult #704, Request for Trademark Review, HFD-530, 01/07/97]. However, it was noted that the USP does not use the term nasal spray in monograph titles and it was thus recommended that the established name for this product be mometasone furoate monohydrate nasal solution to be in conformance with recognized USP dosage form descriptors.

8.0. CLINICAL STUDIES

8.1. Trial C93-013: Controlled, Pivotal Study of Mometasone for the Treatment of Seasonal Allergic Rhinitis (SAR)

Principal Investigator: Robert B. Berkowitz, M.D.
Atlanta Allergy and Immunology Research Foundation
6667 Vernon Woods Drive
Atlanta, GA 30328

Participating Centers: 10 U.S. centers

8.1.1. OBJECTIVE

The objective of this study was to investigate the safety and efficacy of mometasone furoate in the treatment of symptoms of seasonal allergic rhinitis (SAR).

8.1.2. STUDY DESIGN

The study was a phase III, randomized, multi-center, double-blind, active- and placebo-controlled study to determine the safety and efficacy of mometasone furoate 200 µg administered intranasally once daily (qd), vs. the active control, beclomethasone (Vancenase AQ) 168 µg administered twice daily (bid), and vs. placebo for 28 days (4 weeks) in the treatment of seasonal allergic rhinitis (SAR).

8.1.3. PROTOCOL

8.1.3.1.a. POPULATION: Male or female subjects, ≥ 12 years of age, with SAR documented by a positive response to allergen skin prick tests [171:11, 172:413].

(I) Inclusion Criteria [171:13, 174:415]:

1. History of seasonal allergic rhinitis of at least 2 years duration.
2. If not performed within 2 years of study entry, demonstration of a positive response to skin (via prick method) testing to the relevant seasonal allergen. The wheal size must have been 3 millimeters (mm) larger than diluent control; diluent not specified in the protocol).
3. Clinical evidence of active symptoms at both screening and baseline. Nasal congestion and one other nasal symptom

severity must each be at least moderate (score ≥ 2). The combined score of nasal symptoms must total at least 6 at both the screening and baseline visit [171:23, 174:413, 415]. Physical findings must be compatible with SAR.

4. Other than SAR, subjects must in good health and free of clinically significant disease that would interfere with the study schedule or evaluation of SAR.
5. Ability to adhere to dose and visit schedules and record symptom scores accurately and consistently twice daily in a diary.
6. Nonpregnant women of childbearing potential must have been using a medically acceptable form of birth control for at least 3 months prior to screening and were to continue its use for the duration of the study.

(II) Exclusion Criteria [171:14, 174:415-417]:

1. History of asthma which required therapy with inhaled or systemic corticosteroids.
2. Clinical evidence of large nasal polyps, marked septal deviation, or any other nasal structural abnormality that may significantly interfere with nasal airflow, as determined by the principal investigator.
3. History of an upper respiratory or sinus infection that required antibiotic therapy within 2 weeks prior to study enrollment.
4. History of significant renal, hepatic, neurologic, cardiovascular, hematologic, metabolic, cerebrovascular, respiratory, gastrointestinal, or other significant medical illness, which in the judgement of the principal investigator could interfere with the study or require medical treatment that would interfere with the study.
5. History of posterior subcapsular cataracts.
6. History of allergy to corticosteroids, or a history of multiple drug allergies.
7. Subject dependency on nasal, oral, or ocular decongestants; as determined by the principal investigator, or diagnosis of rhinitis medicamentosa.
8. Subject use of any chronic medication which could affect the course of SAR.
9. Use of any investigational drug within the previous 90 days unless the investigational drug was a nasal corticosteroid or has a short (≤ 12 hours) duration of action, in which case the washout period was to be 30 days.
10. Presence of any clinically relevant abnormal vital signs,

laboratory test results outside the normal range, or clinically significant abnormal ECG.

11. Subjects on immunotherapy, unless on maintenance therapy.
12. Pregnant or nursing women, pre-menarchal females or women of child-bearing potential not using a medically acceptable form of birth control.

(III) Concurrent Medication Restrictions [171:18-19, 174:417-419]:

(A) General Considerations:

1. No subject was permitted to concurrently receive any medication linked with a clinically significant incidence of hepatotoxicity (e.g. methotrexate, 17α-alkylsteroids) or which may cause significant liver enzyme induction (e.g. barbiturates).
2. All previous and concomitant medications taken for the month prior to study entry (exception: astemizole or intramuscular/intra-articular corticosteroids, 3 months) including any over-the-counter drugs, must be recorded in the case report form. The daily dose, route of administration, duration of treatment and reason for use, was to be recorded on the case report form. No significant dose change in chronic medication was allowed during the study.

(B) Medications restricted before screening (Visit 1) [171:18, 174:417-418]:

	Medication	Time Discontinued Prior to Visit 1
1.	Cromolyn sodium, all forms	2 weeks
2.	Corticosteroids, nasal or ocular	2 weeks
3.	Corticosteroids, inhaled, oral or intravenous	1 month
4.	Corticosteroids, intra-muscular or intra-articular	3 months
5.	High potency topical corticoids-Class 3 or higher in potency, For dermatological use [Stoughten/Cornell Scale, 172:449-450]	1 month
6.	Antihistamines, short acting (e.g. chlorpheniramine)	12 hours

	Medication	Time Discontinued Prior to Visit 1
7.	Antihistamines, long acting (e.g. cetirizine, loratadine, hydroxyzine)	96 hours
8.	Terfenadine, clemastine	48 hours
9.	Astemizole	3 months
10.	Topical nasal and ocular decongestants	24 hours
11.	Oral decongestants	24 hours
12.	Systemic antibiotics	2 weeks
13.	Immunotherapy	24 hours

(C) Concurrent medications restricted after screening and for the duration of the study [171:18-19, 174:418-419]:

1. Systemic, inhaled, topical nasal, and topical ocular corticosteroids.
2. High potency topical corticosteroids (≥ class 3).
3. Cromolyn sodium.
4. Antihistamines (short-acting antihistamines, such as chlorpheniramine) allowed between screening and baseline as long as the washout period was 12 hours before baseline.
5. Topical (nasal and ocular decongestants).
6. Oral decongestants.
7. Immunotherapy 24 hours prior to any visit.
8. Systemic antibiotics (unless on stable dose 1 month prior to the study with the dose remaining unchanged for duration of the study).
9. Aspirin or nonsteroidal anti-inflammatory agents, unless on a stable low dose 1 month prior to the study with the dose remaining unchanged for duration of the study.

(D) Medications allowed during the study duration [171:19]:

1. Acetaminophen.
2. Inhaled or oral beta-agonists on an as needed basis, for asthma.
3. Theophylline, if on a stable dose before and during the study.
4. Topical antimicrobials.
5. Medium to mild potency (≤ class 4) topical corticosteroids for dermatological use only if the patient had been on a stable dose for at least 2 weeks prior to study.
6. Thyroid replacement therapy, if on a stable dosage before and during the study,

7 Saline eye drops, as needed.

8 Hormone replacement therapy for postmenopausal women, if on a stable dosage before and during the study.

8.1.3.1.b. PROCEDURE:

(1) Screening Visit (Visit 1) [171:20-21,172:422-423]:

A complete medical history (including allergy history), physical examination (including a nasal exam), laboratory evaluation, 12-lead ECG, and confirmation of the subject's allergen hypersensitivity with skin prick testing (if not performed within the last 2 years) was performed at the screening visit. Subjects were to be symptomatic at both the screening and baseline visits with physical findings compatible with seasonal allergic rhinitis.

Symptoms and overall condition of the SAR were rated using the following set of (A) nasal and non-nasal symptoms and according to the following (B) symptom severity scale:

(A) Seasonal Allergic Rhinitis Symptom Categorization [171:23, 172:429]:

Nasal Symptoms:	Non-nasal Symptoms:
Rhinorrhea (nasal discharge/ runny nose)	Itching/burning eyes
Stuffiness/congestion	Tearing/watering eyes
Nasal itching	Redness of eyes
Sneezing	Itching of ears or palate

(B) Seasonal Allergic Rhinitis Symptom Severity Scale [171:23, 172:429]:

Symptom Severity Score:	Severity Definition:
0= None	No sign/symptom evident.
1= Mild	Sign/Symptom clearly present but minimal awareness; easily tolerated.
2= Moderate	Definite awareness of sign/symptom which is bothersome but tolerable.
3= Severe	Sign/symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping.

Reviewer's Note:
According to this symptom rating scale, any given study subject could

achieve a: minimum score=0 or maximum score=12; for either nasal symptoms or non-nasal symptoms, respectively; and a minimum score =0, maximum score=24 for combined nasal and non-nasal symptoms.

Using this scale, study subjects were to have at least moderate nasal congestion and 1 other moderate nasal symptom (i.e. score ≤ 2). The combined score of nasal symptoms was to be at least 6.

Subjects were given diary cards and rescue medication cards and were to be trained in the accurate recording of symptoms in the diary (to be recorded twice daily at the same time of the day), and trained in the documentation of symptom scores for investigator review. Symptoms were to be scored 'reflectively' over the previous 12 hours by subjects and were not supposed to represent an 'instantaneous' assessment of the subject's SAR symptoms at the time of recording. From the screening visit to the baseline visit only, the amount and time of use of rescue medication (only chlorpheniramine allowed) was recorded in the rescue medication diary, in addition to the severity of symptoms prior to the dose. All concomitant medications, including any over-the-counter drugs were recorded. The daily dose, route of administration, duration of treatment and reason for use were also recorded. The subject or parent/guardian (if subject ≤ 18 years of age) was instructed to return to the office within 7 days for the baseline visit (Visit 2).

(II) Baseline Visit (Visit 2= Day 1) [171:21-22, 172:424-426]:

Again, during the baseline visit, subjects were re-evaluated in terms of their allergic rhinitis symptoms, physical exam (including nasal exam), vital signs, adverse events, concomitant medications taken, laboratory tests, and ECGs. Subjects were to continue to meet all inclusion and exclusion criteria at this visit in order to qualify to enroll in the study. For any laboratory abnormality, the subject could be included in the study if the abnormal result was expected in the disease setting and was considered unlikely to create an increased risk or the abnormal laboratory value was considered clinically insignificant and would not interfere with the conduct of the study or interpretation of results [171:21,25-26]. Using the scoring scale described in Section 8.1.3.1.b., the subject's overall condition of rhinitis must have been rated as moderate (score ≥ 2) in order to participate in the study. Nasal congestion and one other nasal symptom severity must each have been at least moderate (score ≥ 2) in severity. The combined score of nasal symptoms must have totaled at least 6.

Reviewer's Note: Regarding the symptom scoring system employed in Protocol C93-013, the actual protocol [174: 413], unlike the study synopsis [171:29] did not include in the entry criteria at screening and baseline a moderate rating (score≥ 2) of the symptom severity score.

Following the performance of all medical and laboratory procedures,

subjects who met entry criteria had a treatment number assigned and were randomized in a 1:1:1 ratio (using a SAS random number generator) to one of the following 3 treatment groups [171:15, 172:414, 431]:

STUDY GROUP	a.m. dosing	p.m. dosing	Total Dose (µg/day)
(A) Mometasone (SCH 32088)	Mometasone (200 µg)	Placebo	200
(B) Beclomethasone (Vancenase AQ)	Beclomethasone (168 µg)	Beclomethasone (168 µg)	336
(C) Placebo	Placebo	Placebo	0

Subjects received 8 sprays per day (2 sprays in each nostril from the a.m. bottle each morning and 2 sprays in each nostril from the p.m. bottle each evening). Subjects were instructed about dosing and received the first dose at the study center. Both subjects and principal investigator were blinded to treatment identity as all 3 treatments were packaged in identical spray bottles which were of the Vancenase AQ bottle prototype [171:15, Telecon with Ms. Paula Rinaldi, Regulatory Affairs, Schering Plough, Inc., 08/28/97]. Subjects received new diary cards on which to record symptoms (reflectively over the previous 12 hours and prior to dosing with study drug) and were likewise to record any concomitant medications taken on these diary cards. After this visit, subjects were not allowed further rescue medication (chlorpheniramine) use.

In summary, the study was designed to recruit 27-40 subjects with documented SAR in each of the 10 centers to ensure a total of at least 270 evaluable subjects. Ideally, all subjects were to be enrolled within a 5-day period and were to begin treatment at a time point when the pollen counts were elevated or rising.

(III) Evaluation Visits [171:22, 172:426-430]:

Evaluation visits were defined as follows:
Visit 3=Day 4 ± 1 day,
Visit 4=Day 8 ± 2 days,
Visit 5=Day 15 ± 2 days,
Visit 6=Day 22 ± 2 days,
Visit 7=Day 29 ± 2 days.

During the follow-up visits, subjects had their diary cards checked for completeness and accuracy of recording. Subjects underwent a nasal examination and diary cards were reviewed to evaluate allergic rhinitis symptoms. Based on this data (diary review and symptom scoring), the overall condition of rhinitis was

assessed by the principal investigator. Response to therapy was evaluated by the investigator and subject, based upon the subject's clinical status over time since the baseline visit using the symptom scale (0-3 rating) defined in Section 8.1.3.1.b. and using the following (C) therapeutic response scale:

(C) Therapeutic Response Scale [171:24, 172:430]:

1= Complete Relief	Virtually no symptoms present.
2= Marked Relief	Symptoms are greatly improved and although present, are scarcely troublesome.
3= Moderate Relief	Symptoms are present and may be troublesome but are noticeably improved.
4= Slight Relief	Symptoms are present and only minimal improvement has been obtained.
5= Treatment Failure	No relief, symptoms unchanged or worse than pretreatment baseline.

New diary cards were issued and medication bottles were collected from the subjects at the last visit. Safety evaluations were made at these evaluation visits and are discussed in Section 8.1.4.3. Clinical laboratory tests were performed on Day 29 (Visit 7). Daily pollen counts were maintained by each study center.

The basic study procedure is outlined in Table I. below.

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Table I. Study Procedure for SAR Study C93-013

Table 1
Schedule of Study Procedures and Evaluations (Study no. C93-013)

			28 Day Treatment Period				
	Screening Days -1 to -7 (Visit 1)	Baseline Day 1 (Visit 2)	Day 4 (Visit 3)	Day 8 (Visit 4)	Day 15 (Visit 5)	Day 22 (Visit 6)	Day 29 (Visit 7)
Informed Consent	X						
Check Inclusion-Exclusion Criteria	X	X					
Review Concomitant Medications	X	X	X	X	X	X	X
Medical and Allergy History	X						
Physical Examination	X						X
Nasal Examination	X	X					X
Vital Signs	X	X	X	X	X	X	X
Body Weight	X						X
Height	X						
Physician Assessment of Rhinitis Symptoms	X	X	X	X	X	X	X
Patient and Physician Assessment of Overall Condition	X	X	X	X	X	X	X
Patient and Physician Assessment of Response to Treatment			X	X	X	X	X
Allergy Skin Test*	X						
12 Lead ECG	X	Review					X
Laboratory Tests	X	Review					X
Urinalysis	X	Review					X
Serum Pregnancy Test	X	Review					X
Dispense Study Drug		X					
Study Drug Administered in Office		X					
Dispense Diary	X	X	X	X	X	X	
Retrieve and Review Diary Cards		X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X
Collect Study Drug							X
Drug Compliance Check			X	X	X	X	X

a: If not done in past 2 years

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8.1.3.2. CLINICAL ENDPOINTS

(I) Primary Efficacy Variable [171:31-32, 36-37, 172:435-436]:
The average change from baseline in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject diaries):

(1) Average Change in Total nasal symptom score=

15 Day Interval Score[(Nasal a.m. average $_{\text{Day 1-15}}$) + (Nasal p.m. average$_{\text{Day 1-15}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 3 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 3 Consecutive Days Prior to Baseline Visit}}$)]/2

where the **total nasal symptom score=[discharge+ stuffiness+ sneezing+ itching]**, as previously defined in Section 8.1.3.1.b.

Reviewer's Note: The sponsor, in determining this variable when one of the two averages (a.m. or p.m. average) in the above function was missing for a subject, calculated the overall average based on the non-missing average. If both the a.m. and p.m. averages were missing, then the overall average was also missing. For subjects missing either the baseline or the post-baseline visit score for a given variable and visit, no change from baseline calculation was possible and these subjects were not included in any of the efficacy analyses or summaries of that variable at that visit. For this reason, the number of subjects included in the analysis and corresponding summary table may vary from variable to variable and across time points. For each 15-day time interval, the daily composite score defined above was averaged over all non-missing days in the interval, separately for the a.m. and p.m. evaluations, to obtain 2 distinct averages for that interval. These 2 (a.m. + p.m.) averages were then averaged to obtain an overall average for the interval.

(II) Secondary Efficacy Variables:

(1) The average change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30 (a.m. and p.m. combined):

Average Change in Total nasal symptom score$_{\text{Day 16-30}}$=

Day 16-30 Interval Score[(Nasal a.m. average $_{\text{Day 16-30}}$) + (Nasal p.m. average$_{\text{Day 16-30}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 3 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 3 Consecutive Days Prior to Baseline Visit}}$)]/2

where the **total nasal symptom score=[discharge+ stuffiness+ sneezing+ itching]**.

(2) Endpoint total nasal symptom score (a.m. and p.m. combined):
The endpoint score was defined as the last available post-baseline value for each study subject, pooled across the 10 participating centers. The total nasal symptom score was determined as per the 0-3 point SAR symptom severity score [171:23].

(3) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, and the endpoint visit). Again, nasal and non-nasal symptom scores determined as per the 0-3 point SAR severity score [171:23].

(4) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, and the endpoint visit). Total non-nasal scores determined as per (2) and (3) above.

(5) Physician's evaluation of total nasal symptoms (for Baseline visit, Day 4, 8, 15, 22, 29, and the endpoint visit). Total nasal symptom score determined as per (2)-(4) above.

(6) Physician's evaluation of total symptoms (for Baseline visit, Day 4, 8, 15, 22, 29, and the endpoint visit). Total symptom score determined as per (2)-(5) above.

(7) Physician's evaluation of total non-nasal symptoms (for baseline visit, Day 4, 8, 15, 22, 29, and the endpoint visit). Total non-nasal symptoms determined as per (2)-(6) above.

(8) Subject's self-evaluation of overall disease condition using the SAR 0-3 point severity scale for study days 4, 8, 15, 22, 29, and the endpoint visit [171:24].

(9) Physician's evaluation of subject's overall disease condition using the SAR 0-3 point severity scale for study day 4, 8, 15, 22, 29, and the endpoint visit [171:24]. Again, the baseline score for physician-rated responses was based exclusively on the baseline visit (visit 2).

(10) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study day 4, 8, 15, 22, 29, and the endpoint visit [171:24].

(11) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study day 4, 8, 15, 22, 29, and the endpoint visit [171:24],

Reviewer's Note: For all physician rated responses, the baseline score was based on the baseline visit only (visit 2), whereas for all subject rated responses, the baseline score was based on an average of the baseline visit and the 3 previous visits. Of note, secondary efficacy variables (1)-(2) and (8)-(11) were listed in the study synopsis [171:37] but discussed in a general outline format in the study protocol itself [174:437]. Therefore, listed as

secondary efficacy variables (3)-(7) above are additional clinical parameters assessed by the sponsor and relevant to determination of treatment efficacy.

8.1.3.3. STATISTICAL ANALYSIS:

A sample size of 90 valid subjects per treatment group or 270 valid subjects total was calculated to detect a treatment difference of approximately 1.5 units or more with respect to the primary efficacy variable--the mean change from baseline in the total nasal symptom score (diary scores averaged over the first 15 days of treatment) based on an estimated pooled standard deviation of 3.0 units with a power of 90% at an α=0.05 (2-tailed). A total of 345 subjects were randomized and 340 were considered evaluable by the sponsor.

Efficacy and safety analyses for this study were based on the following two subject populations:

(1) Efficacy evaluable subjects- randomized subjects who met eligibility criteria and completed at least 1 valid post-baseline visit. The sponsor's primary efficacy analysis was based on this population.

(2) Intent-to-Treat (ITT) Population- all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline evaluation. The sponsor's confirmatory efficacy analyses and all summaries of safety data were based on this population.

The primary efficacy variable was analyzed for all efficacy evaluable and intent-to-treat subjects (pooled across all centers) using a two-way analysis of variance (ANOVA) which extracted sources of variation due to treatment, center, and treatment by center interaction. The primary efficacy comparison of mometasone vs. placebo was then based on the least squares (LS) means from the ANOVA using a 5% two-sided significance level. The beclomethasone group was included only to help validate the efficacy study with reference to a currently marketed nasal corticosteroid. No adjustment for multiple comparisons was made using this primary efficacy comparison.

Analysis of secondary efficacy variables was performed using the same two-way ANOVA described above for the primary efficacy variable.

For both the efficacy population and the intent-to-treat population comparability of treatment groups at baseline was assessed by comparing the three treatment groups with respect to demographic and disease characteristics (gender, age, race, weight, and disease condition). Continuous variables (age, weight, duration of disease condition, and duration of current episode) were analyzed by a two-way analysis of variance (ANOVA) which extracted sources of variation due to treatment and center (SAS GLM). Discrete variables (gender, history of asthma, and presence or absence of perennial rhinitis) were analyzed by categorical linear models (SAS CATMOD), race was analyzed by Fischer's exact test for Caucasian vs. non-Caucasian.

Reviewer's Note: For the purposes of efficacy and safety review of this and all studies in this submission, the intent-to-treat population was utilized rather than the sponsor's efficacy evaluable population.

8.1.4. RESULTS

8.1.4.1. SUBJECT DEMOGRAPHICS

(A) A total of 345 subjects were randomized into the study, with 1 immediate drop-out and 4 subjects excluded from the efficacy analyses; thus resulting in 340 subjects comprising the efficacy evaluable population and 344 subjects comprising the intent-to-treat population. The distribution of subject populations is summarized in Table II. below:

Table II: Distribution of Subject Populations [171:40-41]

	Mometasone (SCH 32088)		Beclomethasone (BDP)		Placebo	Total
Efficacy Population	111	(1 subject dropout + 1 subject did not meet entry criteria)	113	(1 subject had insufficient efficacy data, 1 subject had an unacceptable baseline, 1 subject had unacceptable concomitant medication)	116	340
Safety Population (ITT)	112	(1 subject immediate dropout)	116		116	344
Total # Randomized	113		116		116	345

(B) Pooled demographic data with regard to subject characteristics in the safety population (ITT) is summarized in Table III below [171:42].

Table III: Subject Demographics (Protocol C93-013): Intent-to-Treat Population

	SCH 32088 (n=117)	BDP (n=116)	Placebo (n=116)	Overall Treatment P Value*
Age (years)				
Mean	35	35	35	0.80
Median	34	35	36	
Range (Min-Max)	12-68	13-74	12-71	
Gender				
Female	52	52	72	0.03
Male	50	64	44	
Race				
Caucasian	97	102	100	0.94
Black	11	7	8	
Other	4	7	8	
Weight (lbs)				
Mean	170	177	165	0.07
Median	168	171	161	
Range (Min-Max)	83-360	76-350	88-270	
Duration of Condition (Years)				
Mean	19	20	20	0.97
Median	16	18	17	
Range (Min-Max)	2-68	2-58	2-64	
Duration of This Episode of SAR (Days)				
Mean	17	13	14	0.13
Median	13	10	10	
Range (Min-Max)	2-182	2-182	2-91	
Perennial Allergic Rhinitis				
No	51	50	58	0.60
Yes	51	66	58	
History of Asthma				
No	96	100	102	0.91
Yes	16	16	14	

Sch 32088=Mometasone furoate

Reviewer's Note: Statistically significant differences were noted among the treatment groups regarding gender distribution. The placebo treatment group had more female subjects than either of the two active treatment groups; thus, there was a slight imbalance in weight in terms of gender. The treatment groups were comparable with regard to the other demographic and disease characteristics. Of note, the majority of subjects participating in each study arm was comprised of Caucasians, with a mean age of approximately 35 years of age and a mean duration of SAR of 19-20 years. Greater than half of the subjects in all treatment arms had perennial allergic rhinitis (PAR) and approximately 85% of subjects did not have asthma.

(C) Subject Distribution by Disease Severity at Baseline in Efficacy Evaluable Subjects [171:46]:

Treatment Group	% Moderate	% Severe
SCH 32088	72%	28%
BDP	83%	17%
Placebo	84%	16%

Reviewer's Note: The mometasone treatment group was noted to be comprised of a greater % of subjects with severe seasonal allergic rhinitis at baseline, as compared with the active control and placebo group.

(D) Subject Discontinuation

A total of 23 subjects (10 treated with Mometasone, 7 treated with Beclomethasone, 6 treated with placebo) discontinued the study prior to scheduled completion. This data is summarized in Table IV. [171:43].

Table IV: Number and Percentage of Randomized Subjects Who Completed Treatment and Number/(%) Who Discontinued the Study with Reasons for Discontinuation

	TREATMENT GROUP			
	Mometasone (n=113)[1]	**Beclomethasone** (n=116)	**Placebo** (n=116)	**Total** (n=345)
Number (%) Completed	103 (91%)	109 (94%)	110 (95%)	322 (93%)
Reason for Discontinuation				
–Adverse event	5 (4%)	2 (2%)	4 (3%)	11 (3%)
–Treatment Failure	1 (<1%)	1 (<1%)	2 (2%)	4 (1%)
–Noncompliance with Protocol	0	1 (<1%)	0	1 (<1%)
–Subject did not Return	4 (4%)	3 (3%)	0	7 (2%)
TOTAL # (%) DISCONTINUED	10 (9%)	7 (6%)	6 (5%)	23 (7%)

[1] n=number of randomized subjects at the time of study initiation.

Reviewer's Note: In all treatment arms, the total % of subject discontinuation was less than 10% of the total enrolled.

(E) Subject Validity

Twenty-one subjects (7 treated with mometasone, 4 treated with beclomethasone, and 10 treated with placebo) valid for efficacy had data invalidated for some visits. These subjects and the reasons for invalidation are summarized in Table 9 of the NDA [171:44].

8.1.4.2. EFFICACY ENDPOINT OUTCOMES

(1) Primary Efficacy Variable (Change in total nasal symptom score)

All efficacy analyses in this review were based on the intent-to-treat population (n=112 for mometasone, n=116 for beclomethasone (BDP), n=116 for placebo) for the primary efficacy variable--the average change from baseline in the total nasal symptom scores from patient diaries over the first 15 days of treatment. For the average change from baseline in total nasal symptom scores over the day 1-15 interval, both active treatment groups--mometasone and beclomethasone, respectively; were significantly more effective than placebo ($p<0.01$). Furthermore, the mometasone and beclomethasone treatment groups were not statistically significantly different than each other ($p=0.08$), although the beclomethasone group showed a numerical advantage with regard to response, compared with the mometasone group. Because of study design and underpowering to detect a difference between these 2 groups, no conclusion can be made regarding the true meaning of a p-value of 0.08 in this context. The mean % decrease in total nasal symptom scores for subjects receiving mometasone (200 µg qd) was 25%, in comparison with a 37% decrease in subjects receiving beclomethasone (168 µg bid) and a 16% decrease in the placebo treatment group [172:296].

Reviewer's Note: Of note, the findings for the efficacy evaluable group were the same as that for the above intent-to-treat group with the exception of a 17% decrease in total nasal symptom scores for the placebo group [171:48, 159].

Regarding any potential difference of mometasone drug effect over the course of the day (i.e. a.m. vs. p.m.) and detection of waning of drug effect as demonstrated by a change in the primary efficacy variable, a subset analysis comparing the combined a.m. and p.m. total nasal scores vs. the a.m. total nasal and vs. the p.m. total nasal symptom scores for days 1-15 was performed. No significant difference in symptom scores was found between any of these three mometasone groups (with the combined a.m. and p.m. nasal $score_{DAY\ 1\text{-}15}$=5.3, a.m. nasal $score_{DAY\ 1\text{-}15}$= 5.4, p.m. nasal $score_{DAY\ 1\text{-}15}$= 5.1), nor was any significant a.m. vs. p.m. difference noted in the beclomethasone and placebo treatment groups [172:296-298]. Comparison of the mometasone group vs. placebo for the a.m. total nasal symptom score for days 1-15 (end of dosing interval) indicates that mometasone treatment had a statistically significant ($p=0.02$) effect in decreasing total nasal symptoms for a 24 hour duration, as compared with placebo.

Reviewer's Note: The a.m. and the p.m. scoring system represents an integration of the subject's symptoms over the previous 12 hours and does not represent a 'snap-shot' of the subject's clinical status at the particular time of symptom recording.

A summary of all of these findings for the primary efficacy variable is provided in Table V. below

A sub-analysis of the primary efficacy variable on a per week basis was performed using the SAS data files provided by the sponsor (performed by Dr. Jim Gebert, Biostatistics, DPDP, FDA). A summary of the efficacy findings for week 1 and week 2 are summarized in Tables V.a. and V.b. Overall, a greater response in total nasal symptoms was noted for the 2 active treatment groups, mometasone and beclomethasone, during week 1 of treatment but subjects continued to show a clinical response, albeit less dramatic, during week 2 of treatment.

Separate analysis of a.m. vs. p.m. differences in drug efficacy for week 1 vs. week 2 of the study (Table V.a. and Table V.b.) showed that for the first week of treatment (days 1-7, Table V.a.) the treatment group receiving mometasone had slightly greater nasal symptoms during the a.m. recording as compared with the p.m. recording. A post-hoc analysis of significance was not performed comparing the differences between these two symptom recording times. Both the a.m. and p.m. scores for week 1 and week 2 of treatment demonstrated that mometasone had a statistically significant effect in reducing total nasal symptoms of SAR compared with placebo, but that this effect was greater by the second week of treatment.

An analysis of the impact of rescue medication use between screening and baseline was performed by the sponsor and 14% (46/340) subjects were found to have used rescue medication between these 2 visits. The rescue diary scores were used to adjust for the rescue medication users whenever their regular diary entry time fell into the 12 hour wash-out period for chlorpheniramine. Adjustment of the baseline score by the sponsor by rescue diary scores had a small effect which did not affect any conclusions regarding the primary efficacy variable [172:605].

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Table V.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Primary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [172 296-298]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS A-B	A-C	B
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE																
-am & pm nasal	112	7 6	2 2	116	7 3	2 2	116	7 6	2 0	2 0	0 47	<.01	0 02	0 25	0 8	
-am nasal	112	7 7	2 2	116	7 3	2 2	116	7 7	2 0	2 0	0 3	< 01	0 02	0 18	0 98	
-pm nasal	111	7 5	2 3	115	7 3	2 4	116	7 4	2 1	2 2	0 73	0 01	0 0C	0 43	0 74	
DAYS 1-15																
-am & pm nasal																
RAW	112	5 3	2.2	116	4.5	2.1	116	6.1	2.0	2.0	<.01	<.01	0.11	<.01	<.01	
CHG	112	-2.3	2 6	116	-2.9	2.1	116	-1.5	2.1	2.2	<.01	0.09	0.05	0.08	<.01	
%CHG	112	-25	38.2	116	-37	25.6	116	-16	29.2							
-am nasal																
RAW	112	5 4	2 3	116	4 5	2 1	116	6 1	2 1	2 0	< 01	< 01	0 11	< 01	01	
CHG	112	-2 2	2 7	116	-2 8	2 1	116	-1 6	2 1	2 2	< 01	0 06	0 05	0 05	02	
%CHG	112	-25	36 2	116	-36	27 3	116	-18	28 3							
-pm nasal																
RAW	111	5 1	2 2	115	4 4	2 2	116	6 0	2 1	2 0	< 01	< 01	0 09	0 01	< 01	
CHG	111	-2 4	2 8	115	-2 9	2 3	116	-1 4	2 2	2 4	< 01	0 11	0 05	0 17	< 01	
%CHG	111	-22	62 0	115	-36	28 2	116	-14	32 7							

SD = Standard Deviation CHG=Change T X I = Treatment by investigator interaction
# P values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table V.a.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Weekly Analysis of the Primary Efficacy Variable: WEEK 1 (Intent-to-Treat (ITT) POPULATION)

[SAS Datafiles for NDA 20-762]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS(A-B	A-C	E
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-(
BASELINE																
-am & pm nasal	112	7 6	2.2	116	7 3	2.2	116	7.6	2 0	2.0	0.47	<.01	0 02	0.25	0.8	
am nasal	112	7 7	2 2	116	7 3	2 2	116	7 7	2 0	2 0	0 3	< 01	0 02	0 18	0 98	
pm nasal	111	7 5	2 3	115	7 3	2 4	116	7 4	2 1	2 2	0 73	0 01	0 06	0 43	0 74	
DAYS 1-7																
-am & pm nasal																
RAW	112	5.7	2.3	116	4.9	2.1	116	6.5	2.1	2.0	<.01	<.01	0.24	0.01	<.01	
CHG	112	-1 9	2.5	116	-2.4	1.9	116	-1.1	2.1	2.1	<.01	0.15	0.05	0.11	<.01	
%CHG	112	-21	35 0	116	-30	25.2	116	-11	29.7							
-am nasa																
RAW	112	5 9	2 4	116	5 0	2 1	116	6 6	2 2	2 1	< 01	< 01	0.21	< 01	02	
CHG	112	-1 8	2 5	116	-2 4	2 0	116	-1 1	2 0	2 1	< 01	0 13	0 08	0 05	02	
%CHG	112	-20	33 9	116	-30	26 8	116	-12	29 1							
pm nasal																
RAW	111	5 5	2 2	115	4 9	2 2	116	6 4	2 1	2 0	< 01	< 01	0 28	0 05	< 01	
CHG	111	-2 0	2 6	115	-2 4	2 1	116	-1 0	2 2	2 3	< 01	0 19	0 05	0 33	< 01	
%CHG	111	-19	53 8	115	-29	29 0	116	-8 9	33 7							

SD= Standard Deviation CHG=Change T X I = Treatment by investigator interaction

P-values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table V.b.

Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Weekly Analysis of the Primary Efficacy Variable: WEEK 2 (Intent-to-Treat (ITT) POPULATION)
[SAS Datafiles for NDA 20-762]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS(A-B	A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-(
BASELINE																
--am & pm nasal	112	7.6	2 2	118	7.3	2 2	116	7 6	2.0	2.0	0.47	<.01	0.02	0.25	0.8	
--am nasal	112	7 7	2 2	116	7 3	2 2	116	7 7	2 0	2 0	0 3	< 01	0 02	0 18	0 98	
- pm nasal	111	7 5	2 3	115	7 3	2 4	116	7 4	2 1	2 2	0.73	0.01	0.06	0 43	0 74	
DAYS 8-15																
--am & pm nasal																
RAW	111	5 0	2.3	114	4.0	2.3	114	5.8	2.2	2.1	<.01	<.01	0.03	<.01	0.01	
CHG	111	-2.6	3.0	114	-3.2	2.4	114	-1.8	2.3	2.5	<.01	0.04	0.05	0.08	0.01	
%CHG	111	-29	43.5	114	-42	29.2	114	-21	31.6							
- am nasal																
RAW	111	5 0	2 4	114	4 1	2 3	114	5 8	2 3	2 2	<.01	<.01	0 04	< 01	0 01	
CHG	111	-2 6	3 0	114	-3 2	2 4	114	-1 9	2 3	2 5	<.01	0 03	0 04	0 01	0 03	
%CHG	111	-29	40 5	114	-41	31 0	114	-22	30 5							
--pm nasal																
RAW	110	4 8	2 4	112	4 0	2 4	113	5 7	2 3	2 2	< 01	<.01	0 04	0 01	< 01	
CHG	110	-2 7	3 0	112	-3 3	2 6	113	-1 8	2 4	2 6	< 01	0 08	0 06	0 11	0 01	
%CHG	110	-24	72 7	112	-42	31 8	113	-19	35 6							

SD= Standard Deviation CHG=Change T X I = Treatment by investigator interaction
# P-values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Analysis of the impact of each individual nasal symptom: rhinorrhea, nasal congestion, nasal itching, sneezing (a.m. and p.m. combined) on the determination of the final total nasal symptom score (a.m. and p.m. combined, a.m. alone, p.m. alone) for the day 1-15 interval in each of the 3 treatment groups was performed to rule out excessive contribution and therefore skewing of results by any given one parameter [172:305-313]. The nasal congestion score [172:308], closely followed by the nasal discharge score [172:305], was found to contribute a slightly greater numerical weight in the determination of the final nasal symptom score than the other 3 parameters for all 3 treatment groups but this difference was not consistent across all 3 groups. Furthermore, as expected, nasal congestion (a.m. and p.m. combined, a.m. alone, p.m. alone) showed a greater and a statistically significant response to treatment with the 2 active treatments (mometasone and beclomethasone) than it did with placebo treatment [172:308-310]. Regarding clinical response in terms of the each nasal symptom, in addition to nasal congestion, statistical significance was achieved for mean change in the other 3 nasal symptoms (a.m. and p.m. combined, a.m. alone, p.m. alone) [172:305-316] in the mometasone treated subjects for days 1-15 with the exception of a marginally statistically significant response (p=0.08) of the change in the a.m. sneezing scores of mometasone treated subjects vs. placebo [172:305, 312].

In terms of categorizing treatment response by age and sex, pooled data from all 10 centers for the primary efficacy variable reveal that female subjects overall had a greater response to mometasone than to beclomethasone, in contrast to the male subjects. Both active treatments demonstrated a greater response in both sexes than did placebo, as expected [171:199]. For male and female subjects combined, subjects > 64 years of age (n=5 total) had a greater response than other age groups (12-17 yrs. and 18-64 yrs.) to any of the 3 treatment arms, followed by the 18-64 year age group (n=313) which demonstrated a greater response to any of the 3 treatment arms than the 12-17 age group (n=22)--the 'least responsive' of the 3 age ranges [171:199].

Review of the pollen counts (ragweed, other weeds, total weeds) across the 10 centers participating in this study revealed a significant elevation in the pollen counts in 9 of 10 centers (exception center C93-013-10) for days 1-15 of the study, which took place from the end of August, 1993 to mid-September, 1993 [174:3429-3438]. This less intense pollen exposure in center C93-013-10 is supported by a proportionate decrease in the baseline and 15 day interval total nasal symptom score (a.m. and p.m. combined, a.m. alone, p.m. alone)[171:169,184,196]. Despite a numerical advantage of mometasone treatment over placebo at this center (-2.2 change or 30% decrease in symptoms vs. -0.8 change or 8.9% decrease in the 15 day interval average total nasal symptom score); in terms of the primary efficacy variable, this difference was not found to be statistically significant (p=0.12). Because each of the 10 centers had approximately the same number of subjects enrolled, this less significant overall response for all treatment groups in center C93-013-10 did not alter the pooled efficacy results for the study.

An assessment of data consistency across the 10 centers participating in protocol C93-013, shows that although the treatment by center interaction was marginally significant (p=0.05) (Refer to Table V. or [172:296]), mometasone was numerically favored over placebo at 8 of the 10 centers [172:604]. Six centers showed that numerically, beclomethasone reduced the mean nasal symptom score the most, followed, in turn by mometasone, and then placebo. Two centers showed numerically, that mometasone reduced the mean nasal symptom score most, followed by beclomethasone, and then placebo. Of the last 2 centers (center C93-013-06-Dr. Moss and C93-013-09-Dr. Stricker), placebo was found to reduce the mean nasal symptom score the most. As there were more male patients (9 out of 11 subjects in center C93-013-06 and 10 of 12 subjects in center C93-013-09) in the mometasone groups at these 2 centers, and a gender by treatment interaction was noted for mometasone in this study, results found by these 2 investigators are consistent with previous gender effects noted in the study. Except for these specific issues, the 10 centers participating in the study did not show significant variability of efficacy results. Based on the overall findings of this study, and including the 2 centers which showed decreased efficacy of mometasone compared with placebo, the pooled results for the primary efficacy variable nonetheless appear to be reasonable results.

(II) Secondary Efficacy Variables (Intent-to-Treat population):

The change from baseline in the total nasal symptom scores averaged over days 16-30 and the endpoint interval were considered secondary efficacy variables. These timepoints were analyzed using the same model described for the primary efficacy variable. All other composite (total) and individual diary symptom scores and physician evaluated composite and individual symptom scores, as well as the subject's and physician's evaluation of overall disease condition and therapeutic response, were also considered secondary efficacy variables. All of these secondary variables were analyzed using the same two-way ANOVA as used for analysis of the primary efficacy variable.

(1) **Average change in the total nasal symptom score$_{\text{Day 16-30}}$ (a.m. and p.m.):**

A review of the combined (a.m. and p.m.) average change in the total nasal symptom score for days 16-30, as summarized in Table VI., showed a further decrease in the total nasal symptom score from a mean of 5.3 (for days 1-15) to a mean of 4.4 (days 16-30) for the mometasone treatment group (11% difference). This symptom score decrease by day 16-30 of treatment was comparable to that of the beclomethasone treatment group which showed a decrease to a mean score of 3.6 (or 12 % difference) for the day 16-30 interval from a mean score of 4.5 (days 1-15). Of note, most of the response in total nasal symptom scores for both mometasone and beclomethasone was found to occur within the first 2 weeks of treatment (Tables V and VI). This is despite the finding that pollen counts were noted to have decreased significantly by the third to fourth weeks of the study in 5

of the 10 study centers (013-02, C93-013-03, C93-013-04, C93-013-05, and C93-013-09) and by week 4 in 2 additional study centers (C93-01306 and C93-013-07) [174:3429-3470]. No significant difference in a.m. and p.m. scores were noted for either of the active treatments, thus supporting evidence that mometasone appears to be effective over 24 hour dosing (mometasone group: 4.5=a.m. score vs. 4.4=p.m. score).

In summary, an overall greater numerical response (37% decrease) to treatment by days 16-30 was seen in the beclomethasone group (49% decrease) than in the mometasone group (36% decrease), although both active treatments were found to have greater efficacy than placebo (30% decrease in total nasal symptom scores).

(2) Endpoint total nasal symptom score (a.m. and p.m.):

Analysis of the endpoint total nasal symptom scores demonstrated a greater response of the mometasone treatment group than placebo. Using the last available post-baseline value for each study subject as the endpoint determination, endpoint nasal symptom score values were not found to be significantly different from nasal symptom scores for the 16-30 day interval. Again, distinction between the a.m. and p.m. scores revealed a numerically small but statistically insignificant difference between a.m. and p.m. dosing with a slight decrease in total nasal symptoms during the p.m. measurement (4.6=a.m. score vs. 4.4=p.m. score). These results are summarized in Table VII.

Table VI.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR: Secondary Efficacy Variable: Total Nasal Symptom Score$_{DAY16-30}$
ITT Population [172 296-298]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS A-B	A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	
BASELINE																
-am & pm nasal	112	7.6	2.2	116	7.3	2.2	116	7.6	2.0	2.0	0.47	<.01	0.02	0.25	0.8	
-am nasal	112	7.7	2.2	116	7.3	2.2	116	7.7	2.0	2.0	0.3	<.01	0.02	0.18	0.98	
-pm nasal	111	7.5	2.3	115	7.3	2.4	116	7.4	2.1	2.2	0.73	0.01	0.06	0.43	0.74	
DAYS 16-30																
-am & pm nasal																
RAW	108	4.4	2.5	112	3.6	2.3	112	5.2	2.6	2.3	<.01	<.01	0.02	0.01	0.03	
CHG	108	-3.2	3.0	112	-3.7	2.6	112	-2.4	2.7	2.6	<.01	0.01	0.01	0.16	0.03	
%CHG	108	-36	50.4	112	-49	31.1	112	-30	38.7							
-am nasal																
RAW	108	4.5	2.6	112	3.7	2.4	112	5.2	2.6	2.3	<.01	<.01	0.02	0.04	<.01	
CHG	108	-3.2	3.1	112	-3.6	2.6	112	-2.5	2.6	2.6	0.01	<.01	0.25	0.06	<.01	
%CHG	108	-37	44.6	112	-47	32.6	112	-31	35.3							
-pm nasal																
RAW	108	4.4	2.6	111	3.5	2.4	112	5.1	2.7	2.4	<.01	<.01	0.02	0.01	0.02	
CHG	108	-3.2	3.1	111	-3.8	2.7	112	-2.3	2.8	2.8	<.01	0.01	0.02	0.12	0.03	
%CHG	108	-30	88.9	111	-50	33.7	112	-28	40.2							

SD = Standard Deviation CHG=Change T X I = Treatment by investigator interaction
# P-values are from 2 way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table VII.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR: Secondary Efficacy Variable: Endpoint Analysis of the Total Nasal Symptom Score.
ITT Population [172 296-298]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARI: A-B	PAIRWISE COMPARI: A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	
BASELINE																
--am & pm nasal	112	7.6	2.2	116	7.3	2.2	116	7.6	2.0	2.0	0.47	<.01	0.02	0.25	0.8	
--am nasal	112	7.7	2.2	116	7.3	2.2	116	7.7	2.0	2.0	0.3	<.01	0.02	0.16	0.98	
--pm nasal	111	7.5	2.3	115	7.3	2.4	116	7.4	2.1	2.2	0.73	0.01	0.06	0.43	0.74	
ENDPOINT																
--am & pm nasal																
RAW	112	4.5	2.6	116	3.7	2.3	116	5.2	2.6	2.3	<.01	<.01	0.02	<.01	0.03	
CHG	112	-3.1	3.0	116	-3.7	2.6	116	-2.3	2.7	2.6	<.01	0.01	<.01	0.1	0.04	
%CHG	112	-35	50.0	116	-48	31.3	116	-29	37.0							
--am nasal																
RAW	112	4.6	2.7	116	3.7	2.4	116	5.3	2.6	2.4	<.01	<.01	0.02	0.01	0.05	
CHG	112	-3.1	3.1	116	-3.6	2.6	116	-2.4	2.7	2.6	<.01	<.01	<.01	0.14	0.07	
%CHG	112	-35	45.0	116	-47	32.6	116	-29	35.6							
--pm nasal																
RAW	111	4.4	2.5	115	3.6	2.4	116	5.2	2.7	2.4	<.01	<.01	0.02	0.01	0.01	
CHG	111	-3.1	3.1	115	-3.7	2.7	116	-2.3	2.8	2.8	<.01	0.01	0.01	0.12	0.02	
%CHG	111	-29	87.7	115	-49	34.0	116	-27	40.6							

SD= Standard Deviation CHG=Change T X I = Treatment by investigator interaction
# P-Values are from 2 way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)
ENDPOINT: Last available post-baseline value for each subject

(3) **Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, and the endpoint visit)** [172:299-301]:

Total symptom scores were not found to be statistically significantly decreased in the mometasone treatment group compared to placebo for either the day 1-15 interval (p=0.08), the day 16-30 interval (p=0.37), or the endpoint visit (p=0.38). This is in contrast to the beclomethasone treatment group which showed a statistically significant response in total symptom scores as compared with placebo for all 3 time intervals.

(4) **Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, and the endpoint visit)** [172:302-304]:

Total non-nasal symptom scores, as defined in Section 8.1.3.1.b., were not found to be statistically significantly decreased in the mometasone treatment group compared to placebo for either the day 1-15 interval (p=0.75), the day 16-30 interval (p=0.63), or the endpoint visit (p=0.63). In terms of each individual non-nasal symptom, a review of the response of each respective symptom to mometasone [172:317-320] failed to show a statistically significant symptom score response. These results, along with a review of the clinical response for individual nasal symptoms are summarized in Table VIII. Aside for the day 1-15 interval (p=0.03), beclomethasone was likewise not found to have a clinically significant improvement in total non-nasal scores, as compared with placebo.

Table VIII. Change in Individual SAR Symptoms with Mometasone Treatment

SAR SYMPTOM	*Statistically Significant Response$_{DAY\ 1-15}$ (Yes=Y/No=N)	Statistically Significant Response$_{DAY\ 16-30}$ (Y/N)	Statistically Significant Response$_{Endpoint}$ (Y/N)
NASAL			
--Rhinorrhea	Yes	No (p=0.06)	No (p=0.06)
--Congestion	Yes	Yes	Yes
--Itching	Yes	No (p=0.09)	No (p=0.10)
--Sneezing	Yes	No (p=0.11)	No (p=0.12)
NON-NASAL			
--Eye Itching	No (p=0.68)	No (p=0.33)	No (p=0.32)
--Eye Tearing[1]	No (p=0.98)	No (p=0.37)	No (p=0.39)
--Eye Redness	No (p=0.70)	No (p=0.64)	No (p=0.61)
--Ear/palate itching	No (p=0.37)	No (p=0.61)	No (p=0.55)

*Statistically Significant Response= Response of mometasone treatment group symptom scores, as compared with placebo, based on an α=0.05, 2-tailed, via 2-way ANOVA

[1] Eye tearing symptom score taken from efficacy population (ITT not submitted by sponsor)

[2] p values were calculated based on the change in symptom score from baseline.

(5) **Physician's evaluation of total nasal symptoms (for the Baseline visit, Days 4, 8, 15, 22, 29, and the endpoint visit)** [172:326]:

With the exception of Day 22, subjects in the mometasone treatment group were found to have a statistically significant decrease in total nasal symptoms, as compared with placebo. Again, beclomethasone was found to have a clinically and statistically significant and a numerically greater response than mometasone in decreasing total nasal symptoms at all time points.

(6) **Physician's evaluation of total symptoms (nasal + non-nasal, for Baseline visit, Days 4, 8, 15, 22, 29, and the endpoint visit)** [172:327]:

With the exception of Day 4, 8, and marginally, the endpoint visit, subjects in the mometasone treatment group were not found to have a statistically significant decrease in total symptoms compared with placebo, although numerically a small decrease in symptom scores was noted with mometasone treatment. In contrast, beclomethasone demonstrated a statistically significant decrease in total symptoms at all time points ($p < 0.01$).

(7) **Physician's evaluation of total non-nasal symptoms (for Baseline visit, Days 4, 8, 15, 22, 29, and the endpoint visit)** [172:328]:

With the exception of Day 8, subjects in the mometasone treatment group were not found to have statistically significant decrease in total non-nasal symptoms compared with placebo, although again, numerically a small decrease in symptom scores was noted with mometasone treatment. With the exception of Day 15, subjects in the beclomethasone treatment group were noted to have a statistically significant improvement in total non-nasal symptoms at all visits, compared with placebo.

(8) **Subject's self-evaluation of overall condition (for Days 4, 8, 15, 22, 29, and the endpoint visit)** [172:338]:

With the marginal exception of Days 4 and 22, subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall condition compared with placebo; which by the endpoint visit, was comparable numerically to the beclomethasone treatment group (symptom score=1.4, mometasone group vs. symptom score=1.3 beclomethasone group).

(9) **Physician's evaluation of subject's overall condition (for Days 4, 8, 15, 22, 29, and the endpoint visit)** [172:337]:

Subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall condition compared with placebo at all study visits. Furthermore, responses for the mometasone and beclomethasone group were comparable at all study visits.

(10) **Subject's self-evaluation of overall response to treatment (for Days 4, 8, 15, 22, 29, and the endpoint visit)** [172:340]:

Subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall response to treatment, as compared with placebo at all study visits. The beclomethasone treatment group demonstrated a statistically significant and slightly greater numerical response to treatment than did the mometasone group, as had been previously noted in several of the other secondary efficacy variables.

(11) **Physician's evaluation of subject's overall response to treatment (for Days 4, 8, 15, 22, 29, and the endpoint visit)** [172:339]:

Again, subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall response to treatment, as compared with placebo at all study visits. The beclomethasone treatment group demonstrated a statistically significant response compared with placebo which was slightly greater numerically than the response of the mometasone group; again, consistent with previous analyses of the primary efficacy variable and several secondary efficacy variables.

A summary of the secondary efficacy variable findings for mometasone is

Variables (3)-(11))

Table IX. Secondary Efficacy Variables of SAR and Treatment with Mometasone

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1	Subject Average Δ Total Nasal Sx Score$_{DAYTIME}$	Yes
2	Subject Endpoint Total Nasal Sx Score	Yes
3	Subject Total Sx Score	No
4	Subject Total Non-nasal Sx Score	No
5	Physician's Total Nasal Sx Score	Yes
6	Physician's Total Sx Score	No
7	Physician's Total Non-nasal Sx Score	No
8	Subject overall condition evaluation	Yes
9	Physician overall condition evaluation	Yes
10	Subject overall Rx Response evaluation	Yes
11	Physician overall Rx Response evaluation	Yes

Δ=Change, Sx=Symptom, Rx=Treatment

Reviewer's Note: Summary of Efficacy Findings

Overall mometasone was found to be effective in reducing total nasal symptoms and improving the subject's overall condition at a dose of 200 µg po qd, as related to seasonal allergic rhinitis symptoms over the course of all study visits. Because of a lack of a statistically significant effect on non-nasal symptoms, mometasone did not demonstrate a significant effect on decreasing total symptoms of SAR, the total non-nasal symptoms or any of the individual non-nasal symptoms of SAR.

Mometasone did not demonstrate a significant waning of clinical efficacy based on separate a.m. and p.m. scoring of symptoms in subject diaries, a finding which supports once a day (qd) dosing of mometasone.

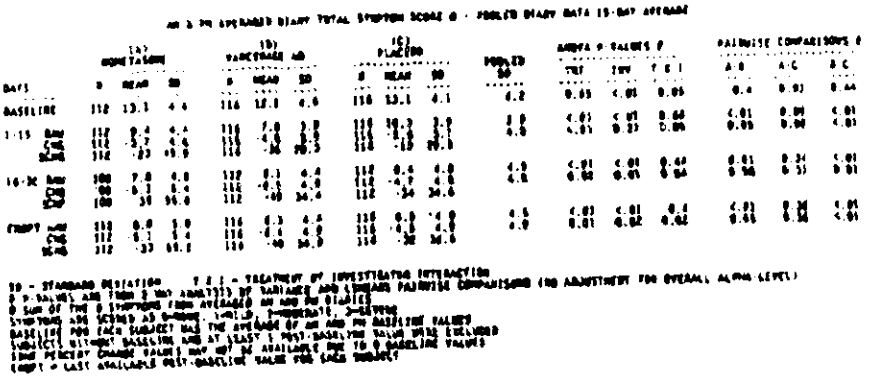
In terms of the primary efficacy variable, mometasone demonstrated a small but a clinically significantly greater effect in female than male subjects, and in individuals ≥ 18 years of age. No commentary can be made regarding efficacy and racial differences as the majority of enrolled subjects were Caucasian.

In summary, given a reasonable study design to assess a therapeutic response in the treatment of seasonal allergic rhinitis and reasonable clinical efficacy results, mometasone was found to be effective in decreasing the symptoms of SAR as compared with placebo.

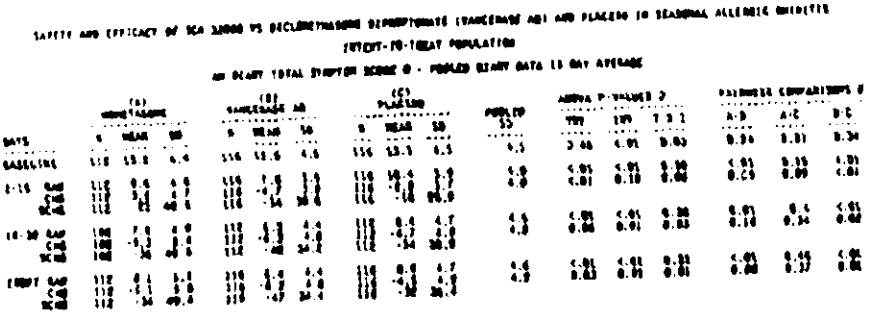
ATTACHMENT 1:
Secondary Efficacy Variables of SAR and Response to Mometasone Treatment:

(3) Subject's evaluation of total symptom scores:

(A) Subject a.m. and p.m. combined scores [172:299]:

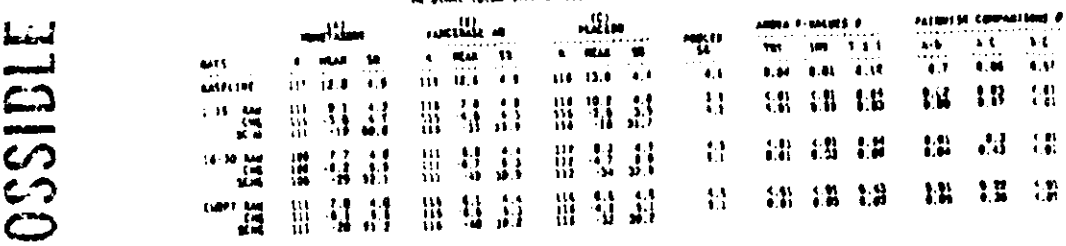


(B) Subject a.m. scores [172:300]:



ATTACHMENT 1--continued

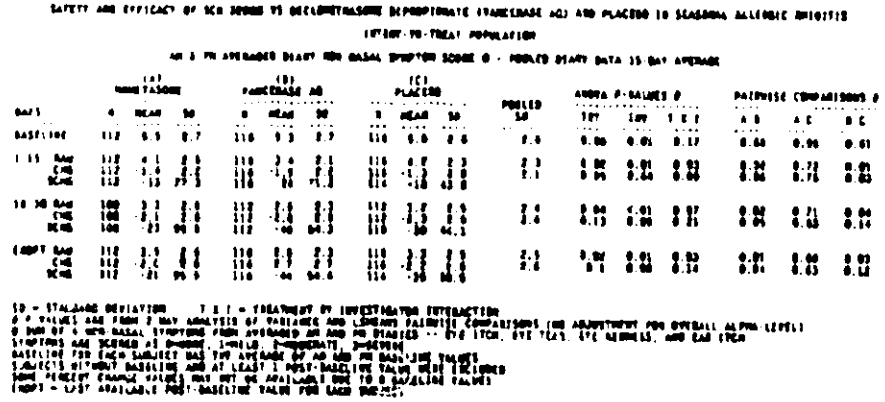
(C) Subject p.m. scores [172:301]:



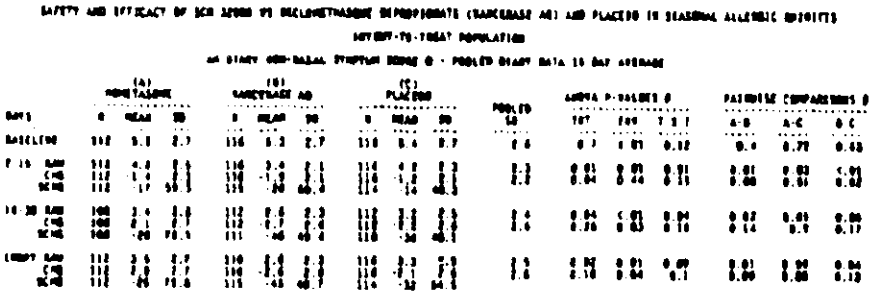
ATTACHMENT 1--continued

(4) Subject's evaluation of total non-nasal symptom scores:

(A) Subject a.m. and p.m. combined scores [172.302]:



(B) Subject a.m. scores [172:303]:



ATTACHMENT 1--continued

(C) Subject p.m. scores [172:304]:

SAFETY AND EFFICACY OF SCH 32580 VS BECLOMETHASONE DIPROPIONATE (VANCERASE AQ) AND PLACEBO IN SEASONAL ALLERGIC RHINITIS

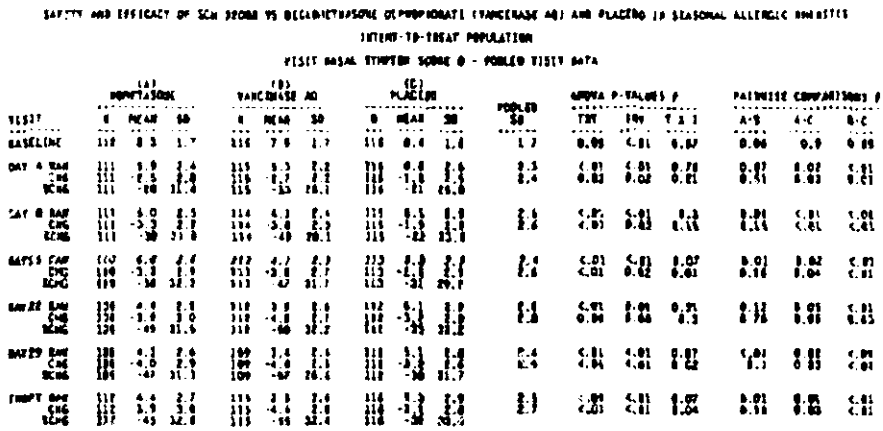
(INTENT-TO-TREAT POPULATION

PM DIARY NON-NASAL SYMPTOM SCORE @ - PROLED DIARY DATA 15-DAY AVERAGE

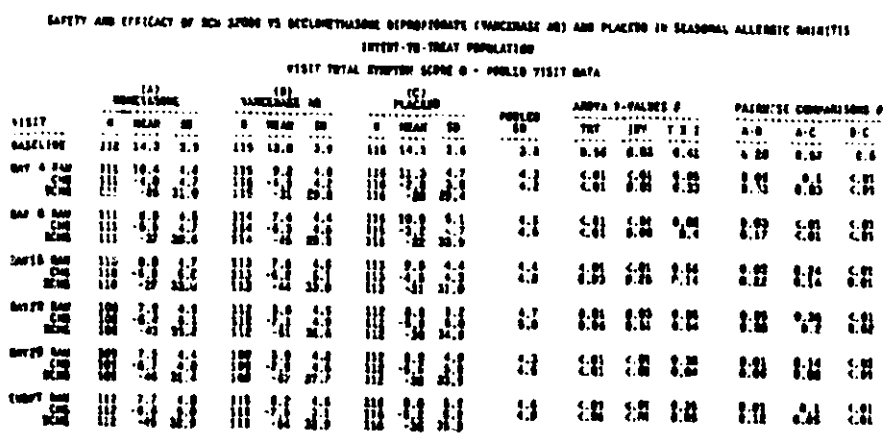
	(A) [illegible]			(B) VANCERASE AQ			(C) PLACEBO			POOLED	ANOVA P VALUES @			PAIRWISE COMPARISONS #		
DAY	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	CEN	T X C	A:B	A:C	B:C
BASELINE	111	0.3	0.6	116	0.3	0.6	114	0.3	0.7	0.6	0.81	0.94	0.22	1.00	0.50	0.66
1-15	[illegible]															
16-30	[illegible]															
ENDPT	[illegible]															

ATTACHMENT 1--continued

(5) Physician's evaluation of total nasal symptoms [172:326]:

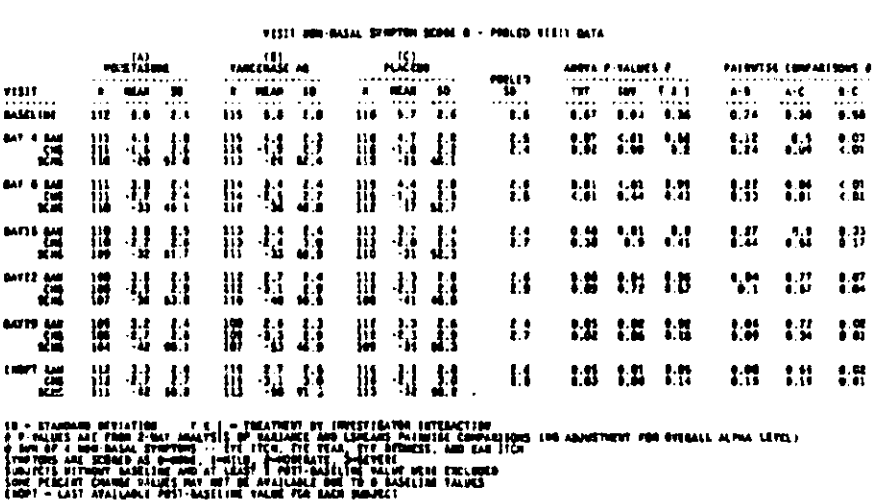


(6) Physician's evaluation of total symptoms [172:327]:



ATTACHMENT 1--continued

(7) Physician's evaluation of total non-nasal symptoms [172:328]:



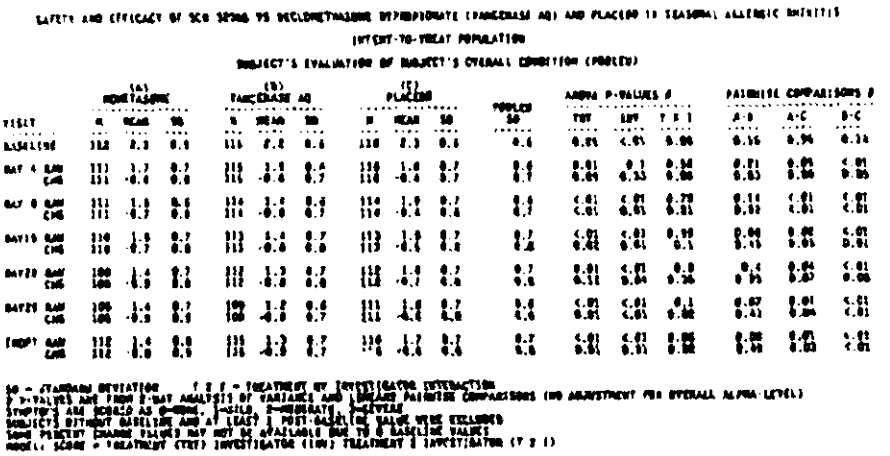
VISIT NON-NASAL SYMPTOM SCORE @ - POOLED VISIT DATA

VISIT	(A) FEXOFENADINE N	(A) FEXOFENADINE MEAN	(A) FEXOFENADINE SD	(B) TAVEGIL AD N	(B) TAVEGIL AD MEAN	(B) TAVEGIL AD SD	(C) PLACEBO N	(C) PLACEBO MEAN	(C) PLACEBO SD	POOLED SD	ANOVA P-VALUES # TRT	ANOVA P-VALUES # INV	ANOVA P-VALUES # T X I	PAIRWISE COMPARISONS # A-B	PAIRWISE COMPARISONS # A-C	PAIRWISE COMPARISONS # B-C
BASELINE	112	8.8	2.1	115	8.8	1.8	116	8.7	2.0	0.6	0.87	0.01	0.36	0.74	0.36	0.50
DAY 4 ABS	111	-1.1	1.8	115	-1.0	1.3	116	-1.1	1.8	0.5	0.87	<.01	0.48	0.11	0.1	0.02
SCHE	110	-1.0	1.8	115	-1.0	1.3	116	-1.0	1.7	0.4	0.91	0.00	0.3	0.24	0.04	<.01
MEAN	110	-10	47.4	113	-10	42.4	115	-11	46.1							
DAY 8 ABS	111	-2.0	2.1	114	-2.1	2.1	113	-2.1	2.0	0.6	0.01	<.01	0.71	0.01	0.04	<.01
SCHE	111	-2.0	2.1	114	-2.1	2.2	113	-2.1	2.0	0.6	0.01	<.01	0.71	0.01	0.04	<.01
MEAN	110	-33	48.1	117	-34	46.8	113	-33	47.7							
DAY15 ABS	110	-3.0	2.3	113	-3.0	2.4	113	-2.8	2.5	0.7	0.30	<.01	0.41	0.07	<.01	0.33
SCHE	110	-3.2	2.3	113	-3.2	2.4	113	-2.8	2.5	0.7	0.30	<.01	0.41	0.07	<.01	0.33
MEAN	109	-32	41.7	111	-33	40.9	110	-31	42.3							
DAY22 ABS	108	-3.1	2.3	111	-3.2	2.4	111	-3.0	2.5	0.6	0.08	0.01	0.05	0.01	0.27	0.07
SCHE	108	-3.1	2.3	111	-3.2	2.4	111	-3.0	2.5	0.6	0.08	0.01	0.05	0.01	0.27	0.07
MEAN	107	-34	43.8	110	-40	40.5	108	-41	40.8							
DAY29 ABS	105	-3.2	2.4	108	-3.3	2.3	111	-3.2	2.6	0.9	0.03	0.00	0.08	0.05	0.22	0.08
SCHE	104	-3.2	2.4	107	-3.3	2.3	109	-3.0	2.6	0.9	0.03	0.00	0.08	0.05	0.22	0.08
MEAN	104	-42	40.3	107	-43	40.9	109	-39	40.3							
LWOT ABS	111	-3.2	2.3	113	-3.3	2.4	113	-3.1	2.6	0.6	0.03	0.01	0.05	0.05	0.18	0.05
SCHE	111	-3.2	2.3	113	-3.3	2.4	113	-3.1	2.6	0.6	0.03	0.01	0.05	0.05	0.18	0.05
MEAN	111	-42	40.3	113	-48	41.5	113	-42	40.8							

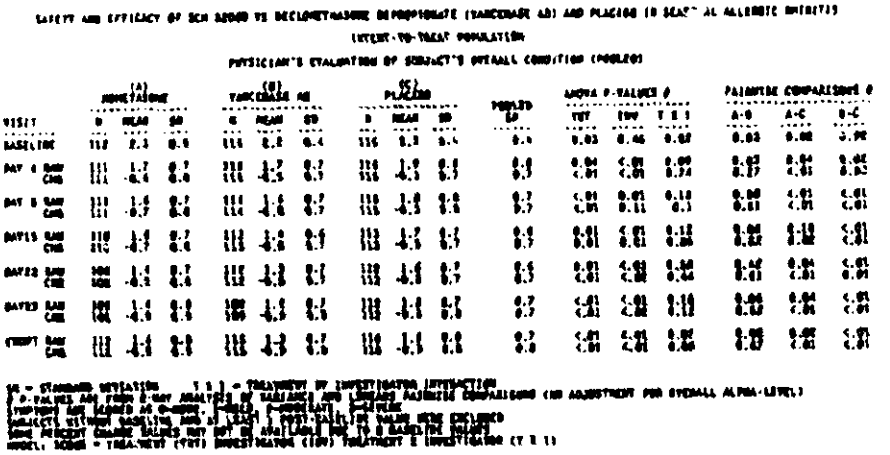
SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LEAST-SQUARES PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA LEVEL)
@ SUM OF 4 NON-NASAL SYMPTOMS : EYE ITCH, EYE TEAR, EYE REDNESS, AND EAR ITCH
(SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
LWOT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

ATTACHMENT 1--continued

(8) Subject's self-evaluation of overall condition [172:338]:



(9) Physician's evaluation of subject's overall condition [172:337]:



ATTACHMENT 1--continued

(10) Subject's self-evaluation of overall response to treatment [172:340]:

SAFETY AND EFFICACY OF SCH 32088 VS BECLOMETHASONE DIPROPIONATE (VANCERASE AQ) AND PLACEBO IN SEASONAL ALLERGIC RHINITIS

INTENT-TO-TREAT POPULATION

SUBJECT'S EVALUATION OF SUBJECT'S OVERALL RESPONSE TO TREATMENT (POOLED)

	(A) SCH 32088			(B) VANCERASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
VISIT	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
DAY 4 AM	111	3.3	1.0	115	3.2	1.0	116	3.0	0.9	0.9	0.01	<.01	0.00	0.4	0.02	<.01
DAY 8 AM	111	3.0	1.0	114	2.9	1.0	115	2.8	1.0	1.0	<.01	<.01	0.37	0.04	<.01	<.01
DAY15 AM	110	3.0	1.1	113	2.8	0.9	113	2.7	1.0	1.0	<.01	<.01	0.31	0.05	0.02	<.01
DAY22 AM	108	2.9	1.1	112	2.7	1.1	112	2.7	1.1	1.0	<.01	<.01	0.54	0.06	0.1	<.01
DAY29 AM	105	2.9	1.1	108	2.6	1.0	111	2.7	1.1	1.0	<.01	<.01	0.37	0.01	0.02	<.01
ENDPT AM	112	3.0	1.2	115	2.7	1.1	116	2.9	1.1	1.1	<.01	<.01	0.33	0.01	0.01	<.01

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LINEARS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
RESPONSE IS SCORED AS: 1=EXCELLENT 2=GOOD 3=FAIR 4=POOR 5=TREATMENT FAILURE
MODEL: SCORE = TREATMENT (TRT) INVESTIGATOR (INV) TREATMENT X INVESTIGATOR (T X I)

(11) Physician's evaluation of subject's overall response to treatment [172:339]:

SAFETY AND EFFICACY OF SCH 32088 VS BECLOMETHASONE DIPROPIONATE (VANCERASE AQ) AND PLACEBO IN SEASONAL ALLERGIC RHINITIS

INTENT-TO-TREAT POPULATION

PHYSICIAN'S EVALUATION OF SUBJECT'S OVERALL RESPONSE TO TREATMENT (POOLED)

	(A) SCH 32088			(B) VANCERASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
VISIT	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
DAY 4 AM	111	3.5	1.1	115	3.2	1.1	116	3.1	1.1	1.0	0.00	<.01	0.16	0.29	0.03	0.00
DAY 8 AM	111	3.0	1.0	114	2.7	1.1	115	2.8	1.1	1.0	<.01	<.01	0.40	0.00	<.01	<.01
DAY15 AM	110	3.0	1.1	113	2.8	1.0	113	2.9	1.0	1.0	<.01	<.01	0.11	0.07	0.02	<.01
DAY22 AM	108	2.9	1.1	112	2.7	1.1	112	2.9	1.2	1.1	0.00	<.01	0.37	0.02	0.04	0.01
DAY29 AM	105	2.9	1.2	108	2.8	1.2	112	2.9	1.2	1.1	<.01	<.01	0.93	0.01	0.04	<.01
ENDPT AM	112	2.9	1.2	115	2.8	1.2	116	3.1	1.3	1.1	<.01	<.01	0.00	0.01	0.00	<.01

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LINEARS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
RESPONSE IS SCORED AS: 1=EXCELLENT 2=GOOD 3=FAIR 4=POOR 5=TREATMENT FAILURE
MODEL: SCORE = TREATMENT (TRT) INVESTIGATOR (INV) TREATMENT X INVESTIGATOR (T X I)

8.1.4.3. SAFETY ANALYSIS

A review of safety data was performed on the safety (intent-to-treat) population which consisted of all randomized subjects who received at least one post-baseline evaluation. For the safety population, 112 subjects were treated with mometasone and 116 subjects each were treated with beclomethasone or placebo.

Safety data consisted of clinical adverse events (further characterized as treatment emergent [171:38], treatment related (severe and non-severe) [171:39], and treatment unrelated [171:39]), laboratory test values, vital signs, and pertinent physical exam findings such as nasal septal perforation or ulceration.

Overall, analysis of the safety data for protocol C93-013 indicates that mometasone was safe and well tolerated by subjects. Adverse events were similar to those observed with beclomethasone and in general, similar to those seen with nasal corticosteroid use. The incidence of adverse events was found to be highest in the placebo treatment group. No significant difference in adverse event rates was found based on age, gender, or race.

Adverse events were reported by 54% of subjects treated with mometasone, compared to 55% of subjects treated with beclomethasone, and in contrast to 67% of subjects treated with placebo [171:68]. The most frequently reported adverse events are summarized in Table IX. of the NDA submission [171:68]. For a complete listing of adverse events, please refer to [171:69-72].

Headache was reported as the most frequent adverse event and was found to be present in 35% of subjects treated with mometasone, 25% of subjects treated with beclomethasone, and 31% of subjects treated with placebo [171:68]. All other adverse events were present in fewer than 10% of study subjects in either of the 3 treatment arms. The second most frequent adverse event was pharyngitis (present in 7% of mometasone subjects, 5% of beclomethasone subjects, and 6% of placebo subjects) [171:68], followed by epistaxis (present in 3% of mometasone subjects, 3% of beclomethasone subjects, and 2% of placebo subjects [171:68]). In general, epistaxis was mild or moderate in severity, intermittent, and of short duration in all treatment groups. In summary, the most frequent adverse events cited were symptoms known to be associated with seasonal allergic rhinitis itself, and not necessarily related to drug use per se.

Reviewer's Note: Importantly, the majority of adverse events were not considered to be 'related to treatment' by the principal investigators. Based on analysis of adverse events as 'possibly', 'probably', or 'related to treatment', the most frequent treatment-related adverse event was headache (reported in 8% of subjects treated with mometasone, 1% of subjects treated with beclomethasone, and 4% of subjects treated with placebo).

One serious[1] adverse event consisting of elevated liver enzymes (SGOT, SGPT) at the end of treatment was reported for one subject treated with beclomethasone who also consumed some alcohol prior to his final study visit (Subject C93-013-10, #23 [171:78, 172:405] which normalized at a re-test 5 weeks later. No other clinically relevant abnormal laboratory test results were reported in this study. Although there were scattered laboratory test values outside the normal ranges for several subjects, as assessed by shift tables, none were remarkable.

No clinically relevant changes in mean values from pretreatment were noted in any of the subjects' vital signs or body weight. Shift tables were similar among all 3 treatment groups. Nasal examinations performed at each visit generally revealed nasal mucosal findings consistent with SAR such as boggy or erythematous mucosa indicative of nasal turbinate swelling. No nasal septal perforations or ulcerations were detected in any of the study subjects. ECGs performed pretreatment and at endpoint failed to reveal any relevant abnormal findings.

Regarding subject discontinuations due to adverse events, a total of 11 subjects (5 treated with mometasone, 2 treated with beclomethasone, and 4 treated with placebo) discontinued treatment because of adverse events. Only 3/11 of these subjects had discontinued treatment 'possibly' due to adverse events incurred by the treatment given (all other cases were unrelated to treatment) and 2 of these 3 subject discontinuations had 'mild' symptoms (subject C93-013-09, #26: nasal burning, pharyngitis, subject C93-013-09, #2: sneezing) [171:78]. Of mometasone treated subjects, the adverse events associated with subject discontinuation consisted of the following: ear infection, viral infection, upper respiratory infection, pharyngitis, nasal burning, and coughing [171:78]. No subject deaths were reported for any of the 3 treatment arms of study C93-013 [171:78].

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[1]Serious is defined as any adverse event which resulted in death, hospitalization, or prolongation of an existing hospitalization, a permanent or significant disability, or was considered life-threatening. Reports of

Table IX. Most Frequent Adverse Events Associated with Mometasone Treatment [171:68]:

Table 21 Incidence of Frequently[a] Reported Treatment Emergent Adverse Events[b] - Safety Population (Study No. 93013)

	Number[c] (%) of Patients		
	SCH 32088 (n=112)	BDP (n=116)	Placebo (n=116)
Any Adverse Event	**60 (54)**	**64 (55)**	**78 (67)**
Body As a Whole - General Disorders			
chest pain	4 (4)	0	2 (2)
fatigue	0	2 (2)	3 (3)
fever	1 (1)	1 (1)	3 (3)
headache	39 (35)	29 (25)	36 (31)
Gastrointestinal System Disorders			
dyspepsia	3 (3)	3 (3)	2 (2)
Hearing and Vestibular Disorders			
earache	3 (3)	3 (3)	2 (2)
Musculoskeletal System Disorders			
musculo-skeletal pain	3 (3)	6 (5)	3 (3)
myalgia	2 (2)	5 (4)	3 (3)
Reproductive Disorders, Female[d]			
dysmenorrhea	3 (6)	2 (4)	5 (7)
Resistance Mechanism Disorders			
infection, viral	5 (4)	3 (3)	8 (7)
Respiratory System Disorders			
coughing	2 (2)	3 (3)	3 (3)
epistaxis	3 (3)	4 (3)	2 (2)
nasal burning	5 (4)	5 (4)	8 (7)
nasal irritation	1 (1)	1 (1)	6 (5)
pharyngitis	8 (7)	6 (5)	7 (6)
rhinitis	1 (1)	2 (2)	4 (3)
rhinitis, aggravated	1 (1)	0	4 (3)
sinusitis	0	5 (4)	1 (1)
sneezing	0	1 (1)	7 (6)
upper respiratory infection	4 (4)	1 (1)	1 (1)
Vision Disorders			
eye pain	3 (3)	2 (2)	1 (1)

a=occurring in ≥ 3% of any treatment group.
b=without regard to relationship.
c= # of subjects reporting adverse events at least once during the study. Some subjects reported > 1 adverse event.
d=% calculated based on total female population.

8.1.5. Reviewer's Conclusion of Study Results:

In this SAR trial 112 subjects received mometasone treatment, 116 subjects received the active comparator beclomethasone, and 116 subjects received placebo treatment.

With the exception of a greater percentage of subjects in the placebo group consisting of female subjects, and a greater percentage of subjects with a 'severe' rating of SAR (subject self-rated 0-3 score) comprising the mometasone treatment group, all 3 treatment arms were otherwise similar in demographic and clinical

characteristics.

Results that Support Approval:

Mometasone administered at a dose of 200 µg qd was statistically better than placebo in decreasing the average change from baseline in the subject self-rated total nasal symptom score (rhinorrhea, nasal congestion, nasal itching, and sneezing) for days 1-15 of treatment--the primary efficacy variable ($p<.01$). Mometasone provided an approximately 25% decrease in the total nasal symptom score as compared to a 16% decrease achieved with placebo treatment [TableV.]. Separation of the subject self-rated total nasal symptom score by week 1 and week 2 of treatment indicates that mometasone was effective in decreasing total nasal symptoms during both weeks, with a clinically significant improvement in symptoms achieved by week 1 of treatment. Of the 4 nasal symptoms, mometasone appeared to exert its greatest effect on decreasing the severity of nasal congestion, closely followed by rhinorrhea (nasal discharge).

Mometasone was likewise statistically better than placebo in decreasing the average change from baseline in the subject self-rated total nasal symptom score for days 16-30 of treatment ($p=0.03$), and the subject self-rated total nasal symptom score at the endpoint visit ($p=0.04$). Physician-rated subject total nasal symptom scores taken during study visits were likewise significantly reduced with mometasone treatment, as compared with placebo [Attachment 1 (5)]. Additional treatment response was gained during the third and fourth weeks of treatment with mometasone, in addition to efficacy achieved by the second week of mometasone treatment.

Finally, both subject and physician overall SAR evaluation and both subject and physician treatment response evaluation [Attachment 1 (8)-(11)] support greater efficacy of mometasone in reducing the symptoms of SAR, as compared with placebo.

Results that did not Support Approval:

Overall, mometasone did not demonstrate a statistically significant or clinically relevant effect in decreasing any of the subject self-rated or physician rated non-nasal symptoms of SAR (eye itching, eye tearing, eye redness, ear or palatal itching), at any of the study intervals (day 1-15, day 16-30, endpoint visit), as compared with placebo. Because of this lack of significant effect on the non-nasal symptoms of SAR, mometasone likewise did not have a statistically significant effect on decreasing the total non-nasal symptom score in treated subjects, as compared with placebo. As the non-nasal symptoms of SAR represent a group of secondary efficacy measurements which clinically are less important symptoms of SAR, lack of significant efficacy of mometasone on these parameters does not change the overall conclusion about efficacy of mometasone in the treatment of SAR. Furthermore, non-nasal symptoms are generally less likely to be affected by medications administered intranasally, therefore a lack of significant response with intranasal corticosteroid administration (also seen with beclomethasone) is not unexpected

Other Results:

Mometasone (200 µg qd) appeared to exert its effect at decreasing the nasal symptoms of SAR throughout the day, with similar subject self-rated total and individual nasal symptom scores achieved during the a.m. and p.m. measurements. Hence, mometasone administered as a 200 µg dose once a day demonstrated a reasonable 24 hour duration of effect in this study

Safety:

Overall, mometasone was safe and well-tolerated administered as a once a day, 200 µg dose. No serious adverse events occurred in subjects treated with mometasone, not were any deaths reported. Similar to placebo, headache was the most common adverse event associated with mometasone use, followed by pharyngitis and then, epistaxis. No nasal septal perforations were reported. This study (because of study duration) did not evaluate posterior subcapsular cataract formation or hypothalamic-pituitary-adrenal (HPA) axis suppression.

Summary:

Based on the results of this seasonal allergic rhinitis (SAR) trial, mometasone demonstrated adequate evidence of efficacy and safety compared with placebo in the treatment of the symptoms of SAR.

8.2. Trial C92-011. Dose Ranging Study of the Safety and Efficacy of Mometasone furoate (Sch 32088) in Seasonal Allergic Rhinitis (SAR)

Principal Investigator: Multi-center (15 investigators).
Participating Centers: 15 U.S. Centers

8.2.1. OBJECTIVE:

1. To determine the dose response relationship among four different dosages of mometasone furoate.
2. To determine the efficacy and safety of a four-week course of mometasone at the four different dosages compared to placebo.

8.2.2. STUDY DESIGN:

This was a Phase II, randomized, multi center, placebo-controlled, parallel group study of 4 different dosages of mometasone: 50 µg, 100 µg, 200 µg, and 800 µg qd, delivered via nasal spray, for the treatment of symptoms of seasonal allergic rhinitis (SAR).

Bioavailability measurements of plasma mometasone furoate levels (HPLC assay methods) were performed on plasma obtained from two study centers (C92-011-04 and C92-011-15), where subject plasma was collected pre-dose (0 hour) and at one and two hours post-dose on Day 28 of the study.

8.2.3. PROTOCOL

8.2.3.1.a. POPULATION:

Significant entry criteria consisted of the following: (1) age between 18-65 years of age, (2) demonstration of IgE-mediated hypersensitivity to an appropriate seasonal allergen via skin testing (prick or intradermal) with wheal size ≥ 3 mm larger than saline control, (3) presence of symptomatic allergic rhinitis rated as moderate in severity (≥ 3 on a 0-6 point scale) [165:13, 93], with a total nasal symptom score ≥ 10, and nasal congestion plus one other nasal symptom each scored at least moderate (i.e. ≥ 3) [165:10, 83]. The symptom severity was scored as summarized in Table (A):

Table (A) Symptom Severity Score [165:13, 93]:

SEVERITY SCORE	SEVERITY DEFINITION
0	None
1	Trivial or doubtful
2	Mild; clearly present, but causing little or no discomfort
3	Moderate; annoying, but not causing marked discomfort
4	Moderately severe; causing marked discomfort
5	Severe; some interference with sleep or activities but not incapacitating.
6	Incapacitating.

Based on the severity scale, subject scores for total nasal symptoms (=rhinorrhea + nasal congestion + sneezing + nasal itching) could range from a value of 0-24.

8.2.3.1.b. PROCEDURE:

After meeting the study criteria at the screening (Visit 1) and baseline visit (Visit 2, Day 0), study enrollable subjects were randomly assigned to 1 of the 5 treatment arms, given diaries in which to record any adverse events and to rate the 8 allergic rhinitis symptoms reflectively over the previous 12 hours: rhinorrhea, nasal congestion, sneezing and nasal itching (nasal symptoms); eye itching/burning, tearing of eyes, eye redness, itching of ears and/or palate (non-nasal symptoms) according to the severity scale listed in Table (A), and given study medication to be taken twice daily (1 spray per nostril given once in the a.m. and once in the p.m.) [165: 75]. Blinding of medications was such that subjects received study medication from 2 different bottles and were instructed to take one spray from each bottle (bottle A and B) in each nostril each morning [165:11, 84-85]. The appearance of these bottles in terms of their likeness to one another was not described in either the study protocol or study report. These bottles contained either 25 µg/spray (study groups A and B), 50 µg/spray (group C), or 200 µg/spray (Group D) of mometasone, used in combination with placebo bottles of 0 µg/spray of mometasone. Subjects were prohibited from all rescue medication use upon study entry.

On follow-up evaluation visits (Visit 3=Day 3, Visit 4=Day 7, Visit 5=Day 14, Visit 6=Day 21, and Visit 7=Day 28), subjects underwent nasal examination, had their diary cards and response to therapy reviewed by the principal investigator and safety evaluations completed Response to therapy was rated on a 1-5 scale [165:13, 86] by both the subject and investigator.

The primary efficacy variable was defined prospectively by the sponsor as the mean change from baseline in the 'physician'-evaluated total nasal symptom

score. While subjects rated their own nasal and non-nasal symptoms, these were not utilized as an efficacy endpoint by the sponsor, except in the DPAS (daily placebo adjusted score) which was not utilized in this review. In this medical officer review, subject rated total nasal symptom scores were analyzed and are discussed in the 'Results' section (8.2.4.). The intent-to-treat population rather than the sponsor's efficacy evaluable population was used for this analysis. Other symptom score results of interest were changes from baseline in: (1) total symptom scores, and (2) the individual symptoms of nasal congestion and rhinorrhea.

8.2.4. RESULTS:

8.2.4.1.a. Efficacy Results

A total of 480 subjects were enrolled into the study with 1 immediate dropout, leaving 479 subjects randomized to receive 1 of the 5 treatments in the double-blind period (the ITT population). Of these 479 subjects, 96 subjects were randomized to receive mometasone 50 µg qd, 95 subjects were randomized to receive mometasone 100 µg qd, 98 subjects were randomized to receive mometasone 200 µg qd, 95 subjects were randomized to receive mometasone 800 µg qd, and 95 subjects were randomized to receive placebo [165:18]. An additional 5 subjects were excluded from the efficacy analyses; thus, 474 subjects comprised the efficacy evaluable population.

The pooled demographic data across all treatment arms for efficacy evaluable subjects showed more males than females (320/154) and more Caucasians than Blacks enrolled (428/46) [165:21]. The mean age for all treatment arms was 37 years, 37-51 % of subjects also had perennial rhinitis, and 76-88 % of subjects did not have a history of asthma [165:21]. Aside from sexual or racial imbalance, the study subjects had otherwise similar characteristics. In summary, the five treatment arms had overall similar demographic characteristics.

Of concern in this study was the lack of consistency of pollen counts (ragweed, other weeds, total weeds) across the 15 study centers with sub-optimal elevation in pollen counts detected for a significant portion of the study interval in 9 of 14 centers (C92-011-01, -02, -05, -07, -08, -09, -12, -13, -15) [167: 1423-1488]. Pollen count results were not included for study center C92-011-06, nor was the rationale for withholding this information provided by the sponsor.

Based on a review of the sponsor-defined primary efficacy variable (mean change in physician evaluated total nasal symptom scores for the ITT population), all 4 doses of mometasone demonstrated a numerically superior response of SAR nasal symptoms to treatment at all study time points, as compared with placebo [166:615]. Given that the baseline physician rated total nasal symptom scores for the 4 mometasone doses were very similar in numerical value to one another (12.24, 13.39, 13.61, and 13.36 for the 50 µg, 100 µg, 200 µg, and 800 µg doses of mometasone, respectively) and so were similar to the placebo score (13.32), the reported mean change in physician rated total nasal symptom scores for

subjects in the active treatment groups represents a true change in total nasal symptoms with mometasone treatment at the 4 doses tested [166:615, Table I.].

All doses of mometasone treatment (50 µg, 100 µg, 200 µg, and 800 µg) demonstrated a consistent and statistically significant decrease in SAR symptoms after Day 7 of treatment ($p<.01$), with most distinction between the effectiveness of the different doses of mometasone demonstrable at Days 3 and 7 of treatment [166:615]. Whereas the doses of 50 and 100 µg showed less consistent effectiveness at these earlier time points in the study in terms of numerical values (although statistical significance was reached at each dose of mometasone studied), the 200 µg dose provided consistent and adequate effectiveness throughout the study. Overall, the 200 µg dose of mometasone demonstrated the most favorable dose-response, with a decrease in physician rated total nasal symptom scores similar, if not superior at Day 3, 7, and 14, to the 800 µg dose of mometasone (i.e. the 800 µg dose offered no additional effectiveness in reducing allergic rhinitis symptoms than the 200 µg dose) [166:615]. Subject rated total nasal symptom scores through subject diary recordings paralleled physician rated total nasal symptom scores, although the scores were lower numerically [166:618]. Since no baseline diary scores were collected per protocol, the data are presented as adjusted mean scores and not change from baseline. The adjusted data utilized baseline scores determined by the investigator [165:29]. Based on these data (Table II.), subject rated total nasal symptom scores for all 4 doses of mometasone were statistically significantly lower than scores for the placebo group [166:618]. The mometasone 200 µg qd group, however, demonstrated lower numerical scores for all study visits (Day 3-Day 28) than the mometasone 50 or 100 µg qd groups. The mometasone 800 µg qd group did not consistently show a greater numerical response in subject rated total nasal symptom scores than the mometasone 200 µg qd group. These data again, support the 200 µg dose of mometasone as being the most appropriate dose for treatment of SAR symptoms. Subject evaluated individual symptom score results (the individual 4 nasal and individual 4 non-nasal SAR symptoms) from the subject diaries were consistent with physician-evaluated results [167: 767-916]. Tables and line listings submitted for this study did not include a.m. vs. p.m. SAR symptom scores for comparison.

Trends for the physician-evaluated change in total symptoms (nasal + non-nasal) [167: 658-659] and individual symptoms of nasal congestion and rhinorrhea were similar to that seen with the total nasal symptom score [167:668-669, 671-672]. Again, the 50 µg and 100 µg doses were less effective than the 200 µg dose at the early time points and the 800 µg dose did not offer any additional benefit over the 200 µg dose.

Review of the non-nasal symptom score for all four mometasone treatment groups [167:676-677] showed a less consistent response to corticosteroid treatment, as expected. The 200 µg mometasone dose demonstrated a statistically significant response up to Day 14 of treatment and the 800 µg dose showed a statistically significant response after Day 14 of treatment. The 50 µg and 100 µg doses did not demonstrate as consistent a response in decreasing non-nasal

symptoms as did the 200 µg and 800 µg doses. Thus, results of this analysis support the 200 µg dose as having the most consistent clinical response, with no added benefit seen with the 800 µg dose.

Results for the male and female subgroups were similar in inference to those of the overall population, while the number of subjects in the non-Caucasian subgroup was too small to draw meaningful conclusions.

8.2.4.1.b. Bioavailability Results:

Analysis of the bioavailability of mometasone furoate [170: 3541-3545, 3605-3610], based on analysis with a limit of quantitation of 50 pg/ml of mometasone, revealed that except for one value of 77.6 pg/ml obtained 1 hour post-dosing of mometasone [170: 3544, 3608], all plasma concentrations of mometasone were below the limit of quantitation [170:3544-3545, 3605-3610]. This data supports the conclusion that mometasone has generally low systemic bioavailability when given at a dose of 50, 100, 200 or 800 µg qd.

Table I.

Dose Ranging Study of the Efficacy of Mometasone vs. Placebo in the Treatment of SAR: Total Nasal Symptoms (Primary Efficacy Variable, Physician Rated Symptoms)--ITT POPULATION [166:615]

TREATMENT	(A) Mometasone 50 µg		(B) Mometasone 100 µg		(C) Mometasone 200 µg		(D) Mometasone 800 µg		(E) Placebo			PAIRWISE COMPARISONS A-E	B-E	C-E	D-E
DAYS	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	Pooled STD	A-E	B-E	C-E	D-E
BASELINE															
RAW	95	13.24	95	13.39	98	13.61	95	13.36	95	13.32	2.51	0.89	0.85	0.43	0.93
DAY 3															
RAW	95	8.88	94	9.29	97	8.36	95	8.38	95	10.37	3.56	<.01	0.06	<.01	<.01
Change	95	-4.36	94	-4.11	97	-5.13	95	-4.98	95	-2.95	3.9	0.01	0.06	<.01	<.01
DAY 7															
RAW	93	8.11	93	7.72	94	7.0	93	7.53	91	9.56	3.76	0.01	<.01	<.01	<.01
Change	93	-5.2	93	-5.69	94	-6.55	93	-5.78	91	-3.79	4.17	0.03	<.01	<.01	<.01
DAY 14															
RAW	89	7.15	91	7.0	94	6.51	91	6.63	88	9.47	3.64	<.01	<.01	<.01	<.01
Change	89	-6.09	91	-6.36	94	-7.01	91	-6.69	83	-3.81	3.79	<.01	<.01	<.01	<.01
DAY 21															
RAW	88	6.53	90	6.48	92	5.9	88	5.61	83	8.81	3.79	<.01	<.01	<.01	<.01
Change	88	-6.68	90	-6.97	92	-7.59	88	-7.7	83	-4.33	4.36	<.01	<.01	<.01	<.01
DAY 28															
RAW	86	5.66	86	6.44	88	5.52	86	5.36	81	8.15	3.52	<.01	<.01	<.01	<.01
Change	86	-7.48	86	-6.98	88	-7.91	86	-7.98	81	-5.04	4.2	<.01	<.01	<.01	<.01
ENDPOINT															
RAW	95	6.25	95	6.93	97	5.87	95	5.95	95	8.86	4.1	<.01	<.01	<.01	<.01
Change	95	-6.99	95	-6.49	97	-7.68	95	-7.44	95	-4.51	4.57	<.01	<.01	<.01	<.01

Change is relative to baseline value (Day 1). STD=Standard deviation.

Total Nasal Symptoms=Sum of Rhinorrhea + Nasal Congestion + Sneezing + Nasal Itching; scored for each individual symptom on a scale of 0-6.

P-values from 2-way ANOVA, α=0.05 (2-tailed). Differences of ~.42 units between treatments detectable at a power of 80% given a sample size of 90 subjects per treatment group

Table II.

Dose Ranging Study of the Efficacy of Mometasone vs. Placebo in the Treatment of SAR: Total Nasal Symptoms (Primary Efficacy Variable, Subject Rated Symptoms)--ITT POPULATION (166:618)

TREATMENT	(A) Mometasone 50 µg		(B) Mometasone 100 µg		(C) Mometasone 200 µg		(D) Mometasone 800 µg		(E) Placebo			PAIRWISE COMPARISONS A-E	B-E	C-E	D-E
DAYS	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	Pooled STD	A-E	B-E	C-E	D-E
DAY 3															
RAW	92	9.41	92	9.93	96	8.98	92	9.31	92	11.05	3.27	<.01	0.02	<.01	<.01
Adjusted RAW	92	9.45	92	9.84	96	8.89	92	9.34	92	11	3.02	<.01	0.01	<.01	<.01
DAY 7															
RAW	93	8.27	92	8.17	93	7.17	92	7.74	92	10.11	3.62	<.01	<.01	<.01	<.01
Adjusted RAW	93	8.3	92	8.15	93	7.12	92	7.69	92	10.16	3.54	<.01	<.01	<.01	<.01
DAY 14															
RAW	88	7.42	89	7.3	92	6.37	89	6.46	87	9.24	3.53	<.01	<.01	<.01	<.01
Adjusted RAW	88	7.51	89	7.33	92	6.3	89	6.52	87	9.31	3.51	<.01	<.01	<.01	<.01
DAY 21															
RAW	88	6.97	88	6.54	93	6.08	87	5.88	83	8.74	3.67	<.01	<.01	<.01	<.01
Adjusted RAW	88	7.05	88	6.47	93	6.06	87	5.93	83	8.87	3.66	<.01	<.01	<.01	<.01
DAY 28															
RAW	85	6.06	86	5.95	89	5.56	85	5.55	80	8.37	3.69	<.01	<.01	<.01	<.01
Adjusted RAW	85	6.14	86	5.91	89	5.58	85	5.57	80	8.5	3.68	<.01	<.01	<.01	<.01
ENDPOINT															
RAW	94	6.53	94	6.43	96	5.74	95	5.89	95	8.86	3.97	<.01	<.01	<.01	<.01
Adjusted RAW	94	6.54	94	6.42	96	5.74	95	5.91	95	8.93	3.97	<.01	<.01	<.01	<.01

STD=Standard deviation, P-values are from 2-way ANOVA, α=0.05 (2-tailed)
Total Nasal Symptoms=Sum of Rhinorrhea + Nasal Congestion + Sneezing + Nasal Itching; scored for each individual symptom on a scale of 0-6.

8.2.4.3. ADVERSE EVENTS

Four hundred and seventy-nine (479) subjects received the double-blind treatment, including a total of 384 subjects in the various mometasone dose groups [165:18]. One subject was excluded from the total count because he never received drug. A total of 53 subjects discontinued the study prior to scheduled completion (10 treated with mometasone 50 µg, 8 treated with mometasone 100 µg, 10 treated with mometasone 200 µg, 9 treated with mometasone 800 µg, and 16 treated with placebo). Twenty three subjects discontinued because of treatment failure and 18 subjects terminated the study because of adverse events. The remainder of subjects terminated the study due to noncompliance, lack of study visit follow-ups, or inability to meet entry criteria.

Adverse events were reported in 65% of mometasone 50 µg qd subjects, 62% of mometasone 100 µg qd subjects, 60% of mometasone 200 µg qd subjects, 68% of mometasone 800 µg qd subjects, and 60% of placebo group subjects [165:48, 169:2152]. The most frequently reported adverse event was headache, which was reported for 31-41% of subjects in the various mometasone treatment groups, compared to 33% of subjects in the placebo treatment group [165:50, 169:2152]. Pharyngitis was the next most frequently reported adverse event; it was reported for 8-18% in the mometasone treatment groups, compared to 9% in the placebo treatment group [165:49, 169:2157] There was no significant dose-response relationship for the incidence of either headache or pharyngitis. The third most frequent adverse event was epistaxis, which ranged in frequency from 3-11% in the mometasone treatment subjects, compared with 2% in the placebo group [165:49, 169:2157]. A dose response relationship was noted for epistaxis with mometasone treatment, with highest incidence of epistaxis associated with the 800 µg treatment group [165:49]. One subject (C92-011-13, #028), a 33 year old female in the 800 µg qd mometasone group developed a nasal ulcer of moderate severity at Visit 5, deemed possibly related to the study medication. No nasal septal perforations were reported. Viral infections were rather low in frequency (1-4%) in this study for all 4 mometasone doses [169:2156]. No cases of cases of herpes simplex, nasal or oral candidiasis were reported in any of the 4 mometasone treatment groups or the placebo group. Most other adverse events were mild to moderate in severity, and generally unrelated to treatment.

Of subjects who discontinued treatment (18 total), the most common reason for discontinuation were upper respiratory tract and/or ear infections, seen in 5 subjects [165:60]; and headache, coughing, epistaxis, or rhinitis. Serious adverse events (otitis externa- 1 report in the mometasone 50 µg qd group, confusion/dizziness/blurred vision-1 report in the mometasone 100 µg qd group, bacterial infection-1 report in the mometasone 200 µg qd group, and elevated LFTs-1 report in the mometasone 800 µg qd group) were reported for 4 subjects [165:60]. In all of these subjects adverse events were unexpected; three were considered by the investigator to be possibly or probably related to study medication and one was considered unrelated [165:59]. No subject deaths were reported.

Laboratory test results overall showed no clinically meaningful changes from pretreatment in any of the treatment groups, however clinically relevant changes in SGOT and/or SGPT were observed in 4 subjects [165:62-63]. In 2 of the 4 subjects, liver function tests normalized to baseline normal levels post-discontinuation of the study drug and were felt by the respective investigators to be 'possibly' related to treatment (subject C92-011-05, #028-mometasone 100 µg qd dose and subject C92-011-05, #015-mometasone 800 µg qd dose) [165:60-62]. Subject C92-011-05, #28, a 26 year old male, had an SGOT of 42 U/L and an SGPT of 27 U/L at screening which increased to an SGOT of 159 U/L and an SGPT of 79 U/L by Visit 7 of the study [165:62]. This subject completed the study and follow-up LFTS 2 weeks after completion revealed a normalized SGOT of 29 U/L and an SGPT of 44 U/L. A hepatitis panel was negative and by temporal association the subject was felt to have LFT elevation 'possibly' related to treatment with mometasone 100 µg qd. The second subject (C92-011-05, #15), a 31 year old male had no history of liver disease and normal liver enzymes at screening (SGOT=14 U/L and SGPT=17 U/L) which increased to an SGOT of 169 U/L and an SGPT=123 U/L by Visit 5 [165:61]. A hepatitis panel was negative. This subject's LFTS decreased toward normal 11 days after discontinuation of mometasone 800 µg qd but only completely normalized 5 weeks post-treatment. Of the other 2 subjects with abnormal LFTs (subjects C92-011-14, #15 and C92-011-10, 20#), one subject had an elevated SGOT and SGPT at screening (this subject was subsequently discontinued from the study because he did not meet enrollment criteria) and the other subject had a minimally elevated SGPT at screening (SGPT=37 U/L) and continued the study with mild increase in SGPT (up to SGPT=152 U/L) but no clinical sequelae [165:61].

No clinically relevant changes in mean values from pretreatment were observed in vital signs, ECGs, physical examinations or nasal examination results for the pooled population or any of the demographic sub-groups.

8.2.5. CONCLUSIONS:

The finding of significant seasonal allergic rhinitis symptom decrease with mometasone treatment, as compared with placebo confirms the results of other studies, although the subject pollen exposure was less significant than demonstrated in other studies. Overall, the objectives listed above were variously met:

1. All mometasone doses (50, 100, 200, and 800 µg) showed better efficacy than placebo at reducing the symptoms of SAR, in particular the nasal symptoms associated with SAR.
2. Although the 50 µg and 100 µg doses of mometasone showed statistically significant efficacy compared with placebo in decreasing total nasal symptoms of SAR, a numerically smaller decrease in symptom scores was seen, particularly during the first week of treatment, compared to the 200 µg dose of mometasone.
3. The most appropriate therapeutic dose of mometasone is the 200 µg dose.

4. The 800 µg dose of mometasone did not offer additional effectiveness in reducing symptoms than the 200 µg dose and may have been associated with a higher frequency of adverse events (headache, pharyngitis, and epistaxis).
5. Overall, all doses of mometasone were well tolerated.

8.3. Trial C93-184. Onset of Action of Mometasone furoate (SCH 32088) nasal spray (50μg/spray) vs. Placebo in Seasonal Allergic Rhinitis (SAR).

Principal Investigator: Robert B. Berkowitz, M.D.

Participating Centers: 5 U.S. Centers

8.3.1. OBJECTIVE:

1. To determine the onset of relief of symptoms of SAR following treatment with mometasone nasal spray, 200 μg administered once daily.
2. To further characterize clinical efficacy and safety of 200 μg of mometasone used in the treatment of symptoms of SAR.

8.3.2. DESIGN:

This was a phase III, randomized, double-blinded, multicenter, placebo-controlled, parallel group 2 arm study of mometasone 200 μg qd vs. placebo, administered via nasal spray (2 sprays/nostril each morning) for 14 days.

8.3.3. PROTOCOL:

8.3.3.1.a. POPULATION:

Significant entry criteria consisted of the following: (1) age ≥ 12 years of age, (2) demonstration of IgE-mediated hypersensitivity to an appropriate seasonal allergen by positive skin testing via prick or intradermal testing. With prick testing, wheal size must have been ≥ 3 mm larger than diluent control, and with intradermal testing, wheal size must have been ≥ 10 mm larger than diluent control (diluent not specified in protocol), (3) presence of symptomatic allergic rhinitis at both screening and baseline with the symptom of nasal congestion rated by the subject as at least moderate in severity (≥ 2, using a 0-3 symptom severity scale where: 0=none, 1=mild, 2=moderate and 3=severe symptoms) [175:23], the subject-evaluated combined total nasal symptom score rated to be at least 7, and the physician-evaluated overall subject condition rated to be ≥ 2 (moderate) in severity (0-3 symptom scale: 0=none, 1=mild, 2=moderate, and 3=severe symptoms) [175: 19-20]. Based on the severity scale, subject scores for total nasal symptoms (= rhinorrhea + nasal congestion + sneezing + nasal itching) could range from a value of 0-12.

8.3.3.1.b. PROCEDURE:

After meeting the study entry criteria at the screening (Visit 1=Day 0) and baseline visit (Visit 2, Day 1), study enrollable subjects were randomly assigned to 1 of 2 treatment groups: (1) mometasone 200 μg qd or (2) placebo, administered as 2 sprays/nostril every morning [175:19-21, 177:668-680]. At the time of the baseline visit, subjects also completed the SF-36 Health Survey-a quality of life

assessment survey which was prospectively used to assess global functioning and subject well-being [177:678, 692-693]. After randomization, subjects received 2 different types of diary cards: (1) the 'usual' type of diary card which was used to record symptoms reflectively over the previous 12 hours along with recording of any concomitant medications taken, and (2) a 'special' diary card which was used for the first 72 hours of treatment to record (twice daily) the subject's response to treatment for each 12 hour time period (using a slight, moderate, marked, etc. 'response to therapy' rating system (score 1-5)) and the date and time (i.e. hour of the day) that the subject first experienced noticeable symptom relief ('noticeable' per the subject's own subjective recording). Subjects who never noticed noticeable relief during the 72 hour period were to indicate this on the 'special' diary card [175:25]. For both diaries, symptoms were recorded in the a.m. prior to dosing and in the p.m. approximately 12 hours after dosing. The scoring system used to assess response to therapy was based on the subject's status relative to the baseline visit and employed a 1-5 scale (1=complete relief, 2=marked relief, 3=moderate relief, 4=slight relief, and 5=no relief) [175:24, 177:684].

Subjects were prohibited from rescue medication use upon study entry with the exception of medium-mild potency (≤ class 4) topical corticosteroids for dermatological use, topical antimicrobials, inhaled or oral beta-agonists as needed for asthma, or theophylline; if on a stable dose before and during the study [175:18, 177:673].

On follow-up evaluation visits (Visit 3=Day 4, Visit 4=Day 8, Visit 5=Day 15), rating of seasonal allergic rhinitis symptoms as per subject diary cards was reviewed by the principal investigator along with symptoms observed at the time of the visit and the overall condition of rhinitis was assessed. Response to therapy was evaluated by the subject and investigator based on the 1-5 rating scale [175:20-21, 177:681-683]. At the final visit, prior to any procedures being performed, a followup SF-36 'Quality of Life' Health Survey was completed by each subject. Safety evaluations were performed at each follow-up study visit [175:25-26, 177:686-689].

The initial primary efficacy variable (which was later changed by the sponsor prior to unblinding of subjects [175:34]) was defined as the time to onset of relief, i.e. the first 12-hour interval during which the subject experienced at least 'moderate' relief of nasal symptoms (defined as a score ≥ 3 by evaluation of therapeutic response (1-5 score) rating system discussed above) [175:24, 34-35, 177:691]. Using a log-rank test to compare the two treatments, a sample size of 90 subjects per treatment group, and an α level=0.05; a difference in onset time between the two treatments arms could prospectively be detected with 90% power, if the rates of onset of symptom relief at 12 hours were 61% for the placebo group and 77% for the mometasone group [177:692].

Reviewer's Note: Subjects without at least moderate relief by the end of the third day of treatment were 'censored' at 72 hours per the protocol [175:35, 177:691], i.e. these subjects were not used in the assessment of the primary

efficacy variable or survival analysis [177:691]. A major study flaw of the latter method of 'censoring' which may enrich the study for subjects likely to respond to the study drug within the prospectively stated period of time, is the inability to study subjects who take longer to respond or account for those who do not respond altogether.

A change to the planned primary efficacy analysis was made by the sponsor after the protocol was finalized, but before the data were unblinded which changed the primary efficacy variable from the first 12-hour interval in which the subject first experienced at least 'moderate' relief (therapeutic response score ≥ 3) to the actual clock time (in hours) to the first experience of moderate symptom relief [175:34, 177:691]. This latter primary efficacy variable represents the endpoint utilized in this review of study C93-184.

For the purposes of review of trial C93-184 this amended 'time to onset of relief' parameter was treated as the new primary efficacy variable. Total nasal symptom scores for days 1-8 post-initiation of treatment with mometasone vs. placebo for the efficacy evaluable population (ITT data not available in the NDA submission) were also utilized in the assessment of onset of action of mometasone. As these data were not 'censored', an assessment of all subjects' (responders and non-responders) response to treatment could be determined.

Secondary efficacy variables consisted of: (1) the raw symptom scores and changes from baseline for the total nasal symptoms, total symptoms (nasal + non-nasal), and individual symptom scores (averaged over the 14 day study period), (2) subject and physician evaluated composite and individual symptom scores, and (3) subject and physician evaluation of overall disease condition and therapeutic response, along with the proportion of subjects experiencing at least 'moderate' relief of SAR symptoms during the first 3 days of treatment with study drug [175:35, 177:69]. Baseline was defined as the mean of the respective symptom scores for the baseline visit and 3 prior consecutive study days [175:32].

The study utilized a self-administered Short Form-36 (SF 36) Health Survey to assess the subject's health-related quality of life (HQL) by eight parameters: (1) physical functioning, (2) physical role, (3) bodily pain, (4) general health, (5) vitality, (6) social functioning, (7) emotional role, and (8) mental health [175:38]. The HQL analysis for all eight HQL parameters included: assessment of treatment group balance at baseline, within treatment comparisons for changes from baseline to day 15/endpoint; and between treatment comparisons for day 15/endpoint and for changes from baseline to day 15/endpoint. The eight parameters were rated on a scale from 0 (low) to 100 (high) [175:70]. This analysis was performed on 189 subjects within the efficacy population (n=197) using data collected at baseline (Day 0) and endpoint (Day 15 or last valid visit). Inherent problems with this quality of life analysis which were addressed by Dr. Robert Meyer (FDA Pulmonary Division, HFD-570) in a fax dated 09/09/96, were the following: (1) lack of specifi ation a priori of the assumptions used in conducting the assessment, (2) lack of a prospective definition of what measures

constitute 'clinically relevant subject improvement' as well as statistical considerations for multiple comparisons--instead relying on a 5-point difference between active and placebo groups to support a clinically relevant improvement [177:692], (3) the generalized nature of the parameters measured, (most of which cannot be considered particularly relevant to seasonal allergic rhinitis, per se), and (4) lack of instrument validation of SF-36 for use in allergic rhinitis. Given the inherent weaknesses of the instrument chosen, the HQL was not evaluated as supporting evidence for the efficacy of mometasone.

8.3.4. RESULTS:

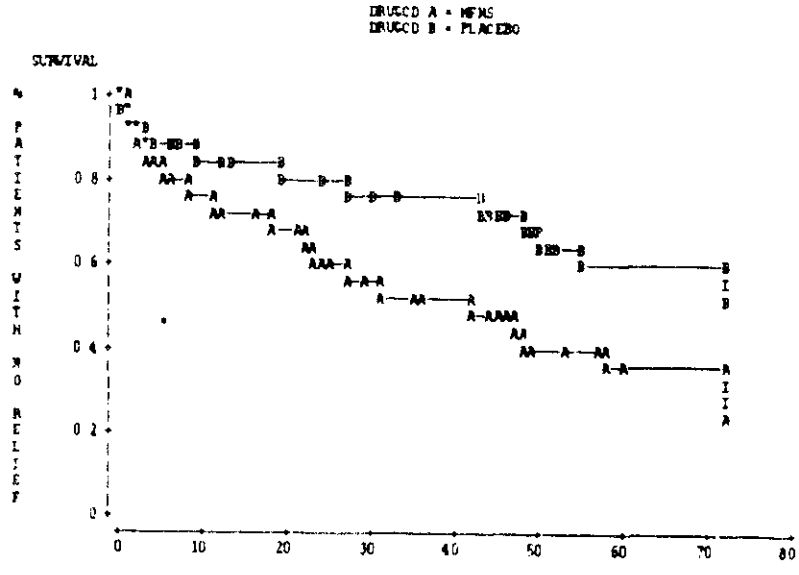
A total of 201 subjects were enrolled into the study, with 1 immediate dropout post-randomization, leaving 200 subjects in the safety (intent-to-treat) population. Three additional subject exclusions resulted in 197 subjects analyzed in the efficacy population. For the ITT population, 101 subjects comprised the mometasone group and 99 subjects comprised the placebo group [175:39].

The pooled demographic data for the intent-to-treat (ITT) population across the 5 treatment centers participating in the study showed comparable clinical and demographic characteristics for both treatment groups, with the minor exception of a slightly longer mean and median duration of SAR in the placebo group (mometasone group mean=16 years, median=15 years vs. placebo group mean=19 years, median=17 years; p=0.05) [175:41] and a slightly greater number of female subjects enrolled (111 females, 89 males) [175: 41]. As seen in previous mometasone trials in this NDA submission, the majority of enrolled subjects were Caucasian (87-88%) [175: 41].

Again, of concern in this study, and as noted in the other allergic rhinitis studies in this NDA submission was the lack of consistency of pollen counts across treatment centers. All five of the five participating treatment centers demonstrated inadequate elevation of pollen counts for at least 1 of the 2 weeks of the study duration [178:1939-1943].

Analysis of the primary efficacy variable of time to onset of 'noticeable' relief in mometasone vs. placebo treated subjects via the log-rank test showed that the mean and median (50%) onset time to relief of symptoms was 39.2 and 35.9 hours, respectively for the mometasone treatment group, compared to 53.4 and > 72 hours, respectively for the placebo treatment group (ITT population) [175:239]. For the mometasone group, a total of 23 subjects (23%) were censored (i.e. excluded) from data analysis due to lack of response by 72 hours, and for placebo subjects, a total of 49 (50%) of subjects were censored from data analysis due to lack of response by 72 hours. These results were similar for both the ITT and efficacy evaluable subjects [175:119, 239]. A Kaplan-Meier plot of onset of action of mometasone vs. placebo (ITT population) is represented in Figure 1 below.

Figure 1: Primary Efficacy Variable (ITT Population): Duration (in hours) to onset of 'noticeable' relief of SAR symptoms of mometasone vs. placebo treated subjects [175:239-240].



NOTE: DURATION (NUMBER OF HOURS) = (RELIEF DAY - START DAY) * 24 + (RELIEF TIME - START TIME)

MEDIAN (50%) ONSET TIME TO RELIEF: MFNS = 35.9 HRS
PLACEBO > 72 HRS
LOGRANK TEST APPROX. P-VALUE = 0.0001

TESTS OF EQUALITY OVER STRATA

TEST	CHI-SQUARE	DF	APPROX P-VALUE
LOGRANK	17.000644	1	0.0001
WILCOXON	15.235279	1	0.0001
-2*LN(L)	16.972378	1	0.0001

The special diary data (which also assessed only the non-censored subjects) were analyzed via Fisher's exact test comparing the proportion of efficacy evaluable subjects in each treatment group experiencing at least moderate relief of symptoms during the first 3 days of treatment. The proportion of mometasone treated subjects experiencing at least moderate relief was significantly greater ($p<0.01$) than that of the placebo group at all time points except the a.m. of Day 2 [175:47, 122]. A numerically greater percentage of subjects in both the mometasone and placebo groups demonstrated at least 'moderate' relief of SAR symptoms during the p.m. recording, especially prior to Day 3 of treatment (no statistical comparison of the a.m. vs. p.m. recordings performed in this study). Nonetheless, these small numerical differences between a.m. and p.m. recordings are unlikely to be clinically relevant after Day 3 of treatment based on the data provided which is summarized in Table I.

Table I: Percentage and Proportion of Subjects Experiencing at Least Moderate Relief (Efficacy Population), [175:, 47, 122]

	Mometasone (200 µg)	Placebo	*P-Value
Day 1			
–a.m.	-	-	-
–p.m.	28.4% (27/95)	12.6% (12/95)	0.01
Day 2			
–a.m.	29.2% (28/96)	18.8% (18/96)	0.13
–p.m.	41.2% (40/96)	19.8% (19/96)	<0.01
Day 3			
–a.m.	52.1% (50/96)	27.1% (26/96)	<0.01
–p.m.	59.1% (49/83)	32.5% (26/80)	<0.01
Day 4			
–a.m.	59.5% (47/79)	27.3% (21/77)	<0.01
–p.m.	-	-	-

* Fisher's exact test.

Based on the data in Table I., at Day 3 of treatment with mometasone, slightly greater than 50% of subjects were shown to demonstrate at least 'moderate' relief of SAR symptoms.

Review of total nasal symptoms for the efficacy population (ITT not available in NDA 20-762) for Days 1-8 of treatment indicates that although a greater numerical decrease in the total nasal symptom score in mometasone treated subjects was demonstrable by 12 hours post-initiation of treatment, as compared

with placebo [175: 126], a statistically significant mean change in the total nasal symptom score for mometasone treated subjects, as compared with placebo was only seen in the a.m. of Day 2--the 24 hour interval post-initiation of treatment. More importantly, this decrease in total nasal symptoms was only consistently statistically significantly lower for the mometasone treated subjects (as compared with placebo) by the a.m. of Day 3, or approximately 2.5 days after initiation of treatment [175:125]. After this time point, subsequent measurements of the mean change in total nasal symptoms for mometasone treated subjects demonstrated a statistically significant decrease, as compared with placebo. A summary of these data are summarized for days 1-4 of the treatment period in Table II. below.

Regarding the mean change in subject evaluated total nasal symptom scores for the day 1-15 interval (ITT population), mometasone treated subjects experienced a -3.3 unit change (or 39% decrease) in total nasal symptoms from baseline, compared to a -1.8 unit change (or 20% decrease) in total nasal symptoms from baseline in placebo treated subjects (p=0.03 for mometasone vs. placebo) [175:241]. These findings in subject rated total nasal symptom scores for mometasone vs. placebo treated subjects are similar to those reported in the other SAR studies in this NDA submission and support the efficacy of mometasone in SAR treatment.

Intent-to-treat (ITT) analyses for the secondary efficacy variables support greater efficacy of the mometasone treatment group compared with placebo for all parameters listed with the exception of the total non-nasal symptom score and the individual non-nasal symptoms (of eye tearing, eye redness, eye itching and ear/palate itching) [175:241-288].

Table II: Total Nasal Symptom Scores and Mean Change in Total Nasal Symptom Scores for Mometasone vs. Placebo Treatment, Days 1-4 Post-Initiation of Treatment (Efficacy Population) [175-125-126]

		Mometasone (200 µg)	Placebo	*P-Value
Baseline				
–a.m.		8.5	8.5	0.82
–p.m.		8.2	8.6	0.21
Day 1				
–a.m.	RAW	-	-	-
	CHANGE	-	-	-
–p.m.	RAW	6.9	7.9	0.01
	CHANGE	-1.4	-0.7	0.09
Day 2				
[2]–a.m.	RAW	7.1	8.0	0.01
	CHANGE	-1.3	-0.6	0.01
–p.m.	RAW	6.4	7.1	0.06
	CHANGE	-1.8	-1.5	0.35
Day 3				
–a.m.	RAW	6.3	7.4	< 0.01
	CHANGE	-2.2	-1.1	< 0.01
–p.m.	RAW	5.6	6.8	0.01
	CHANGE	-2.6	-1.8	0.05
Day 4				
–a.m.	RAW	5.8	7.1	< 0.01
	CHANGE	-2.7	-1.4	< 0.01
–p.m.	RAW	5.2	6.8	0.01
	CHANGE	-3.0	-1.8	0.05

*P-values are from 2-way ANOVA and LSMeans pairwise comparisons between mometasone treatment and placebo.

[1]DAY 1, p.m. score represents the 12 hour dosing interval.

[2]DAY 2, a.m. score represents the 24 hour dosing interval.

8.3.4.3. ADVERSE EVENTS:

Two hundred and one subjects (201) were randomized into the study and 200 subjects received the double-blind treatment (101 mometasone group subjects and 99 placebo subjects) [175:39]. One subject received the first dose of study medication and then was an immediate dropout with no follow-up efficacy or safety data. A total of 7 subjects (2 treated with mometasone and 5 treated with placebo) discontinued the study prior to scheduled completion. Two subjects discontinued the study because of treatment failure, 2 subjects (in the placebo group) discontinued because of adverse events, 2 subjects discontinued because of noncompliance, and 1 subject discontinued because of inability to meet study eligibility requirements [175:67]. Of the 2 placebo group subjects discontinuing treatment because of adverse events (subject C93-184-03 #36 and #40), the cause of discontinuation of treatment was the flu and upper respiratory infection, respectively, which were felt by the individual investigators not to be related to study drug [175: 67].

In general, the frequency of subjects reporting adverse events in study C93-184 was somewhat lower than that seen in the other mometasone trials. The most frequently reported adverse event was headache, reported by 14% of subjects in the mometasone treatment group and 15% of subjects in the placebo group [175:63]. Pharyngitis was reported in 4% of subjects in both treatment groups [175:64]. Nasal burning was the third most commonly reported adverse event (3% of subjects in both treatment groups) [175:64]. Of note in this study epistaxis was reported in < 1% of subjects treated with mometasone, compared with 3% of placebo subjects [175:64]. Epistaxis was subjectively rated as mild or moderate and of short duration in both treatment groups [175: 61-63]. No nasal septal perforations or ulcerations were reported in this study. Viral infections were noted in 3% of subjects in the mometasone treatment group compared with 1% in the placebo control group [175:63]. One case of moniliasis was found in the mometasone group, with none in the placebo control group [175:63]. No serious adverse events or subject deaths were reported in this study.

Overall, no clinically relevant changes in the median laboratory values or laboratory shifts from pre-treatment to post-treatment were detected in either treatment group. Reversible increases in SGOT and/or SGPT were observed in 3 subjects, 1 from the mometasone treatment group and 2 from the placebo group [175:68-69]. Of these 3 subjects, one subject (C93-184-02, #27) had possible gallstone disease with exaccerbation requiring an ER evaluation and another (subject C93-184-02, #35) had ingested alcohol during treatment with study drug [175:69]. The third subject (C93-184-01, #28) developed an increasing SGPT at Visit 2 (SGPT=52), with increase in SGOT to 76 U/L and increase in SGPT to 144 U/L by Visit 5 [175:69]. Two days post-treatment, the subject's LFTs continued to increase (to an SGOT=101 U/L and An SGPT=376 U/L) but eventually returned toward normal (SGOT=45 U/L, SGPT=96 U/L) 3 weeks later. The etiology of this subject's LFT elevations was not determined.

No significant change in mean values from pre-treatment to post-treatment

were observed for vital signs or body weight in any treatment group. Nasal examinations performed at scheduled visits were consistent with allergic rhinitis. Post-treatment ECGs were not performed in this study but screening ECGs were unremarkable. No significant differences based on subject age, race, or gender were noted in this study, although some sub-groups (non-Caucasian and age 12-17 years of age) were too small in number to make meaningful conclusions.

In summary, a review of the safety data obtained during this study indicates that mometasone was well tolerated.

8.3.5. CONCLUSIONS:

1 Mometasone intranasal spray treatment at 200 µg qd demonstrated a statistically significant decrease in the total nasal symptoms for all subjects receiving mometasone treatment by 24 hours of treatment, as compared with placebo however this decrease was only consistently significantly lower than placebo approximately 2-3 days post-initiation of treatment with mometasone (the a.m. of Day 3).

2. Enrichment for mometasone treatment responders by censoring those subjects who did not demonstrate a subjectively 'noticeable' response to mometasone treatment by 72 hours of treatment indicates that of these 'responder' subjects, a statistically significant number of mometasone treated subjects had a consistently 'moderate' response to treatment by 36 hours of treatment.

3. Mometasone treatment at 200 µg qd was well tolerated and did not reveal any new safety concerns, as compared with placebo treatment.

8.4. Trial 192-200. Efficacy and Safety of Mometasone Furoate (SCH 32088) Aqueous Nasal Spray in Seasonal Allergic Rhinitis (SAR).

Principal Investigator: 19 international investigators.

Participating Centers: 19 international centers.

8.4.1. OBJECTIVE:

1. To determine the efficacy of a 4 week course of therapy with mometasone at 2 dose levels: 100 and 200 µg qd in the treatment of SAR, compared with placebo.
2. To determine the efficacy of mometasone 200 µg qd compared with beclomethasone dipropionate (Beconase) 200 µg bid (=400 µg qd) in the treatment of SAR.
3. To further characterize the safety profile of mometasone nasal spray.

8.4.2. STUDY DESIGN

This was a phase III, randomized, multi center (international), double-blind, double-dummy, placebo-controlled, parallel group design of two doses of mometasone nasal spray administered via nasal spray for 4 weeks in subjects with SAR.

8.4.3. PROTOCOL

8.4.3.1.a. POPULATION:

The significant entry criteria were: (1) age ≥ 18 years, (2) Positive skin (prick or intradermal) test results to the appropriate seasonal allergen (grass and/or trees), confirmed by a wheal size ≥ 3 mm larger than saline control [201:824-825], and (3) rating of overall disease as at least moderate in severity (≥ 2 on a 4 point scale) with a combined nasal symptom score of ≥ [illegible] nasal congestion plus one other nasal symptom each scored as at least moderate in severity (≥ 2) at both the screening and baseline [illegible] 0-3 symptom scale [199:15, 17, 32; 201:834-835].

The pooled demographic data across all treatment arms for the intent-to-treat (ITT) population (n=497) showed no statistically significant differences among the treatment groups for any demographic parameter [199:51]. Again the majority of subjects in each treatment arm consisted of male and Caucasian subjects. Most subjects did not have a concomitant history of either asthma or perennial rhinitis.

In terms of symptom severity at baseline which used the scoring system in section 8.4.3.1.b. below to rate the overall SAR condition for efficacy evaluable subjects, n=477, (ITT population data not available in sponsor's submission for this variable) [199:49-50, 290], most subjects (78%; 373/477) had SAR of "moderate" severity as determined by the principal investigator. The proportion of

subjects with 'severe' disease was slightly higher (28%; 34/122) in the mometasone 100 µg group, as compared with the other 3 treatment groups (17-23% range) [199:50, 290]. Subject self-rated scores (also the overall SAR condition endpoint for efficacy evaluable subjects) paralleled physician rated scores, albeit with a slightly greater percentage of subjects in the mometasone 100 µg qd group reporting 'severe' overall condition of SAR [199:322]. Baseline total nasal symptom scores for the ITT population revealed little numerical difference between the 4 treatment groups which was not found to be statistically significant [199:272]. In summary, using these 3 variables, SAR symptom scores at baseline (pre-treatment) were not significantly different for the 4 treatment groups.

8.4.3.1.b. PROCEDURE:

An outline of the study procedure and evaluations at each study visit is summarized in Table 1 of the NDA submission for study I92-200 [199:16].

After meeting the study criteria at the screening (Visit 1) and baseline visit (Visit 2, Day 0), study enrollable subjects were randomly assigned during the baseline visit in a 1:1:1:1 ratio to one of the four treatment arms, given rescue medication cards and given diaries in which to record any adverse events and to rate on a twice daily basis the 8 allergic rhinitis symptoms: rhinorrhea, nasal congestion, sneezing, and nasal itching (nasal symptoms); eye itching/burning, tearing of eyes, eye redness, itching of ears and/or palate (non-nasal symptoms) according to the 0-3 symptom severity scale described in previous mometasone SAR studies [199:32]. Subjects were prohibited from all rescue mediation use upon study entry (baseline visit) with the exception of loratadine, given as a maximum dose of 10 mg po qd [199:22; 201:829]. Of note, the following medications were permitted for subject use during the study: mild or low potency topical corticosteroids for dermatological use, topical antimicrobials, inhaled or oral beta-agonists as needed for asthma, or theophylline, if on a stable dose before and during the study, and saline eye drops as needed, for the relief of eye symptoms [199:27; 201:814, 819].

Because the mometasone and [illegible] appearance, a double-dummy study design was used and each bottle type had a matching placebo. Therefore, while subjects received bottles of different appearance, they did not know whether bottles contained active substance or placebo. Each subject received 16 sprays per day (2 sprays per nostril from each of two a.m. bottles each morning and two sprays in each nostril from each of two p.m. bottles each evening) [199:18-19, 23-24].

During evaluation visits 3, 4, 5, 6, and 7 (Day 4, Day 8, Day 15, Day 22, and Day 29, respectively), the overall condition of allergic rhinitis was assessed by the investigator and subject [201:812, 829-833]. This evaluation was to include the entire time period since the previous visit, up to and including the current observation. Response to therapy was evaluated by the investigator and the subject, based upon the subject's status over the prior 72 hours as well as the investigator's observations at the study visit, using the scale defined in Section

3.4.2. of the NDA submission [199:33].

The primary efficacy variable was the mean change in the a.m. and p.m. combined physician evaluated total nasal symptom score (rhinorrhea + nasal congestion + sneezing + nasal itching) over the first week of treatment (from baseline to Day 8 (Visit 4)) [199:31; 20:840-841]. For physician evaluated assessments, 'baseline' in this protocol was defined as the data obtained on Visit 2 (baseline). Secondary efficacy variables of interest consisted of nasal congestion and the total symptom score [199:31].

Again noted in this study, as in the sponsor's other SAR studies, was the lack of consistency of total pollen count elevation in the majority of the study centers (noted in 12 of the 16 centers that submitted pollen count data: I92-200-01, -03, -04, -05, -10, -13, -15, -16, -17, -20, -22, -23) [205:3890-3095]. This was similarly noted in the analysis of tree, grass and weed pollen for the respective centers [205:3906-4022].

8.4.4. RESULTS

A total of 501 subjects with seasonal allergic rhinitis were enrolled into the study, with 4 immediate dropouts, resulting in 497 subjects randomized to receive 1 of the 4 treatments in the double-blind period.

In physician evaluated total nasal symptom scores for the ITT population (the primary efficacy variable), at most time points, both mometasone treatment groups (100 µg and 200 µg) were significantly more effective than placebo ($p \leq 0.01$). For the mean change in the physician evaluated total nasal symptom score from baseline to Day 8 in the pooled ITT population, the mean decrease in total nasal symptoms from baseline for subjects receiving mometasone 100 µg was -4.3 units (52% decrease) in total nasal symptom scores), compared with a -4.7 unit change in total nasal symptom scores (58% decrease) for subjects receiving mometasone 200 µg, a -4.7 unit change (59% decrease) in total nasal symptom scores in subjects receiving beclomethasone, and a -2.4 unit change (35% decrease) in total nasal symptom scores in the placebo group [199:272]. These results were similar to those in the [illegible] [199:244] and in general throughout the study, the two populations gave similar results for the same parameters tested, when so done. The mometasone 200 µg treatment group showed a numerically greater decrease in symptom scores than the mometasone 100 µg treatment group during the first week of treatment. No statistically significant difference was shown between either doses (100 or 200 µg qd) of mometasone and the active comparator, beclomethasone, with the exception of the Day 15 and Day 22 timepoints for the mometasone 200 µg qd dose vs. beclomethasone comparison [199:272]. The clinical significance of this finding is unclear given that no statistical significance was demonstrated between mometasone 100 µg qd and beclomethasone treatment at all timepoints [199:272].

Efficacy results for the primary efficacy variable in the ITT population are summarized in Table 1.

Table 1.
Efficacy of Mometasone (100 µg and 200 µg qd) vs. Beconase (400 µg qd) vs. Placebo in the Treatment of SAR: Primary Efficacy Variable: Total Nasal Symptom Score (Intent-to-Treat (ITT) POPULATION) [199:272]

	(A) Mometasone (100 µg)			(B) Mometasone (200 µg)			(C) Beconase (400 µg)			(D) Placebo			PAIRWISE COMPARISONS					
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	A-B	A-C	A-D	B-C	B-D	C-D
BASELINE	126	8.1	1.6	125	8.0	1.7	125	7.9	1.6	121	8.1	1.7	0.6	0.21	0.46	0.46	0.82	0.63
DAY 4 RAW	124	5.0	2.4	124	4.5	2.7	124	4.1	2.3	119	5.6	2.8	0.15	<.01	0.06	0.1	<.01	<.01
CHG	124	-3.2	2.7	124	-3.6	2.8	124	-3.8	2.8	119	-2.4	2.8	0.36	0.04	0.02	0.26	<.01	<.01
%CHG	124	-37	29.9	124	-44	33.2	124	-47	31.6	119	-29	35.7						
DAY 8 RAW	123	3.8	2.5	123	3.3	2.2	122	3.2	2.3	113	5.3	3.0	0.08	0.03	<.01	0.7	<.01	<.01
CHG	123	-4.3	2.7	123	-4.7	2.4	122	-4.7	2.6	113	-2.7	2.7	0.15	0.14	<.01	0.97	<.01	<.01
%CHG	123	-52	30.4	123	-58	33.6	122	-59	29.7	113	-35	35.4						

SD= Standard Deviation CHG=Change
# P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)
Reference: [199:272]

Similar results were noted in the physician's evaluation of subject therapeutic response [199:74] and the subject's overall evaluation of the overall condition of SAR [199:71-72] in efficacy evaluable subjects (ITT population data not available)--the mometasone 100 µg treatment group was not statistically significantly different from the mometasone 200 µg treatment group at Day 4, however the mometasone 200 µg treatment group was numerically superior. Additionally, the mometasone 200 µg treatment group showed greater efficacy than beclomethasone at Days 15 and 22 (p=0.05 and p=0.04, respectively) [199:272]. Similar results for the ITT population were shown in the analysis of physician evaluated total symptom scores (nasal + non-nasal) [201:1013] and the nasal congestion score [201:1016].

Review of the total nasal symptom scores from the subject diaries for the efficacy evaluable population (ITT data not available) showed that by Day 4 of therapy, the a.m. diary data for the two mometasone treatment groups and the beclomethasone treatment group demonstrated significant efficacy as compared with placebo, thus supporting maintenance of activity during once daily dosing of mometasone and twice daily beclomethasone treatment [199:64, 276, 278].

Analysis of a.m. vs. p.m. subject diary total nasal symptom scores for the 2 mometasone treatment groups indicates that prior to day 5 of treatment a numerical difference of 0.4-0.5 between the a.m. and p.m. total nasal symptom scores (with higher symptom scores in the a.m.) was detectable [199:276, 278]. Only after day 5 of mometasone treatment were minimal numerical differences noted in subject rated total nasal symptom scores between the a.m. and p.m. reflective recording. Statistical comparisons were not performed on the a.m. vs. p.m. scores. Beclomethasone treatment demonstrated a similar pattern of total nasal symptom difference for the a.m. vs. p.m. total nasal symptom scores, however these approached identity (0.1-0.2 difference in scores) on the Day 3 recording, suggesting a somewhat faster [illegible] activity in beclomethasone treated subjects [199:27[illegible]].

While no formal statistical analysis of rescue medication use were performed by the sponsor, overall [illegible]% of subjects in the ITT population used rescue medication at least once. The rates of rescue medication used in the ITT population were 40%, 34%, 35%, and 54%, respectively for the mometasone 100 µg group, mometasone 200 µg group, the beclomethasone group and the placebo group [200:401]. Rates of rescue medication use in the efficacy evaluable population were very similar to those for the ITT population [200:400].

In summary, the lower rate of rescue medication used in the mometasone 200 µg qd group vs. the mometasone 100 µg qd group suggests that mometasone 200 µg qd was more effective in controlling SAR symptoms than mometasone 100 µg qd.

8.4.4.3. ADVERSE EVENTS

For the safety population, 126 subjects received 100 µg of Mometasone, 125 subjects received 200 µg of Mometasone, 125 subjects received

beclomethasone, and 121 subjects received placebo. The incidence of adverse events was greatest in the beclomethasone-treated subjects (49% or 61/125 subjects) [199:79]. The two mometasone treatment groups and the placebo treatment group had similar incidences of adverse events. Adverse events were reported by 44% (56/126) of subjects treated with 100 µg of mometasone, 46% (57/125) of subjects treated with 200 µg of mometasone, and 45% (55/121) of subjects in the placebo group [199:79].

The most frequently reported adverse event was headache; reported in 13% (16/126) of subjects treated with 100 µg of mometasone, 17% (21/125) of subjects treated with 200 µg of mometasone, 17% (21/125) of subjects treated with beclomethasone, and 13% (16/121) of subjects in the placebo group. The second most frequently reported adverse event in this study were gastrointestinal system disorders (dyspepsia, nausea, etc.). These were reported more frequently in the mometasone 100 µg group (12% or 15/126 subjects) and the mometasone 200 µg group (9% or 11/125 subjects), as compared with the beclomethasone (6% or 7/125 subjects) or placebo treatment group (5% or 6/121 subjects). Pharyngitis was the third most commonly reported adverse event; reported in 4% (5/126) of subjects treated with 100 µg of mometasone, 6% (7/125) of subjects treated with 200 µg of mometasone, 6% (8/125) of subjects treated with beclomethasone, and 4% (5/121) of placebo subjects. Epistaxis was reported by 3% (4/126) subjects treated with 100 µg of mometasone, 8% (10/125) of subjects treated with 200 µg of mometasone, 7% (9/125) of subjects treated with beclomethasone, and 3% (4/121) of placebo-treated subjects. And finally, nasal burning was reported by 7% (9/126) of subjects treated with 100 µg mometasone, 3% (4/125) of subjects treated with 200 µg of mometasone, 4% (5/125) of subjects treated with beclomethasone, and 5% (6/121) of placebo-treated subjects [199:79-82].

Infections overall were infrequent in all treatment groups with the highest percentage of viral infections reported in the placebo group (4%) [199:81]. Otitis media was reported in 2% of subjects in the mometasone 100 µg group and in none of the other three treatment groups [199:81]. Sinusitis was reported in 2% subjects in the beclomethasone 100 µg group, 2% of subjects in the mometasone 200 µg treatment group, no subjects in the beclomethasone treatment group and 1% of subjects in the placebo group [200:408]. Urinary tract infection was reported in 2% of subjects in the beclomethasone treatment group and in none of the other three treatment groups [199:82]. No cases of nasal septal perforation were reported.

Of subjects who discontinued treatment (67 total), a greater proportion of placebo-treated subjects discontinued treatment (11% of total subjects) due to treatment failure as compared with the three active treatments [199:52]. A total of 15 subjects discontinued treatment due to adverse events (4 treated with mometasone 100 µg, 5 treated with mometasone 200 µg , 6 treated with placebo, and none treated with beclomethasone) [199:92-93]. Most of the reasons for discontinuation were unrelated to mometasone treatment [199:93] but one adverse event 'possibly' related to mometasone treatment (the 200 µg qd group) in 2

subjects was headache [199:93]. Only one serious adverse event was reported in the placebo group (elective surgery for varicose veins) and was not related to treatment [199:79]. There were no clinically relevant changes in laboratory tests, vital signs, or ECGs in subjects treated with either dose of mometasone [199:79]. No subject deaths were reported.

8.4.5. CONCLUSIONS:

1. Mometasone 100 µg and 200 µg, administered once daily as a nasal spray, was more effective than placebo in decreasing the nasal symptoms of allergic rhinitis. Mometasone 200 µg qd provided a greater numerical decrease in the total nasal symptom scores than mometasone 100 µg qd during the first 3 weeks of treatment.
2. Mometasone 100 µg qd and 200 µg qd are comparable in effectiveness to beclomethasone 200 µg bid (=400 µg qd total dose).
3. Subjects in the mometasone 100 µg qd and 200 µg qd treatment groups tended to use rescue medication less frequently than the placebo group.
4. Mometasone treatment (at both 100 µg qd and 200 µg qd) appeared to demonstrate consistent efficacy for the 24 hour duration for the majority of study subjects after 5 days of treatment.
5. Mometasone 100 µg and 200 µg qd were well tolerated.

8.5. Trial 194-001. Efficacy and Safety of Mometasone furoate aqueous nasal spray vs. placebo and vs. fluticasone propionate (Flonase) in seasonal allergic rhinitis (SAR) patients

Principal Investigator: Michel A. Drouin, M.D.

Participating Centers: 8 Canadian centers.

8.5.1. OBJECTIVE:

1. To evaluate the efficacy of a 2 week course of mometasone aqueous nasal spray 200 µg qd vs. placebo and vs. fluticasone 200 µg qd (the active comparator).
2. To evaluate the safety of mometasone aqueous nasal spray 200 µg qd.

8.5.2. STUDY DESIGN:

This was a Phase III, randomized, multi center, parallel-group, double-blind, double-dummy, active- (fluticasone) and placebo controlled trial of mometasone 200 µg qd, administered via nasal spray for 14 days (2 weeks), to subjects with seasonal allergic rhinitis (SAR).

8.5.3. PROTOCOL

8.5.3.1.a. POPULATION

Significant entry criteria consisted of the following: (1) age ≥ 12 years of age, (2) presence of IgE-mediated hypersensitivity to the appropriate fall aeroallergen, as demonstrated by a positive skin test via prick (≥ 3 mm in diameter larger than diluent control) or intradermal skin test (≥ 7 mm in diameter larger than diluent control; diluent not specified in the protocol) [215:605], and (3) history of at least moderate [illegible] on screening and baseline visits, as determined by nasal congestion and one other nasal symptom score rated at least moderate in severity (≥ 2 on a 0-3 scale), a combined nasal symptom score of ≥ 6, and a rating of the overall condition of rhinitis, as assessed by the principal investigator, as at least moderate in severity [213:20, 215:613, 615].

The treatment groups in this study were comparable with regard to demographic and disease characteristics [213:41] with the minor exception of a greater mean subject weight of 70.2 kgs noted in the age 12-17 fluticasone 200 µg treatment arm, as compared with a respective mean subject weight of 60.1 kgs and 62.1 kgs. for the age 12-17 subset of the mometasone and placebo group [214:561]. A slightly greater number of males than females were enrolled in all three treatment arms. The majority of subjects were Caucasian. Greater than 50% (56-61%) of subjects did not have a history of perennial allergic rhinitis [213:41]. Comparable percentages of subjects in the fluticasone and placebo groups

(29% and 23%, respectively) rated their SAR symptoms as being 'severe', compared with the mometasone treatment group (18%) [213:44].

8.5.3.1.b. PROCEDURE:

After meeting the study criteria at the screening (Visit 1=Day 0) and baseline visit (Visit 2=Day 1), study enrollable subjects were randomly assigned to one of three treatment groups: (1) mometasone 200 µg qd, or (2) fluticasone 200 µg qd, or (3) placebo. The treatment was administered as 2 sprays/nostril from each of 2 bottles (double-dummy design) once daily in the morning [213:14, 215:604]. At the time of the baseline visit, subjects also completed the SF-36 Health Survey-a quality of life assessment survey which was prospectively used to assess global functioning and subject well-being [213:38, 215:659-664]. This survey was also used in the SAR trial C93-184. Because the SF-36 Survey is not a validated instrument for seasonal allergic rhinitis and analyses were performed post-hoc by the sponsor, the SF-36 survey was not included in the efficacy review of this trial.

After study randomization, subjects received two different types of diary cards: (1) one in which clinical symptoms were recorded twice daily at the same time of the day (each a.m. and p.m. prior to administration of study medication) and (2) a rescue medication diary card in which the amount and time of rescue medication use was recorded, in addition to the severity of the symptoms just prior to taking the dose [213: 21, 215:614, 617]. No rescue medications were allowed after study screening with the exception of loratadine (the designated 'rescue medication'). A maximum dose of loratadine 10 mg po qd was allowed per subject [213:21, 215:608-609, 617]. Other medications permitted during the study consisted of: saline eye drops, mild potency topical corticosteroids, systemic antibiotics, if on a stable dose 1 month prior to study entry, inhaled or oral beta-agonists for asthma; or theophylline, if on a stable dose before and during the study [213:19, 215:609].

On follow-up evaluation visits (Visit 3=Day 4, Visit 4=Day 8, Visit 5=Day 15), diary cards were reviewed for SAR symptoms [213:617-619, 634]. Based on symptoms observed by the principal investigator at the time of the visit and review of the subject's diary, the subject's overall condition of SAR was assessed. Evaluation included the entire time period since the previous visit, up to and including the current observation. The subject's overall condition was rated as in all other SAR studies in this submission on a 0-3 scale [213:23-24, 215:620-621]. The subject's response to therapy was evaluated by the principal investigator and subject, based on the subject's clinical status over time since baseline using a 1-5 scale (ranging from complete relief to [illegible] [213:24, 215:621]. At the final visit, subjects underwent a nasal examination and completed a follow-up SF-36 'Quality of Life' Health Survey. Safety evaluations were performed at each follow-up study visit [213:22, 24-27, 215:624-626, 634].

The primary efficacy variable was defined as the mean change from baseline in the subject's total nasal symptom score (composite score of: rhinorrhea

+ nasal congestion + sneezing + nasal itching) over the 15 day study period using diary data (a.m. and p.m. scores averaged) for the intent-to-treat population (ITT) [213:35-36, 215:629]. The comparison of mometasone vs. placebo was defined as the primary comparison of interest. 'Baseline' was defined as the mean score (a.m., p.m., or combined a.m. and p.m.) on the day of the baseline visit and scores from the 3 prior consecutive days [213:32].

In this study the intent-to-treat population and the efficacy evaluable population were almost the same [213:39, 215:844]. None of the subjects were excluded from the efficacy evaluable population and only a few visits and the corresponding diary data were invalidated [215:844]. Nonetheless, ITT analysis was performed only for: (1) the primary efficacy variable and (2) the physician evaluation of total nasal symptoms [215:844].

For subjects who took rescue medication between study visits, the last set of symptom scores recorded in the rescue medication diary prior to using rescue medication were considered by the sponsor as the appropriate evaluation of symptoms for the next 24 hour period and thus replaced the corresponding scores in the regular diary for the appropriate 24-hour period in all analyses and summaries of symptom scores [213:30].

Secondary efficacy variables consisted of the following: (1) the raw score for the primary efficacy variable, (2) raw scores and changes from baseline for all other subject-evaluated composite and individual diary symptom scores, (3) physician evaluated composite and individual symptom scores, (4) subject and physician evaluations of overall disease condition, and (5) subject and physician evaluation of the subject's therapeutic response [213:36, 215:630].

8.5.4. RESULTS:

A total of [illegible] subjects with SAR were enrolled into the study, with 2 immediate dropouts, leaving 311 subjects in the ITT population; 104 subjects each received mometasone or fluticasone treatment and 103 subjects received placebo.

Analysis of the primary [illegible] ITT [illegible] change in the subject's total [illegible] Days 1-15) showed that both mometasone and fluticasone effective than placebo in decreasing total nasal symptoms of SAR ($p < 0.01$) [215:855]. In mometasone treated subjects, the total nasal symptom score for the day 1-15 interval decreased by 2.8 units (-36% change), compared with a 1.0 unit decrease (11% change) in placebo treated subjects [215:855]. In comparing the response of the primary efficacy variable for the two active treatments, fluticasone was significantly more effective than mometasone ($p=0.03$) [215:855]. The mean decrease in total nasal symptom scores$_{\text{DAYS 1-15}}$ for the mometasone treatment group was [illegible] symptom scores) for the fluticasone treatment group, and an 11% decrease for the placebo group [215:855]. Separate analyses of the [illegible] scores from subject diaries in the efficacy evaluable population confirmed findings

noted in other SAR studies in this submission; namely, that mometasone demonstrated clinical efficacy when administered once daily [213:155, 165, 175].

Analysis of the secondary efficacy variable of the physician evaluation of subject total nasal symptom scores for the ITT population showed that both active treatments (mometasone and fluticasone) were more effective in reducing total nasal symptoms than placebo ($p < 0.01$) at all study visits (Day 4, 8, 15, and [illegible]). The fluticasone treatment group also demonstrated a greater mean change in total nasal symptoms as compared with the mometasone treatment group ($p \leq 0.03$) for all study visits except Day 4 ($p=0.28$) [215:856]. These results are consistent with those observed in the primary efficacy variable analysis and the secondary efficacy variables of subject and physician evaluation of total symptom scores [213:50-52, 190, 195, 227].

Results for the secondary efficacy variables of individual nasal symptoms for the efficacy evaluable population are summarized in Table 14. of the NDA submission [213:53]. In contrast to the other SAR studies in this submission, in trial I94-001, the greatest mean percent change for both active treatment groups was noted for the nasal symptoms of sneezing and nasal itching (48-59% decrease for the symptom of sneezing in the mometasone group and a 29-54% decrease for symptom of nasal itching in the mometasone group) [213:203-205, 206-208, 223, 224, 226, 231], rather than rhinorrhea and nasal congestion [213:53, 197-199, 200-202, 221, 222, 229, 230]. For all four nasal symptoms, both active treatments demonstrated greater efficacy which was statistically significant compared with placebo; with the fluticasone treatment group showing a greater numerical decrease in each individual nasal symptom, as compared with the mometasone treatment group.

For the total non-nasal symptoms, somewhat discordant results were seen in subject vs. physician rated symptoms. A statistically significant decrease was noted in the mean change in the a.m. and p.m. combined total and individual non-nasal symptoms noted for the Days 1-15 of the subject pooled diary data ($p \leq 0.01$) [213:192, 209, 212, 218]. whereas statistical significance was not [illegible] mometasone and placebo group in the physician evaluated [illegible] data [213:193, 226, 232-235].

And finally, the secondary efficacy variables of subject and physician evaluation of the overall condition of SAR and the subject and physician evaluation of subjects' therapeutic response to treatment supported greater efficacy of the mometasone and fluticasone treatment groups [213:53-61, 237, 262].

An evaluation of rescue medication use in all three treatment groups indicates that more subjects in the placebo group used rescue medication (60/103 subjects or 58%) than the mometasone (49/104 subjects or 47%) or fluticasone treatment group (44/104 subjects or 42%) [217:2185-2186]. Furthermore, of these subjects, those in the placebo group tended to use rescue medication more frequently than in either of the two active treatment groups [217:2185].

And finally, in terms of the ragweed pollen counts recorded at the study centers for this trial, overall, reasonable elevations in the pollen count were

observed in 7 of 8 centers, with only one center (I94-001-03) demonstrating a period of insignificant pollen elevation during the first week of the study [217:2164].

8.5.4.3. ADVERSE EVENTS:

The safety analysis was based on 311 subjects in the ITT population: 101 subjects were treated with mometasone or fluticasone and 103 subjects were treated with placebo. Adverse events were reported in 46% of subjects in the mometasone treatment group, 38% of subjects in the fluticasone treatment group, and 40% of subjects in the placebo group [213:62]. Most adverse events were mild to moderate in severity. Of subjects discontinuing treatment due to adverse events (4 total), none were in the mometasone treatment group [213:71].

Similar to the findings in other mometasone studies of the SAR population, the most frequent adverse event in all three treatment arms was headache; reported in 13% of subjects in both the mometasone and fluticasone treatment groups and 21% of subjects in the placebo group [213:62, 64]. Coughing was reported by 7% of subjects in the mometasone treatment group, 6% of subjects treated with fluticasone, and 14% of subjects treated with placebo. Pharyngitis was reported in 7% of subjects in the mometasone treatment group, 3% of subjects in the fluticasone treatment group and 4% of subjects in the placebo treatment group [213:64]. Epistaxis was less prevalent in this study as compared with the other SAR studies in this NDA submission; with 2% of subjects in the mometasone and fluticasone treatment groups and 1% of subjects in the placebo group reporting epistaxis [213:66]. There were no reports of nasal septal perforation in any of the three treatment groups, however nasal ulcers were reported in 1 subject (subject I94-001-04, #003) in the mometasone 200 µg treatment group on visit 4 of the study [217:2102] and 2 subjects (subject I94-001-04, #016 and #038) in the fluticasone 200 µg treatment group, on visits 5 and 4, respectively [217:2105, 2110]. No deaths were reported in any of the three treatment groups.

In terms of infection, 2% of subjects in the mometasone and placebo treatment groups reported viral infections, whereas no subjects in the fluticasone treatment group reported viral infection [213:66].

No clinically relevant changes in vital signs, physical exam, ECG laboratory tests from pretreatment were noted in any of the three treatment groups. Flag shift distributions of laboratory values failed to reveal any significant patterns of change. Two subjects were noted to have elevations in SGPT (1 in the fluticasone group and 1 in the placebo group) but these were felt to be related to alcohol consumption [213:72].

8.5.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of seasonal allergic rhinitis, as compared with placebo

2. While not a primary comparison, this study also showed that for most study visits (exception Day 4), fluticasone 200 µg qd was significantly more effective in decreasing the symptoms of SAR than mometasone 200 µg qd.
3. More subjects in the placebo treatment group tended to use rescue medication and [illegible] tended to use [illegible] the mometasone or fluticasone treatment group.

8.6. Trial C94-145. Safety and Efficacy of Mometasone furoate nasal spray with the addition of Loratadine vs. Placebo in the treatment of seasonal allergic rhinitis (SAR).

Principal Investigator: Robert Anolik, M.D.

Participating Centers: 16 U.S. centers.

8.6.1. OBJECTIVE:

1. To evaluate the efficacy of a 2 week course of mometasone aqueous nasal spray 200 µg qd vs. loratadine 10 mg. po qd plus mometasone 200 µg qd, vs. loratadine 10 mg. po qd alone, vs. placebo in the treatment of symptoms of SAR.
2. To evaluate the safety of mometasone aqueous nasal spray in the treatment of symptoms of SAR.
3. To characterize the bioavailability of mometasone 200 µg qd in subjects with SAR.

8.6.2. STUDY DESIGN:

This was a Phase III, randomized, multi center, double-blind, double-dummy, placebo-controlled trial of mometasone treatment in subjects with seasonal allergic rhinitis (SAR). Subjects received study drug for a total duration of 2 weeks.

8.6.3. PROTOCOL:

8.6.3.1.a. POPULATION:

Significant entry criteria consisted of the following: (1) age ≥ 12 years of age [185:13, 188:1023], (2) evidence of IgE-mediated hypersensitivity to local seasonal allergen (grass and/or trees but individual species not specified in protocol) documented in 1 year of [illegible] the prick testing method (≥ 3 mm in diameter than saline diluent control) [185:14, 23, 188:1023], (3) history of at least moderate SAR symptoms on screening and baseline visits, as determined by a nasal congestion score at least moderate in severity (score ≥ 2), a nasal symptom score ≥ 6, a non-nasal symptom score ≥ 5, and a combined total symptom score ≥ 11 [185:12, 188:1023], and (4) lack of clinically significant abnormalities, including disturbances in conduction and rhythm, or QT_c ≥ 420 msec on the subject's screening ECG [185:14, 188:1024].

8.6.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the sponsor in Table 1. of Trial C94-145 in the NDA submission [1885:13, 188:1053]. Between the screening and baseline visits, study subjects entered a study run-in phase lasting 3-7 days during which time they received a diary card on which to record their

clinical symptoms reflectively over the previous 12 hours (rhinorrhea, nasal congestion, sneezing, nasal itching, tearing and redness of eyes and itching of ears/palate) twice daily at approximately the same time of the day (each a.m. and p.m.) and any adverse events incurred during this period [185:24, 188:1022, 1034].

After meeting the study entry criteria at the screening (Visit 1=Day 0) and baseline visit (Visit 2=Day 1), study enrollable subjects were randomly assigned in a 1:1:1:1 ratio to one of the four treatment groups: (A) mometasone 200 µg qd + loratadine 10 mg po qd, (B) mometasone 200 µg qd, (C) loratadine 10 mg po qd, and (D) placebo [188:1022, 1030, 1035, 1047].

At the time of screening, in addition to routine screening laboratory tests, subjects at study sites C94-145-02, -03, -04, and -013 had blood drawn (10 ml) for the purpose of measuring plasma concentrations of mometasone, loratadine, and the metabolite of loratadine [185:24, 188:1033, 1040]. Blood for pharmacokinetic studies was obtained pre-dose and at 5 minutes and 1 hour after dosing.

Mometasone treatment was administered as 2 sprays/nostril in the a.m. for the two treatment groups that received mometasone. A double-dummy design using a matching placebo nasal spray and placebo tablet was employed because of the additional loratadine and loratadine + mometasone treatment arms [185:16]. Subjects were blinded to which bottles or nasal sprays contained active substance or placebo [188:1043].

After study randomization, subjects received a new diary card on which to record their clinical symptoms reflectively twice daily at approximately the same time of the day (each a.m. and p.m. prior to dosing with study medication) and any adverse events incurred during the study [188:1036-1037]. Rescue medication use was not allowed after study screening. Medications allowed during the study consisted of: over-the-counter (OTC) pain medications, mild potency topical corticosteroids, topical antibiotics, systemic antibiotics (if on a stable dose for the duration of the study), and inhaled or oral beta-agonists as needed for the treatment of asthma; or theophylline if [illegible] during the study [185:22, 188:1028-1029].

On follow-up evaluation visits (Visit 3=Day 8, Visit 4=Day 15), diary cards were reviewed for SAR symptoms [185:26]. SAR symptoms were rated on a 0-3 severity scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms) as described previously in the other SAR studies in this NDA submission [185:28, 188:1041]. Based on the principal investigator's evaluation of the subject's symptoms observed at the time of the visit and review of the diary, the subject's overall condition was assessed on a 0-3 scale [185:28, 188:1041-1042] by the investigator; in addition to the subject's own assessment. This evaluation was to include the entire time period since the previous visit, up to and including the current observation. Response to therapy was evaluated by the subject and investigator, based upon the subject's clinical status over time since the baseline visit as well as the subject's and investigator's observations at that visit, using the 1-5 therapeutic response scale [185:29, 188:1042].

At the final study visit (Visit 4), the double-blind treatment was completed and follow-up physical exams, laboratory tests, and ECGs were repeated [188:1039]. At the study sites where bioavailability studies were performed (centers -02, -02, -04, and -013), subjects underwent repeat phlebotomy (10 ml total) prior to dosing with the study medication, and at 5 minutes and 1 hour after dosing of study medication to obtain blood for the purpose of measuring plasma mometasone, loratadine, and loratadine metabolite levels [185:27, 188:1040]. Safety evaluations were completed at each study visit and consisted of a review by the principal investigator of any adverse events experienced by the subject, along with a follow-up physical exam, checking of vital signs, and performance of laboratory tests on each study subject [185:29-33, 188:1032-1035, 1038-1040, 1044-1046].

The primary efficacy variables were defined as the: (1) mean change from baseline in the subject's total nasal symptom score (composite of: rhinorrhea + nasal congestion + sneezing + nasal itching) over the 15 day study period using diary data (a.m. and p.m. scores averaged) for the intent-to-treat (ITT) population and (2) the total symptom score over the 15 day study period using diary data (a.m. and p.m. scores averaged) for the intent-to-treat (ITT) population [185:27, 41, 188:1049]. 'Baseline' was defined as the average of the score on the day of the baseline visit and the 3 consecutive days prior to the day of the baseline visit [185:38]. The primary efficacy variable was analyzed using two-way analysis of variance (ANOVA) [185:41, 188:1049].

Four primary efficacy pairwise comparisons were performed:

(1) [mometasone + loratadine] vs. [loratadine]: for the evaluation of the additional efficacy of mometasone over loratadine alone, and

(2) [mometasone + loratadine] vs. [placebo]: for the confirmation of mometasone's clinical efficacy.

Comparisons (1) and (2) used the total nasal symptom score as the primary efficacy variable.

(3) [mometasone + loratadine] vs. mometasone: for the evaluation of the additional efficacy of loratadine over mometasone alone, and

(4) [loratadine] vs. [placebo]: for the confirmation of loratadine's clinical efficacy.

Comparisons (3) and (4) used the total symptom score as the primary efficacy variable.

Secondary efficacy variables consisted of the following study parameters: (1) the raw score for the primary efficacy variable, (2) raw scores and changes from baseline for all other total and individual [illegible]

composite and individual symptom scores, and (3) subject and physician evaluation of overall disease condition and subject therapeutic response [185:42, 188:1049-1050].

8.6.4 RESULTS

A total of 704 subjects with SAR were enrolled into the study, with 2 immediate dropouts, leaving 702 subjects in the intent-to-treat population. One hundred and sixty nine (169) subjects received mometasone plus loratadine, 176 subjects received mometasone, 181 subjects received loratadine, and 176 subjects received placebo [185:44]. Of the sponsor's efficacy evaluable subjects, 166 subjects received mometasone plus loratadine, 166 subjects received mometasone, 175 subjects received loratadine, and 165 subjects received placebo [185:44].

The treatment groups in this study were comparable with regard to demographic and disease characteristics [185:46]. Again, for all four treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the treatment groups was approximately equal. Approximately two-thirds (2/3) of subjects in each of the treatment groups had a history of perennial allergic rhinitis (PAR). In trial C94-145, smoking prevalence in study subjects was addressed and the majority (≥ 90%) of subjects in each of the treatment groups were stated to be non-smokers. Furthermore, no statistically significant treatment group differences at baseline for the primary efficacy parameters, total symptom, and total nasal symptom scores [185:47] were detected. The four treatment groups had comparable severity of SAR at baseline, with approximately two-thirds of subjects in each treatment group having 'moderate' SAR symptoms [185:68].

An evaluation of the pollen count records for the 18 participating centers in the [illegible] for the most part, was consistent with findings in many of the other SAR studies of this NDA submission. [illegible] of the 18 centers (centers C94-145-01, -02, -03, -05, -07, -08, -10, -011, -012, -013, -014, -016, -017, -019, and -020) reported pollen counts [illegible] elevated [illegible] to baseline for at least part of the study duration [193:3682-3688]. The respective tree, grass, weed, and total pollen counts for each center support this conclusion [193:3682-3727].

Analysis of the primary efficacy variable for the ITT population (mean change in the subject's total nasal symptom score (a.m. and p.m. combined) for Days 1-15) showed that the combination of mometasone + loratadine was more effective in reducing the nasal symptoms of SAR as compared with loratadine alone (-3.0 vs. -1.9 points or a 35% decrease vs. a 22% decrease, $p<0.01$) [186:404] and mometasone 200 µg qd was more effective than placebo in reducing the nasal symptoms of SAR (-2.7 vs. -1.3 points or a 32% decrease vs. a 13% decrease, $p<0.01$) [186:404). As noted in the subject pooled visit data, these treatment group differences were already evident by Day 8 of the study [186:407].

For the primary efficacy variable of the total symptom score for the ITT

population (a.m. and p.m. combined, Days 1-15), the combination of mometasone plus loratadine vs. mometasone alone did not show statistical difference between the two groups with regard to efficacy (-5.4 vs. -4.7 points or a 34% change vs. a 30% change, p=0.21) but loratadine did show a statistical significance in decreasing total SAR symptoms compared with placebo (-3.8 vs. -2.6 points or a 23% decrease vs. a 13% decrease, p=0.01) [186:409]. In summary, based on the two primary efficacy variables analyzed in this study, all three active treatment groups showed significantly greater efficacy than the placebo. While not statistically significantly different, the mean decrease in the total nasal symptom scores and total symptom scores from subject diaries were slightly numerically greater for the combination treatment group than for the mometasone treatment group. This difference suggests a small additive effect of loratadine to the mometasone treatment.

No significant differences between a.m. vs. p.m. SAR symptoms of the treatment groups was detected in this study for any of the efficacy variables (primary and secondary), supporting the findings of previous SAR studies in this NDA submission and confirming efficacy of mometasone as a once a day medication for the treatment of SAR symptoms [186:410-411]. Subset analysis by age, sex, and race did not reveal any significant differences from the overall subject population [185:50]. Findings for the primary efficacy variables are summarized in Table I. below.

Table I. Primary Efficacy Variable Analysis for the Intent-to-Treat (ITT) Population for the 4 Treatment Arms of Trial C94-14. [186:404, 407, 409]

PRIMARY EFFICACY VARIABLE			
	Treatment A:	Treatment C:	[1]P-Value
CHG (and % CHG) in Total Nasal Sx Score$_{DAY\ 1\text{-}15}$	-3.0, (-35)	-1.9, (-22)	<0.01
	Treatment B: Mometasone	Treatment D: Placebo	
CHG (and % CHG) in Total Nasal Sx Score$_{DAY\ 1\text{-}15}$	-2.7, (-32)	-1.3, (-15)	<0.01
	Treatment A: Mometasone + Loratadine	Treatment B: Mometasone	
CHG (and % CHG) in Total Sx Score$_{DAY\ 1\text{-}15}$	-5.4, (-34)	-4.7, (-30)	0.21
	Treatment C: Loratadine	Treatment D: Placebo	
CHG (and % CHG) in Total Sx Score$_{DAY\ 1\text{-}15}$	-3.8, (-23)	-2.6, (-13)	0.01

CHG=Change, % CHG=Percent Change, Sx=Score

[1]P-values are from 2-way ANOVA and LSmeans Pairwise Comparisons (no adjustment for overall α-value). P-values are those for the change in symptom score (not % change).

Mometasone was administered in all treatment groups as 200 µg qd.

Loratadine was administered in all treatment groups as 10 mg po qd.

Total Nasal Symptom Score= Composite of: rhinorrhea + nasal congestion + sneezing + nasal itching.

Total Symptom Score= Composite of: rhinorrhea + nasal congestion + sneezing + nasal itching + eye itching/burning + eye tearing + eye redness + ear/palate itching.

Analysis of the secondary efficacy variables support the conclusions derived from analysis of the primary efficacy variables: namely, that the three active treatment groups were statistically more effective than placebo in decreasing the symptoms of SAR and that efficacy of mometasone in SAR symptom relief was sustained throughout the day. In general, the combination treatment of mometasone plus loratadine or mometasone alone was found to be more effective in decreasing the symptoms of SAR than loratadine alone.

The comparison of the combination treatment of mometasone plus loratadine vs. mometasone alone for physician evaluated total nasal symptoms, physician evaluated total symptoms, subject evaluated individual nasal symptoms, and subject and physician evaluated total non-nasal symptoms for the ITT population [189:1263-1300], failed to demonstrate a statistically significant difference between the two treatment groups, with the exception of the individual non-nasal symptom of subject evaluated eye itch (a.m. and p.m. combined, Day 1-15 average) where the combination treatment demonstrated greater efficacy than mometasone alone ($p < 0.01$) [189:1278].

8.6.4.2. BIOAVAILABILITY STUDIES:

Analysis of plasma mometasone furoate levels via a method and analysis of plasma loratadine and its metabolite via a method was performed on blood obtained from 110 subjects at four study centers at screening, at pre-dose, at 5 minutes and 1 hour post-dose on the baseline visit (Day 1) and at pre-dose, 5 minutes and 1 hour post-dose on Visit 4 (Day 15); for a maximum total of 7 plasma samples (C94-145-02, -03, -04, -13) [185:33, 189:1326-1327, 191:2167]. Analysis of the results for plasma mometasone levels showed that all subject samples were below the lower limit of quantitation (LOQ), i.e. below 50.2 pg/ml [189:1329, 1345-1349], although a significant number of plasma samples were either not obtained, not sufficient in volume to perform analysis or results were 'not reportable'; with 'not reportable' being defined as 'no value obtained during the first analysis with inability to repeat sample analysis due to insufficient volume' [189:1327, 1345-1349].

Plasma loratadine (SCH 29851) and loratadine metabolite (SCH 34117) levels were assayed in the same 110 subjects comprising the four treatment groups that underwent analysis of plasma mometasone levels (28 subjects per treatment group) but detectable levels were only found in two of these groups: (1) the combination mometasone plus loratadine group and (2) the loratadine group [191:2167]. Analysis of the results for plasma loratadine (SCH 29851) levels and loratadine metabolite (SCH 34117) levels is summarized in Tables 1. and 2. of Appendix B in the NDA submission [191:2169-2170]. In summary, although no statistically significant treatment difference was noted between the two treatment groups ($p>0.16$), the power to detect a 50% difference in this study was <40% for plasma loratadine levels and was <70% for the plasma loratadine metabolite levels [191:2170]. This low power is related to the high variability of the data , as noted by coefficients of variation which were ≥ 104% for loratadine and > 63% for the loratadine metabolite, respectively [191:2170]. An additional confounding factor consisted of the several outliers which were detected for the 1 hour post-dose concentration difference of loratadine between Day 1 and Day 15 (subject [illegible] and the 1-hour post-dose concentration difference of the loratadine metabolite between Day 1 and Day 15 (subjects 412 and 439) [191:2168]

8.6.4.3. ADVERSE EVENTS:

The safety analysis was based on 702 subjects in the ITT population; 169 subjects were treated with mometasone 200 µg qd plus loratadine 10 mg po qd, 176 subjects were treated with mometasone 200 µg qd, 181 subjects were treated with loratadine 10 mg po qd, and 176 subjects were treated with placebo [185:44]. Adverse events were similar for all four treatment groups, with headache being the most frequently reported treatment-related adverse event.

Overall, adverse events were reported in 37% of subjects in the mometasone plus loratadine treatment group, 36% of subjects in the mometasone

treatment group, 47% of subjects in the loratadine treatment group, and 41% of subjects in the placebo group [185:76-77]. Headache was reported in 19% of subjects in the mometasone plus loratadine group, 14% of subjects in the mometasone group, 21% of subjects in the loratadine group, and 19% of subjects in the placebo group [185:76-77]. As has been previously noted in the other SAR studies in this NDA submission, headache was followed by pharyngitis and epistaxis in terms of frequency of reporting by subjects. Pharyngitis was reported in 4% of subjects in the combination treatment group, 5% of subjects in the mometasone group, 6% of subjects in the loratadine group, and 5% of placebo subjects [185:76-77]. Epistaxis was reported by 4% of subjects in the combination treatment group, 2% of subjects in the mometasone group, 2% of subjects in the loratadine group, and 3% of placebo subjects [185:76-77]. Nasal burning was also reported by 2% of subjects in the combination treatment group and 1% of mometasone subjects. Nasal burning was not reported by any subject in the loratadine or placebo groups [185:79].

There were no reports of nasal septal perforation in any of the four treatment groups, however nasal ulcers were reported in all four treatment groups post-baseline (i.e. after starting treatment) as follows:

(1) combination mometasone plus loratadine: reports in 3 subjects (1 subject on Visit 3, 2 subjects on Visit 4),
(2) mometasone alone: reports in 2 subjects (both on Visit 4), Visit 4),
(4) placebo: reports in 2 subjects (both on Visit 3).

Although noted, it is not clear how subjects would have developed nasal ulcers after receiving only 2 weeks of study drug.

In terms of infection, 1% of subjects in the combination treatment group and mometasone group reported viral infections, while 2% and 0% of subjects reported viral infections in the loratadine and placebo group, respectively [185:7 In this trial, one subject in the loratadine treatment group (subject C94-145-02, noted by the examining physician to have nasal candidiasis (on the baseline visit) [196:5 subjects in either of the other three treatment groups were found to have nasal candidiasis on follow-up clinic visits.

A total of 18 subjects discontinued treatment because of adverse events (2 in the combination treatment group, 4 in the mometasone group, 4 in the loratadine group, and 8 placebo subjects) [185:86]. A common reason for discontinuation due to adverse events was upper respiratory infection (1 subject each in the combination treatment group and mometasone group), although in all cases reported these were not felt to be related to treatment by the principal investigator(s) [185:88]. No deaths were reported in any of the four treatment groups.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the four treatment groups. Flag shift

distributions of laboratory values failed to reveal any significant patterns of change. A flag shift distribution of QT_c intervals for the four treatment groups also failed to reveal significant increase in QT prolongation from baseline. One subject in the combination treatment group was reported as having a QT_c >15-20% the baseline value. One subject (1%) in the combination treatment group, 5 subjects (3%) in the mometasone group, 3 subjects (2%) in the loratadine group, and 1 subject [illegible] value [illegible].

8.6.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of seasonal allergic rhinitis, as compared with placebo. While not statistically significant, the mean decrease in total nasal symptom scores and total SAR symptom scores was numerically greater for the combination treatment of loratadine plus [illegible]. For non-nasal symptoms, the combination treatment demonstrated greater efficacy than mometasone treatment alone in reducing the symptom of eye itch.
2. The other two active treatment groups: the combination treatment of mometasone plus loratadine and loratadine alone also showed statistically greater efficacy in the treatment of symptoms of SAR, as compared with placebo.
3. Analysis of plasma mometasone, loratadine and loratadine metabolite levels in 110 SAR subjects from 4 study centers designated to perform the pharmacokinetic studies, revealed undetectable mometasone levels in all subjects studied, undetectable loratadine (SCH 29851) and loratadine metabolite (SCH 34117) levels in the mometasone and the placebo [illegible] statistically [illegible] or loratadine metabolite levels in the combination mometasone plus loratadine treatment group vs. the loratadine treatment group.

APPEARS THIS WAY
ON ORIGINAL

8.7. Trial C93-193: The effect of mometasone furoate nasal spray on early and late phase inflammation during in-vivo ragweed nasal provocation in patients with seasonal allergic rhinitis (SAR).

Principal Investigator: Marianne Frieri, Ph.D., M.D.

[illegible] Medical Research Center
East Meadow, NY

8.7.1. OBJECTIVE:

1. To determine if pretreatment with mometasone furoate nasal spray 200 µg qd decreases specific parameters of the early and late phase response in nasal inflammation, compared with placebo, in subjects with seasonal allergic rhinitis (ragweed allergy).
2. To evaluate the safety and efficacy of mometasone vs. placebo in the treatment of symptoms of seasonal allergic rhinitis

8.7.2. STUDY DESIGN:

The study was a randomized, double-blind, placebo-controlled, two-period crossover study. The treatment periods consisted of two sequence groups: (1) mometasone followed by placebo, and (2) placebo followed by mometasone; both 14 days in duration, and both separated by a four week washout period.

8.7.3. PROTOCOL:

8.7.3.1.a POPULATION:

Significant entry criteria consisted of the following: (1) age ≥ 18 years [illegible] test to ragweed (wheal size ≥ 3 mm in diameter than diluent control [298:9,10, 300:496], (3) asymptomatic status [illegible] by a total nasal symptom score ≥ 2 (total nasal symptom score=[mean (left nasal discharge + right nasal discharge) + mean (left nasal congestion + right nasal congestion) + nasal itch], and no single symptom, nasal or non-nasal, rated as severe or moderate in severity [298:10, 27, 300:497], and (4) no chronic medication use which could affect the early or late phase response of inflammation, cytokine and/or leukotriene production [298:11, 300:498]. Regarding point (2), subjects allergic to other seasonal or perennial allergens were not to be enrolled in the study if the subject [illegible] developed symptoms due to these allergens during the study [298:9].

8.7.3.1.b PROCEDURE:

[illegible] ing entry criteria at the screening and baseline visits and completing the required physical exam and laboratory testing, study en[illegible]

subjects were randomly assigned at baseline (Visit 2) to one of the two treatment sequences:
(1) mometasone 200 µg qd, followed by placebo, or
(2) placebo, followed by mometasone 200 µg qd.

During the baseline visit, subjects likewise underwent [illegible] analysis of nasal cytology (mast cells, eosinophils, basophils, mononuclear cells, and neutrophils) according to a specific timetable outlined in Table I. below [298:9, 20, 300:530, 533-534]. During the baseline visit 'pretreatment' cytokine levels (IL-1α, IL-4, IL-5, IL-6, and IL-8), histamine content, and leukotriene B_4 levels (LTB_4) were determined without administration of study medication and this determination was followed by nasal antigen challenge with increasing concentrations of antigen at 10 minute intervals: 10 pnu, 100 pnu, and 1000 pnu, respectively, of ragweed antigen in order to determine a baseline response curve to ragweed antigen in the absence of study medication [298:20, 300:507, 511]. Histamine and cytokine levels were analyzed by ELISA, and LTB_4 was analyzed by RIA [298:20, 300:535]. The limits of detection of these parameters were as follows: histamine: 0.2 nM, IL-1α: 0 pg/ml, IL-4: 5 pg/ml, IL-5: 1 pg/ml, IL-6: 3 pg/ml, IL-8: 4.7 pg/ml, and LTB_4: 5 pg/ml [300:535-536]. Nasal cytology was graded on a 0-4 scale according to the quantitative analysis of the mean number of cells per 10 high power fields (HPFs) [298:21,60, 300:537]

After completing the nasal challenge tests, subjects received their first dose of study medication during the baseline visit (administered as 2 sprays per nostril each morning) in the principal investigator's clinic and were instructed to administer 2 sprays per nostril from the bottle each morning for 14 days [298:14, 300:505]. Subjects were not to be enrolled during the ragweed season. As in the previous SAR studies in this NDA submission, permitted medications for this study included: medium potency topical steroids, topical antimicrobials, systemic antibiotics, if on a stable dose for the duration of the study, and inhaled or oral beta-agonists, as needed for asthma; or theophylline, if on a stable dosage before and during the study [298:15, 300:500].

On Visit 3 (Day 15), subjects underwent nasal lavage again according to the specific timetable outlined in Table I which was performed 1 hour after the administration of study medication. Symptom responses to nasal provocation were scored by the principal investigator and the subject according to the 0-3 symptom severity scale [298:22, 300:507-508] at 9 time points: -31, -21, -11, -1 (prior to challenge), 9, 19, 29 minutes, 3 hours 29 minutes, and 6 hours 29 minutes after challenge [298:27]. After completion of the first period of the study, subjects underwent a 4-week washout period, followed by a second treatment period for 14 days beginning on Visit 4 (Day 43) [300:506]. Nasal lavage and provocation were repeated on the last day of the study, Visit 5 (or Day 57 since the start of the study) according to the same procedure as for Visit 3 [298: 27, 300:507]. Safety parameters were analyzed during each study visit [300:509-510, 512].

The primary efficacy variables in the study were defined as the individual

nasal fluid cytokine levels (IL-1α, IL-4, IL-5, IL-6, and IL-8) and nasal fluid LTB_4 level for the mometasone treatment group, compared with placebo [298:29, 300:511]. Summary statistics were calculated for the difference between values at baseline and at the other time points. Using a paired t-test, as well as the nonparametric Wilcoxon signed-rank test, significance of the changes from baseline were assessed [298:30, 300:511-512].

Secondary efficacy parameters consisted of: (1) nasal fluid histamine levels, (2) nasal cytology, and (3) the total nasal symptom score and the individual nasal symptoms of: nasal discharge, nasal congestion, sneezing and nasal itch [298:30, 300:511].

8.7.4. RESULTS:

A total of 21 subjects were randomized to one of the two treatment sequences. One subject (C93-193-01-008) was not evaluable for efficacy because he did not enter the second phase of the crossover study, hence leaving a total of 20 subjects evaluable for efficacy [298:33].

An analysis of the demographic data for the two treatment sequence groups showed comparability for all demographic and disease characteristics with the exception of body weight, which was greater in the placebo/mometasone group ($p=0.05$) [298:34, 55-56]. Overall, more male subjects were enrolled in the study than females, and subjects in the mometasone/placebo treatment sequence tended to be younger with a longer duration of disease than subjects in the placebo/mometasone treatment sequence, although the overall number of subjects was too small to draw a meaningful conclusion [298:34]. Because only one subject was not in the efficacy population compared to the intent-to-treat population, no intent-to-treat efficacy analyses were performed by the Sponsor and thus, all results for the primary and secondary efficacy endpoints were for the efficacy evaluable population [298:55-58].

In assessing the primary and secondary efficacy endpoints, it must be noted that a total of six subjects (4 in the mometasone/placebo group and 2 in the placebo/mometasone group) had invalid lavage times [298;100] and five of these six subjects also had invalid rhinoprobe times [298:34-35, 102]. Taking into account these caveats, the results of the primary and secondary efficacy variable analysis is summarized as follows:

For the pretreatment challenge, within treatment comparison for the efficacy evaluable population, starting from -10 minutes (prior to nasal challenge) showed no change in IL-1α, IL-4, IL-5, or LTB_4 nasal fluid levels [298:37-38, 108-110, 113] and a significant increase in IL-6 and IL-8 levels at the 3 hour 30 minutes and 6 hour 30 minute measurement [298:111-112]. Post-ragweed challenge, no statistically significant treatment effect (between treatment comparison using ANOVA) was observed at any time point for the cytokines or LTB_4 [298:121-123], though the treatment effect approached statistical significance for LTB_4 30 minutes after ragweed challenge ($p=0.075$) [298:127] and for both IL-6 ($p=0.079$) and IL-8 ($p=0.207$) at 6 hours 30 minutes post-treatment

with mometasone [298:37, 40, 125-126]. Table 7 from the NDA submission which summarizes these results is provided below.

Important from the perspective of the late phase allergic response, at almost all time points, IL-4 and IL-5 were not detected during either treatment sequence. Further complicating data analysis was the presence of outliers (which were ≥ 10-fold than the other observations) for IL-6 (while probably important, not consistently considered an important early or late phase response cytokine by all investigators, *(Lemanske RF and Kaliner MA, Late Phase Allergic Reactions. in Allergy: Principles and Practice, 4th Edition, 1993, Mosby-Year Book)*) and LTB_4 nasal fluid levels, thus yielding highly variable results [298:38].

For the secondary efficacy variables, mean histamine levels were significantly reduced by mometasone treatment compared with placebo 30 minutes (20.16 nM pre-treatment vs. 14.25 nM post-treatment, p=0.021) following nasal challenge with ragweed (10 minutes after the highest ragweed antigen dose) [298:193]. For eosinophil counts evaluated in the nasal cytology, both the prechallenge baseline and late phase increases (6 hour 30 minutes) were numerically lower after mometasone treatment, as compared to placebo, although these between treatment differences did not reach statistical significance (p=0.240) [298:40, 188]. The other cell populations did not show between treatment differences with nasal provocation [298:186-187, 189-190]. Mean total nasal symptoms scores were consistently lower after mometasone treatment compared with placebo, with statistically significant treatment differences noted at -21, -1, 19 and 29 minutes [298:207]. In terms of the individual nasal symptoms, the symptom of nasal discharge, followed by nasal congestion showed the greatest response to mometasone treatment, compared with placebo on ragweed challenge [298:201-204]. Nasal itch and throat itch did not demonstrate a statistically significant response with mometasone treatment as compared with placebo on ragweed challenge [298:206-207]. And while the mean number of sneezes was also consistently lower after treatment with mometasone as compared with placebo, a statistically significant difference was only observed at 19 minutes (p=0.047) [298:41, 208].

8.7.4.3.ADVERSE EVENTS:

A total of 21 subjects were evaluated for safety and of these, one subject discontinued treatment (C93-193-01-008) after the first treatment period because of an upper respiratory infection which was of moderate severity and not felt to be related to treatment by the principal investigator [298:33, 43, 53].

Adverse events were reported in 3/20 (15%) of subjects in the mometasone treatment group, compared with 4/21 (19%) of subjects in the placebo group [298:43]. All except two of the adverse events were categorized as respiratory system disorders: pharyngitis, epistaxis, bronchitis, or upper respiratory tract infection [298:42-43]. In contrast to the all other SAR studies in this NDA submission, no reports of headache were noted in this study. No reports of nasal septal perforation, nasal ulceration, nasal or oral candidiasis were reported in this

study. None of the adverse events reported in this study were rated as severe or life-threatening and no subject deaths were reported. Additionally, no clinically significant changes in vital signs, physical exams, or laboratory tests relative to baseline were reported in subjects treated with mometasone. In summary, mometasone was found to safe and tolerable by subjects in trial C93-193.

8.7.5. CONCLUSIONS:

1. IL-1α, IL-4, IL-5, LTB4 nasal fluid levels and nasal cytology showed no significant change with antigen challenge, thus making interpretation of treatment with mometasone difficult if not altogether impossible.
2. Mean histamine levels were significantly reduced in the mometasone 200 µg treatment group, as compared with placebo, 30 minutes and 10 minutes following nasal challenge with the lowest and highest concentrations of ragweed allergen, respectively.
3. Within-treatment comparsions for IL-6, IL-8 and eosinophil counts suggest that mometasone treatment decreased these parameters by the 6 hour 30 minute timepoint, although statistical significance was not reached as compared with placebo. While probably important as pro-inflammatory mediators, IL-6 and IL-8 are not consistently considered late phase cytokines, and thus, the meaning of this decrease is not clear in terms of the late phase allergic response, per se.
4. The mean nasal symptom scores were lower in the mometasone treatment group, as compared with the placebo group and were statistically significantly lower at the 19 and 29 minute timepoints post-allergen challenge.
5. Mometasone 200 µg qd was well tolerated and safe in subjects with SAR.

8.8. Trial I94-139: A pilot study to evaluate the effect of mometasone furoate (MF) nasal spray on the early and late phase reactions following allergen-specific nasal challenge in patients with pollen allergy.

Principal Investigator: G. Walter Canonica, M.D.

Participating Center: Allergy and Clinical Immunology Service, Department of Internal Medicine, Genoa, Italy.

8.8.1. OBJECTIVE:

1. To determine whether pretreatment with mometasone furoate nasal spray, 200 µg qd decreases nasal lavage levels of specific cytokines which are associated with the early and late phase allergic response, as compared with placebo.
2. To evaluate the safety of mometasone furoate nasal spray 200 µg qd.

8.8.2. STUDY DESIGN:

This was a Phase III, randomized, double-blind, placebo-controlled, parallel group study. Subjects underwent an allergen specific nasal challenge at baseline, and again after receiving two weeks treatment with either mometasone or placebo. Nasal lavage was performed before the antigen challenge and at 30 minutes and 6 hours following the challenge.

8.8.3. PROTOCOL:

8.8.3.1.a. POPULATION:

Significant entry criteria consisted of the following: (1) age ≥ 18 years, (2) history of seasonal allergic rhinitis to parietaria (a weed) for at least 2 years, with documentation by a positive skin test to this allergen (prick test wheal size ≥ 3 mm in diameter larger than diluent control, the latter of which is not discussed in the protocol [301:9, 254], (3) no history of anticipated rhinitis symptoms during the time period covering the conduct of the study or positive skin test (by prick or intradermal methods) to a seasonal aeroallergen (trees, grasses, weeds) or perennial allergen (including but not limited to, mites, molds, etc.) [301:16, 252, 254], and (4) clinically asymptomatic status at both screening and baseline visits, with the total nasal symptom score ≤ 2 in severity (0-3 scale) [301:20, 266] and no single symptom (nasal or non-nasal) rated as moderate or severe [301:9, 16, 252, 254].

8.8.3.1.b. PROCEDURE

Study subjects underwent routine medical history, physical exam (including nasal exam) and laboratory testing during the screening visit (Visit 1=Day 0) [301:261-262]. Subject hypersensitivity to parietaria allergen was confirmed by a positive response to skin prick testing (if not performed within the past year)

[301:254, 348-355]. On baseline visit (Visit 2=Day 1), in addition to routine medical evaluation, subjects underwent a baseline nasal challenge with parietaria allergen via nasal insufflation, prior to receiving study medication [301:262-263]. Nasal lavage was performed before allergen challenge, and at 30 minutes (early phase of allergic inflammation) and again at 6 hours (corresponding to the late phase of allergic inflammation) with recording of subject total and individual nasal symptoms [310:18, 252-253].

Nasal lavage secretions were collected for the determination of intracellular adhesion molecule-1 (ICAM-1) expression on epithelial cells (via immunoenzymatic alkaline phosphatase-monoclonal anti-alkaline phosphatase (APAAP) complex and expressed according to a 4 point rating scale, from 0-4), soluble ICAM-1 (via ELISA), eosinophilic cationic protein (ECP, via RIA), interleukin-1β (IL-1β, via ELISA), tumor necrosis factor (TNF-α, via ELISA), granulocyte-macrophage colony stimulating factor (GM-CSF, via ELISA), and nasal cytology (eosinophils, neutrophils, and epithelial cells differentiated by May-Grunwald/Giemsa staining) [301:19, 253]. PGD_2 was originally to be assessed in nasal lavage fluid as well (via RIA), however fluid data for PGD_2 was not available from the principal investigator and thus was not included in this report [301:26-27]. Reason(s) for unavailability of the PGD_2 data from the investigator was not provided by the sponsor.

Following successful performance of all medical, provocation, and laboratory procedures, subjects who qualified for study enrollment had a treatment number assigned and were randomized into one of the two treatment groups: mometasone 200 μg qd or placebo [301:17, 263]. The first dose of study medication was applied in the investigator's office, approximately 6 hours following baseline nasal challenge. Subjects were therein instructed to administer 2 sprays per nostril from the bottle in the a.m. upon arising [301:17, 259, 264]. No concomitant medications were allowed during the course of the study with the exception of: short acting antihistamines for acute relief of symptoms following nasal challenge and office procedures, mild potency topical corticosteroids, topical antibiotics, occasional use of aspirin or NSAIDs, and inhaled or oral beta-agonists as needed for asthma; or theophylline, if on a stable dose before and during the study [301:14-15, 32, 256-258].

On the third and last study visit (Visit 3=Day 15 ± 2 days), after completion of the physical examination, laboratory tests, and symptom scoring; subjects underwent nasal provocation with parietaria allergen approximately 1 hour after administration of study medication [301:18, 264-266]. Nasal lavage was performed as per Visit 2; before allergen challenge, and 30 minutes and 6 hours after allergen challenge with recording of subject total and individual nasal symptoms. Nasal lavage fluid was assessed for the same panel of pro-inflammatory markers as evaluated during Visit 2 [301:19, 266]. A summary of the protocol schedule is provided in Table 1 of the NDA submission [301:8, 276].

The primary efficacy variables consisted of: (1) ICAM-1 expression on nasal epithelial cells, (2) soluble nasal lavage ICAM-1, and (3) soluble nasal lavage

ECP [301:27, 271].

Secondary efficacy variables consisted of: (1) the other pro-inflammatory response markers: nasal cytology, nasal fluid PGD_2 (not performed), IL-1β, TNF-α, and GM-CSF levels, and (2) the nasal symptoms of: the change from baseline of the total nasal symptom score, and the change from baseline in the individual nasal symptoms of nasal discharge, congestion, sneezing, and nasal itch [301:28, 271-272]. 'Baseline' was defined as the appropriate time point (0 minutes, 30 minutes, or 6 hours) evaluated post-nasal provocation during the baseline visit [301:25]. Primary and secondary efficacy parameters were analyzed only for the efficacy evaluable population, as no post-treatment nasal symptom or inflammatory marker response data were recorded for subjects who were excluded from the efficacy population [301:32].

All efficacy parameters were analyzed for between-group differences (mometasone vs. placebo) using the Wilcoxon Rank Sum test (for skewed data) and for within-group differences using the Wilcoxon sign test [301:27, 33-34]. Nasal symptoms were analyzed using a one-way ANOVA [301:28].

8.8.4. RESULTS:

A total of 48 subjects were enrolled in the study (ITT or safety population), with 6 dropouts from the placebo group secondary to viral infection (common cold), leaving 42 subjects in the efficacy evaluable population [301:30-31, 52-53, 74-75]. There were no dropouts from the mometasone treatment group. Since no post-treatment inflammatory marker response data or nasal symptom data were recorded for subjects who were excluded from the efficacy population, no analyses were presented by the sponsor for the ITT population.

Subjects were comparable for all demographic and disease characteristics in the two treatment groups, with slightly more males than females enrolled [301:31, 55-61]. All subjects were Caucasian. None of the subjects reported a history of perennial rhinitis or history of other seasonal allergies [301:343-346].

Within-group comparison to pre-treatment with study drug for the efficacy evaluable population showed a significant mean reduction from pre-treatment in ICAM-1 expression on epithelial cells, IL-1β and ECP levels, and eosinophil and neutrophil counts in the mometasone treatment group ($p \leq 0.05$). A significant mean reduction for ICAM-1 expression on epithelial cells (a primary efficacy variable), as compared with pre-treatment, was also noted in the placebo group ($p=0.01$). For both treatment groups, the other pro-inflammatory markers (soluble ICAM-1, TNF-α, GM-CSF) did not demonstrate a consistent increase during the pre-treatment challenge [301:36], making pre- and post-treatment results difficult, if not impossible, to interpret.

With the exception of ECP which showed a statistically significant difference between the two treatment groups ($p<0.01$) 30 minutes after nasal provocation [301:37, 88], no statistically significant difference between the mometasone and placebo treatment group was noted for change from baseline in 7

out of the 8 pro-inflammatory markers [301:35-37, 81-87]. The mometasone treatment group however, did have a numerically greater and statistically marginally greater reduction in ICAM-1 expression on epithelial cells (p=0.08) 6 hours after nasal provocation [301:35, 83]. Nasal provocation results for these 8 markers of allergic inflammation are summarized in Table I below.

For total nasal symptom scores, the mometasone treatment group showed greater improvement in total nasal symptom scores (mean change in total nasal symptom score$_{\text{post-treatment-pre-treatment}}$ for mometasone=-2.6 (64%) vs. mean change in total nasal symptom score$_{\text{post-treatment-pre-treatment}}$ for placebo=-1.4 (34%), p=0.03) [301:38, 90] and in the individual symptom scores of nasal discharge (mometasone group mean change=
-1.0 (63%) vs. placebo group mean change=-0.4 (29%), p=0.02) [301:39, 91], sneezing (mometasone group mean change=-5.0 (69%) vs. placebo group mean change=-1.3 (41%), p<0.01) [301:41-42, 94], and nasal itch (mometasone group mean change=-0.8 (63%) vs. placebo group mean change=-0.3 (19%), p=0.01) [301:40-41, 93] from pre-treatment compared with placebo at 30 minutes post-nasal provocation. Interestingly, no significant difference in nasal congestion was noted between the mometasone treatment group and placebo group at both 30 minutes (p=0.73) and 6 hours post-nasal provocation [301:40, 92].

Table I: Between-Group Differences in Nasal Cytology and Markers of Nasal Inflammation Pre- and Post- Nasal Provocation [301:35-37]

			MOMETASONE			PLACEBO			
Parameter	**Time of assessment after nasal challenge (h)**		**n**	**Mean**	**Median**	**n**	**Mean**	**Median**	**Wilcoxon Rank Sum p-Value**
Eosinophils (# cells/field mean of 10 fields)	Post-Pre[1]	0 h	24	-0.1	0.0	17	-0.1	0.0	0.50
		0.5 h	21	-1.9	-2.0	16	-0.6	-0.5	0.17
		6 h	24	-2.9	-1.5	16	-1.0	-1.0	0.19
Neutrophils (# cells/field)	Post-Pre	0 h	24	-0.3	0.0	17	-0.1	0.0	0.60
		0.5 h	21	-1.7	-2.0	16	-1.1	-1.0	0.57
		6 h	24	-1.7	-2.5	16	-1.9	-2.0	0.40
ICAM-1 expression on epithelial cells (score[2])	Post-Pre	0 h	24	0.0	0.0	17	-0.1	0.0	0.60
		0.5 h	23	-1.4	-1.0	16	-0.9	-0.5	0.32
		6 h	23	-1.4	-1.0	16	-0.8	0.0	0.08
Soluble ICAM-1 (ng/ml)	Post-Pre	0 h	23	-0.4	0.0	16	0.1	0.1	0.88
		0.5 h	23	0.3	0.0	16	0.2	0.1	0.73
		6 h	23	0.0	0.0	16	0.3	0.1	0.33
IL-1β (pg/ml)	Post-Pre	0 h	23	-135	-1.0	16	-29	13	0.05
		0.5 h	23	52.0	32	15	80.0	45	0.98
		6 h	23	-56.4	-67	16	1.3	-2	0.24
TNF-α (pg/ml)	Post-Pre	0 h	22	-4.3	-13.7	16	5.6	14.6	0.54
		0.5 h	23	-16.0	-6.8	15	6.8	13.7	0.24
		6 h	23	-25.3	-21.0	16	40.5	11.7	0.10
GM-CSF (pg/ml)	Post-Pre	0 h	23	-166	-24	16	-188	10	0.56
		0.5 h	22	294	37	15	201	24	0.64
		6 h	22	-138	-12	16	70	18	0.24
ECP (ng/ml)	Post-Pre	0 h	22	-128	0.0	15	0.0	0.0	0.43
		0.5 h	23	-1.0	0.0	15	-7.8	0.0	<0.01
		6 h	23	-3.8	0.0	16	37.0	-0.2	0.71

[1] Post-treatment assessment minus pre-treatment assessment.

[2] ICAM-1 expression rated according to a 4 point scale, where 0=no (+) cells, 1=mildly (+) on 25% of cells, 2=intensely (+) on 75% of cells, 4= very intensely (+) on all epithelial cells

8.8.4.3.ADVERSE EVENTS:

The safety population consisted of 48 subjects (24 subjects in the mometasone treatment group, 24 subjects in the placebo group), 6 of whom (in the placebo group) discontinued because of the common cold [301:420-421]. The common cold was the only adverse event reported in this study [301:43]. No serious adverse events or subject deaths were reported. No subjects were noted to develop nasal perforation, nasal ulcers, nasal or oral candidiasis [301:425-440]. There were likewise no reports of herpes simplex or other viral illnesses suggestive of immunosuppression. Physical examination (including vital signs and nasal exam) and laboratory test results showed no clinically meaningful changes from pre-treatment in either of the two treatment groups [301:43-44]. ECGs were not performed for safety monitoring during this study.

8.8.5. CONCLUSIONS:

1. An evaluation of the effect of mometasone on markers of chronic allergic inflammation such as ICAM-1, ECP, IL-1β, TNF-α, GM-CSF, and lavage fluid eosinophilia (*Reference: Baraniuk, JN, Pathogenesis of allergic rhinitis, JACI, 1997, 99(2):S763-S772*) showed that mometasone induced a statistically significant response only in nasal lavage ECP levels, as compared with placebo, although within-group analysis for the mometasone treatment group showed significant post-allergen provocation reductions in eosinophils, neutrophils, ICAM-1 expression on nasal epithelial cells, IL-1β, and ECP, as compared with pre-treatment.
2. Mometasone 200 μg qd demonstrated greater efficacy than placebo in reducing total nasal symptoms of SAR, and the individual nasal symptoms of nasal discharge, sneezing, and nasal itch.
3. Mometasone was well tolerated and without significant adverse effects.

8.9. Trial C93-215: Controlled, pivotal study of the prophylactic treatment of seasonal allergic rhinitis with mometasone furoate (SCH 32088) aqueous nasal spray.

Principal Investigator: Donald W. Aaronson, M.D.
Aaronson Asthma & Allergy Associates, Ltd.
9301 Golf Road
Des Plaines, IL 60016

Participating Centers: 9 U.S. Centers

8.9.1. OBJECTIVE:

The objective of this study was to investigate the safety and efficacy of mometasone furoate in the prophylaxis of symptoms of seasonal allergic rhinitis (SAR).

8.9.2. STUDY DESIGN:

The study was a phase III, randomized, multi center, double-blind, double-dummy, active- and placebo-controlled parallel group study to determine the safety and efficacy of mometasone furoate 200 µg administered intranasally once daily (qd) vs. the active control beclomethasone dipropionate (Vancenase AQ) 168 µg, administered twice daily (bid), and vs. placebo for approximately 4 weeks prior to the anticipated onset of the ragweed allergy season and 4 weeks after the onset of the ragweed allergy season (for a total duration of treatment of 8 weeks).

8.9.3. PROTOCOL:

8.9.3.1.a. POPULATION: Male or female subjects, ≥ 12 years of age, with SAR documented by a positive response to ragweed via skin prick or intradermal tests [179:14, 182:854].

(I) Inclusion Criteria [179:14, 182:854-855]:

1. History of moderate to severe seasonal allergic rhinitis (SAR) of at least 2 years duration.
2. If not performed within 14 months of study entry, demonstration of a positive response to ragweed allergen via skin testing (ragweed induced wheal size ≥ 3 mm larger in diameter than diluent control via prick testing or ≥ 7 mm larger in diameter than diluent control via intradermal testing).
3. Clinically asymptomatic status at both screening and baseline . The total nasal symptom score was to be graded ≤ 2 on a 0-3 symptom scale and no single symptom (nasal or non-nasal) could be rated moderate or severe.

4. Other than SAR, subjects must have been in good health and free of clinically significant disease that would interfere with the study schedule or evaluation of SAR.
5. Ability to adhere to dose and visit schedules and record symptom scores accurately and consistently twice daily in a diary.
6. Nonpregnant women or women of childbearing potential must have been using a medically acceptable form of birth control for at least 3 months prior to screening and were to continue its use for the duration of the study.

Reviewer's Note: The diluent control used for skin testing to allergen (saline vs. steriie water) was not specified in either the study protocol or report for this study.

(II) Exclusion Criteria [179:15, 182:855-856]:

1. History of asthma which required therapy with inhaled or systemic corticosteroids.
2. Clinical evidence of large nasal polyps, marked septal deviation, or any other nasal structural abnormality that may significantly interfere with nasal airflow, as determined by the principal investigator.
3. Symptoms due to a common cold or upper respiratory infection at the screening or baseline visit.
4. History of significant renal, hepatic, neurologic, cardiovascular, hematologic, metabolic, cerebrovascular, respiratory, gastrointestinal, or other significant medical illness, which in the judgement of the principal investigator could interfere with the study or require medical treatment that would interfere with the study.
5. History of recurrent sinusitis or chronic purulent postnasal drip.
6. History of posterior subcapsular cataracts.
7. Total nasal symptom score > 2, or one or more nasal and/or non-nasal symptoms rated moderate or severe (symptom score ≥ 2).
8. History of allergic symptoms to a perennial allergen(s) (e.g. dust mite, molds, animal dander) and anticipation of clinically significant symptoms due to this (these) perennial allergen(s) prior to the anticipated start of the ragweed season.
9. History of multiple drug allergies, or allergy to corticosteroids.
10. Subject dependency on nasal, oral, or ocular decongestants, or anti-inflammatory agents; as determined by the principal investigator, or diagnosis of rhinitis medicamentosa.
11. Use of any chronic medication that could affect the course of SAR.
12. Use of any investigational drug within the previous 30 days.
13. Subjects on immunotherapy who had not been on a stable dose for

at least 2 years prior to screening.

14. Presence of any clinically relevant abnormal vital signs, laboratory test results outside the normal range, or clinically significant abnormal ECG.

15. Pregnant or nursing women, pre-menarchal females or women of child-bearing potential not using a medically acceptable form of birth control.

(III) Concurrent Medication Restrictions [179:19, 182:857]:

(A) General Considerations:

1. No subject was permitted to concurrently receive any medication linked with a clinically significant incidence of hepatotoxicity (e.g. methotrexate, 17α-alkylsteroids) or which may cause significant liver enzyme induction (e.g. barbiturates).

2. All previous and concomitant medications taken for the month prior to study entry (exceptions: astemizole or intramuscular/intra-articular corticosteroids taken within 3 months) including any over-the-counter drugs, must be recorded in the case report form. No significant dose change in chronic medication was allowed during the study.

(B) Medications restricted before screening (Visit 1) [179:20, 182:857-858]:

	Medication	Time Discontinued Prior to Visit 1
1.	Cromolyn sodium or Nedocromil	2 weeks
2.	Corticosteroids, nasal or ocular	2 weeks
3.	Corticosteroids, inhaled, oral or intravenous	1 month
4.	Corticosteroids, intra-muscular or intra-articular	3 months
5.	High potency topical corticoids-for dermatological use [Stoughten/Cornell Scale [182:897-898]]	1 month
6.	Antihistamines, short-acting (e.g. chlorpheniramine)	12 hours
7.	Antihistamines, long-acting (e.g. cetirizine, loratadine, hydroxyzine)	96 hours
8.	Terfenadine, clemastine, long-acting OTC forms of chlorpheniramine	48 hours

	Medication	Time Discontinued Prior to Visit 1
9.	Astemizole	3 months
10.	Nasal, ocular, or oral decongestants, and nasal or ocular anti-inflammatory agents	24 hours
11.	Nasal atropine	1 week
12.	Systemic antibiotics	2 weeks
13.	Nasal levocabastine and topical antihistamines	72 hours

(C) Concurrent medications restricted after screening and for the duration of the study [179:20, 182:858]:

1. Systemic, inhaled, topical nasal, and topical ocular corticosteroids.
2. High potency topical corticosteroids (as per the Stoughton-Cornell Scale).
3. Cromolyn sodium or nedocromil, any formulation.
4. Antihistamines.
5. Topical (nasal and ocular) and oral decongestants, or nasal or ocular anti-inflammatory agents.
6. Oral decongestants.
7. Nasal atropine.
8. Systemic antibiotics (unless on a stable dose 1 month prior to the study with dose remaining unchanged for the duration of the study).

(D) Medications allowed during the study duration [179:21, 182:858-859]:

1. Saline eye drops.
2. Inhaled or oral beta-agonists on an as needed basis, for asthma.
3. Theophylline, if on a stable dose before and during the study.
4. Topical antimicrobials.
5. Mild potency (class V, VI, VII) topical corticosteroids for dermatological use.
6. Thyroid replacement therapy, if on a stable dosage before and during the study,
7. Hormone replacement therapy for postmenopausal women, if on a stable dosage before and during the study.
8. Over the counter (OTC) pain relievers.

8.9.3.1.b PROCEDURE

(1) Screening Visit (Visit 1) [179:22-23, 182:861-863]:

A complete medical history (including allergy history), physical examination (including a nasal exam), review of adverse events, laboratory evaluation, 12-lead ECG, and confirmation of the subject's allergen hypersensitivity with skin prick testing (if not performed within the previous 14 months prior to the screening visit) was performed at the screening visit. Subjects were to be clinically asymptomatic at both the screening and baseline visits although an allowance of a total nasal symptom score ≤ 2 was provided, in realization that subjects with a history of moderate to severe SAR symptoms might be clinically asymptomatic yet not be totally free of symptoms. No single symptom (nasal or non-nasal) could be rated moderate or severe (symptom score ≥ 2).

A symptom diary was started by study enrollable subjects on the screening visit and required that subjects rate their SAR symptoms reflectively over the previous 12 hours (see below) twice daily at approximately the same time of the day (each a.m. upon arising and each p.m. prior to going to sleep). Subjects were instructed to return to the principal investigator's office within 14 days for Visit 2.

Symptoms and overall condition of the SAR were rated using the following set of (A) nasal and non-nasal symptoms and according to the following (B) symptom severity scale which has been used throughout this NDA submission:

(A) Seasonal Allergic Rhinitis Symptom Categorization [179:25-26, 182:867]:

Nasal Symptoms:	**Non-nasal Symptoms:**
Rhinorrhea (nasal discharge/ runny nose)	Itching/burning eyes
Stuffiness/congestion	Tearing/watering eyes
Nasal itching	Redness of eyes
Sneezing	Itching of ears or palate

(B) Seasonal Allergic Rhinitis Symptom Severity Scale [179:26, 182:867-868]:

Symptom Severity Score:	Severity Definition:
0= None	No sign/symptom evident.
1= Mild	Sign/Symptom clearly present but minimal awareness; easily tolerated.
2= Moderate	Definite awareness of sign/symptom which is bothersome but tolerable.
3= Severe	Sign/symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping.

Reviewer's Note:
As noted in the SAR pivotal trial (C93-013) which also used this symptom rating scale, any given study subject could achieve a: minimum score=0 or maximum score=12; for either total nasal symptoms or total non-nasal symptoms, respectively; and a minimum score =0, maximum score=24 for combined nasal and non-nasal symptoms.

(II) Baseline Visit (Visit 2=Day 1) [179:23-24, 182:863-865]:

Procedures performed during the screening visit were repeated during the baseline visit. SAR symptoms recorded in subject diaries during the screening phase of the study were reviewed and if subjects qualified for study entry (total nasal symptom score ≤ 2), a new symptom diary was dispensed and baseline entry scores were filled out by the investigator.

Study enrollable subjects were assigned a treatment number and were randomized (using a SAS number generator) in a 1:1:1 ratio to one of the following three treatment groups [180:853, 182:864, 872, 998-1006]:

STUDY GROUP	a.m. dosing	p.m. dosing	Total Dose (µg/day)
(A) Mometasone (SCH 32088)	mometasone (200 µg)	placebo	200
(B) Beclomethasone (Vanceanse AQ)	beclomethasone (168 µg)	beclomethasone (168 µg)	336
(C) Placebo	placebo	placebo	0

Subjects received 8 sprays per day (2 sprays in each nostril from the a.m. bottle each morning on arising and 2 sprays in each nostril from the p.m. bottle each evening, approximately 12 hours after the morning dose was administered). Because labeled mometasone and beclomethasone bottles were not of identical appearance, a double-dummy study design was used and each bottle type had a

matching placebo. Subjects were instructed about dosing and received their first dose of medication at the study center.

Reviewer's Note: The protocol and general study document [179:17, 182:868-869] stated that a double-dummy design was used for double-blinding where subjects did not receive bottles of different shape or appearance at the each time period (i.e. for the a.m. and the p.m. dose) but rather, where subjects received study drug for the a.m. and p.m. dose in Vancenase AQ bottles (for all 3 study medications: mometasone, beclomethasone, and placebo) with labels of two different colors for the a.m. (yellow) and p.m. (blue) dose, respectively.

In summary, the study was designed to recruit approximately 36-42 subjects with documented SAR to each of the 9 centers to ensure a total of at least 324 evaluable subjects. Ideally, all subjects were to be enrolled as cohorts within a 5-day period, approximately 4 weeks prior to the anticipated onset of the ragweed season.

Reviewer's Note: In summary, the study was designed so that subjects would be prophylaxed with study medication for approximately 4 weeks before the start of the ragweed season. By choosing an allergen (ragweed) which attains high airborne levels and historically has a well-defined onset and offset of this season, the study is well-designed from the perspective of trying to maximize the potential to show a difference between active medication and placebo.

(III) Evaluation Visits [179:24-25, 182:865-867]:

Evaluation visits to the physician were defined as follows:

Visit 3=Day 8 ± 2 days
Visit 4=Day 22 ± 2 days
Visit 5=Day 29 ± 2 days
Visit 6=Day 36 ± 2 days
Visit 7=Day 50 ± 2 days
Visit 8=Day 57 ± 2 days
Visit 9=Day 71 ± 2 days

During these follow-up visits, subject symptoms and adverse events were reviewed and physical examinations repeated. Subjects received new diary cards at each visit. Visits 3, 4, and 5 (Days 8, 22, and 29) were intended to occur before the onset of the ragweed season and visits 6, 7, and 8 (Days 36, 50, and 57) were intended to occur after onset of the ragweed season.

Reviewer's Note: A point of confusion in the protocol is the occasional discrepancy between the days and corresponding study visit (e.g. use of day 7

instead of day 8 when referring to Visit 3) [182:867]. This discrepancy is a result of referring to days after the initiation of treatment and does not include day 1 of the study.

During the final visits (Visits 8 or 9), subjects additionally underwent repeat laboratory testing and nasal examination. Visit 9 was incorporated into the study procedure in the event of a delay of the beginning of the ragweed season and requirement for an extra study visit for study completion. Daily ragweed pollen counts were to be maintained by each study center throughout the study. The onset of the pollen season was determined for each center by recording the dates of the first appearance of pollen, the two weeks of highest pollen counts, and the offset of the pollen season.

Reviewer's Note: While it is clear from the study report [179:26] and protocol [182:868], that the investigator would be responsible for maintaining the daily ragweed pollen counts, it is not clear how this information would be conveyed to determine if subjects required an additional study visit on day 71 (Visit 9). In discussing this issue with Schering-Plough, Inc., I was informed that the investigator for each study center will review the dates of onset of the pollen season and inform each study subject individually if an additional study visit (Visit 9) was required.

The study procedure is outlined in Table 1 below [179:13, 182:896].

Table 1

Schedule of Study Procedures and Evaluations (Protocol No. C93-715)

	Screening Visit 1	Baseline[a] Visit 2	Day 8 Visit 3	Day 15 Phone Contact	Day 22 Visit 4	Day 29 Visit 5	Day 36 Visit 6	Day 43 Phone Contact	Day 50 Visit 7	Day 57 Visit 8	Day 71[b] Visit 9
Informed Consent	X										
Check Inclusion/Exclusion Criteria	X	X									
Review Concomitant Medications	X	X	X		X	X	X		X	X	X
Medical and Allergy History	X										
Physical Exam, Including Nasal Exam	X									X	X
Vital Signs	X	X	X		X	X	X		X	X	X
Body Weight	X									X	X
Height	X										
Skin Testing[c]	X										
ECG	X										
Laboratory Tests[d] and Urinalysis	X									X	X
Pregnancy Test[e]	X									X	X
Physician Assessments of Rhinitis Symptoms	X	X	X		X	X	X		X	X	X
Dispense Study Medication		X			X		X			(X)[f]	
Retrieve Study Medication					X		X			X	X
Dispense Symptoms Diary	X	X	X		X	X	X		X	(X)[f]	
Study Drug Administered In Office		X									
Symptoms Diary Card Retrieved and Reviewed		X	X		X	X	X		X	X	X
Telephone Compliance Assessment				X				X			
Adverse Events/Concomitant Illness Assessment	X	X	X		X	X	X		X	X	X

a. Scheduled approximately 4 weeks before the start of the ragweed season.
b. Extra visit was to be scheduled if the ragweed season was delayed. Final visit evaluations were then carried out at Visit 9, rather than Visit 8.
c. Required if not done per unacceptable results) within the previous 14 months.
d. Including a complete blood count, with WBC differential and platelet count, and blood chemistries; see Section 3.4.3 for additional details.
e. All females.
f. If Visit 9 was necessary.

8.9.3.2. CLINICAL ENDPOINTS:

STUDY PERIOD DEFINITIONS:
For the purpose of determining the primary and secondary efficacy variables the following study periods will be defined:

(a) **Prophylaxis period-** the time period from the start of treatment (Baseline visit or Visit 2) until the day before the start of the ragweed season [179:32].

The **start or onset of the ragweed season-** was defined as the date of onset of the appearance of ragweed pollen at each treatment center (as determined by each investigator by the observed ragweed counts and as supported by symptoms in comparable SAR subjects at each treatment center) [182:868].

Reviewer's Note: Neither the study protocol nor the study report state how each treatment center's onset of the ragweed season date will be handled. The study protocol does state that at the end of the study but prior to data analysis, each investigator will provide the date for the onset of the pollen season, the date of the peak pollen season (2 weeks of highest counts), and the offset of the ragweed season. It is not clear from these documents whether each treatment site will have its own onset and offset of the pollen season which will individually be incorporated into the final data analysis or whether these individual dates for the individual centers will be used to determine a mean onset of the pollen season that will subsequently be used for data analysis across all centers. While the mean time period to onset of the pollen season for all study sites is 26 days, this time period varies from 16 to 30 days after the start of treatment for individual sites [179:50], hence application of the 26 day mean would be incorrect for study sites with an earlier onset of the pollen season.

Nonetheless, in clarifying this issue with Schering-Plough, Inc., I was informed that each study center will have its own date of onset and offset of the pollen season, determined by the pollen counts for that center.

(b) **Pollen season-** defined as the time period from the start of the ragweed season (see above) through the last day of treatment [179:32].

(c) **The entire treatment period-** defined as the time period from the first day of treatment through the last day of treatment [179:32].

(d) **Endpoint visit-** defined as the last visit (for physician evaluated variables) or last interval (for diary evaluations) for which the subject had non-missing data [179:32].

(I) Primary Efficacy Variable [179:38, 50-51, 182:874]:

The mean proportion of minimal symptom days during the ragweed pollen season- the days when the **total nasal symptom score** (defined as: the sum of individual symptom scores of: rhinorrhea, nasal congestion, sneezing, and nasal itch) was ≤ 2 based on the average of the a.m. + p.m. diary scores from the start of the pollen season, through the last day of treatment, day 57 or 71 (depending on the onset of the pollen season). In other words, the primary efficacy variable equaled the number of days where subject total nasal symptom scores ≤ 2/total number of days. The primary comparison of the study was a comparison of the mometasone treatment group vs. placebo.

Reviewer's Note: For each study subject, individual symptom severity scores recorded in the subject diary were used to derive the proportion of minimal symptom days during the specified time periods.

(II) Secondary Efficacy Variables [179:39-40, 182:874]:

(1) The proportion of minimal symptom days (total nasal symptom score ≤ 2) during the first week of the pollen season.

(2) The proportion of minimal symptom days (total nasal symptom score ≤ 2) for the entire treatment period.

(3) The proportion of days during the pollen season when the total nasal symptom score=0 (i.e. the proportion of symptom-free days).

(4) The number of days from the start of the pollen season to the first occurrence of a non-minimal symptom day (total nasal symptom score > 2).

(5) The number of days from the start of treatment to the first occurrence of a non-minimal symptom day (total nasal symptom score > 2).

(III) Supplementary Efficacy Variables [179:40]:

(1) Mean change from baseline ('baseline' defined as mean of the a.m. and p.m. symptom score from the subject diary for Visit 2 of the study plus the 3 prior consecutive days [179:35]) in total nasal symptom scores during the ragweed season, as obtained from subject diaries (a.m. and p.m. combined) for: days 1-15, (with further separation into days 1-7 and days 8-15), days 16-30, days 31-45, days 46-61, and the endpoint visit.

(2) Mean change from baseline ('baseline' defined as mean of the a.m. and p.m. symptom score from the subject diary for day 1/Visit 2 of the study plus the 3 prior consecutive days [179:35]) in total symptom scores during the ragweed season, as obtained from subject diaries (a.m. and p.m. combined) for: days 1-15 (with further separation into days 1-7 and days 8-15), days 16-30, days 31-45, days 46-61, and the endpoint visit.

(3) Mean change from baseline ('baseline' defined as mean of the a.m. and p.m. symptom score from the subject diary for day 1/Visit 2 of the study plus the 3 prior consecutive days [179:35]) in total non-nasal symptom scores during the ragweed season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.

(4) Mean change from baseline ('baseline' defined as mean of the a.m. and p.m. symptom score from the subject diary for day 1/Visit 2 of the study plus the 3 prior consecutive days [179:35]) in individual nasal symptom scores during the ragweed season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.

(5) Mean change from baseline ('baseline' defined as mean of the a.m. and p.m. symptom score from the subject diary for day 1/Visit 2 of the study plus the 3 prior consecutive days [179:35]) in individual non-nasal symptom scores during the ragweed season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.

(6) All total (total SAR, total nasal, total non-nasal) and individual symptom scores, as determined by the physician (physician evaluations).

(7) The proportion of minimal symptom days (total nasal symptom score ≤ 2) during the prophylaxis period.

(8) The proportion of days during the prophylaxis period when the total nasal symptom score=0 (i.e. proportion of symptom-free days).

(9) The proportion of days during the entire study when the total nasal symptom score=0 (i.e. proportion of symptom-free days).

Reviewer's Note: In evaluating the supplementary efficacy variables listed above, data for the prophylaxis period in the intent-to-treat population was not provided in the NDA submission (efficacy evaluable population provided) but was generated by Dr. Jim Gebert (Biostatistics, FDA Pulmonary Division, HFD-570) from primary SAS data files provided by the sponsor. Thus, for all supplementary efficacy variables, day 1 of the study refers to the first day or day 1 of the ragweed season.

Furthermore, the proportion of minimal symptom days during the prophylaxis period was not identified in the study protocol, but was chosen for post-hoc analysis to determine how accurately the pollen season was defined. If the pollen season was defined accurately, little difference between the study medications and placebo should have been observed during the prophylaxis period, but larger differences should have been observed during the pollen season.

8.9.3.3. STATISTICAL ANALYSIS [182:872-875]:

A sample size of 108 valid subjects per treatment group or 324 valid

subjects total was calculated to detect a treatment difference of approximately 0.45 units with respect to the primary efficacy variable between the mometasone treatment group and placebo with a power of 90% at an α=0.05 (2-tailed). That is, with an estimated pooled standard deviation of 35%, differences of approximately 16% or more in the proportion of minimal symptom days would be detectable with a power of 90%.

Efficacy and safety analyses for this study were based on the following two subject populations:

(1) Efficacy evaluable subjects-randomized subjects who met eligibility criteria and completed at least 1 valid post-baseline visit. The sponsor's primary efficacy analysis was based on this population.

(2) Intent-to-Treat (ITT) Population- all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline evaluation. The sponsor's confirmatory efficacy analyses and all summaries of safety data were based on this population.

The primary efficacy variable was analyzed for all efficacy evaluable and intent-to-treat subjects (pooled across all centers) using a two-way analysis of variance (ANOVA) which extracted sources of variation due to treatment, center, and treatment by center interaction. Treatment imbalances regarding baseline and demographic variables were handled by including these variables as a covariate in the model. The primary efficacy comparison of mometasone vs. placebo was then based on the least squares (LS) means from the ANOVA using a 5% two-sided significance level. The beclomethasone group was included only to help validate the efficacy study with reference to a currently marketed nasal corticosteroid. No adjustment for multiple comparisons was made using this primary efficacy comparison.

Analysis of secondary efficacy variables (1), (4), and (5) listed above and all supplementary efficacy variables was performed using the same two-way ANOVA described above for the primary efficacy variable. For variables (2) and (3) listed above, a survival analysis based on the log-rank test (SAS LIFETEST) was performed using efficacy evaluable subjects only. The presence or absence of symptoms within the first week after the start of the ragweed season, and the number of days when the total nasal symptom score was zero, was analyzed using logistic regression. Again, treatment imbalances regarding baseline and demographic variables were handled by including the relevant variable as a covariate either in an analysis of covariance, in the Cox proportional hazards, or in the logistic regression model.

For both the efficacy population and the intent-to-treat population comparability of treatment groups at baseline was assessed by comparing the three treatment groups with respect to demographic and disease characteristics (gender, age, race, weight, and disease condition). Continuous variables (age, weight, duration of disease condition, and duration of current episode) were analyzed by a

two-way analysis of variance (ANOVA) which extracted sources of variation due to treatment and center (SAS GLM). Discrete variables (gender, history of asthma, and presence or absence of perennial rhinitis) were analyzed by categorical linear models (SAS CATMOD), race was analyzed by Fisher's exact test for Caucasian vs. non-Caucasian subjects.

Reviewer's Note: For the purposes of efficacy and safety review of this and all studies in this submission, the intent-to-treat population was utilized rather than the sponsor's efficacy evaluable population (except in analyses where ITT population data was not available and not generated from SAS datafiles). Furthermore, the treatment by center interaction for the primary efficacy variable in this study was significant (p=0.02). The mometasone treatment group was numerically favored over placebo at all 9 study centers. This magnitude of difference varied from < 5% (2 centers) to 5-10% (2 centers) and even to >15% (5 centers). At all but 2 centers, beclomethasone was numerically favored over placebo, although the treatment differences were smaller than those seen in the mometasone treatment group. The treatment by center interaction was quantitative rather than qualitative and was felt by the principal investigator to be reasonably consistent, thus allowing combining of data across centers to provide an overall estimate and statistical assessment of the treatment differences.

8.9.4. RESULTS:

8.9.4.1. SUBJECT DEMOGRAPHICS:

(A) A total of 349 subjects were randomized into the study, with 2 subjects having no follow-up visits; hence being excluded from all analyses (safety and efficacy). Thus, 347 subjects were evaluated for safety (intent-to-treat population). An additional 17 subjects were excluded from the efficacy analysis, resulting in 330 subjects evaluated for efficacy. The distribution of subject populations is summarized in Table II. below:

Table II: Distribution of Subject Populations [179:44]

	Mometasone (SCH 32088)	Beclomethasone (BDP)	Placebo	Total
Efficacy Population	114	112	104	330
Safety Population (ITT)	116 (1 subject had no follow-up)	116	115 (1 subject had no follow-up)	347
Total # Randomized	117	116	116	349

(B) Pooled demographic data with regard to subject characteristics in the safety population (ITT) is summarized in Table III. below [179:46].

Table III: Subject Demographics (Protocol C93-215): Intent-to-Treat Population

	MFNS (n=116)	BDP (n=116)	Placebo (n=116)	Overall Treatment P-Value[a]
Age (years)				
Mean	35.6	33.2	33.7	0.26
Median	34.5	33.5	34	
Range (Min-Max)	12-69	12-60	13-62	
Sex				
Female	63	61	62	0.29
Male	53	55	53	
Race				
White	113	109	105	0.14
Black	2	3	6	
Hispanic	0	2	3	
Other	1	2	1	
Weight (lbs)				
Mean	168.4	165.6	174.5	0.19
Median	165	160	170	
Range (Min-Max)	85-350	98-272	109-296	
Duration of Condition (Years)				
Mean	19.0	19.2	19.4	0.99
Median	19.0	15.5	19.0	
Range (Min-Max)	2-62	2-61	2-60	

MFNS=Mometasone
BDP=Beclomethasone

Reviewer's Note: No statistically significant differences were noted among the treatment groups regarding any of the demographic or clinical characteristics. The mometasone treatment group had a numerically greater number of female subjects than the other two treatment groups. Also of

note, the mean weight of subjects comprising the placebo group (174.5 lbs.) was higher than that of the two active control groups (168.4 lbs., mometasone group and 165.5 lbs., beclomethasone group). As noted in the SAR studies, the majority of subjects in the three treatment groups for this prophylaxis SAR study were Caucasian (91-97% range).

(C) Subject Distribution by Disease Severity at baseline in the Intent-to-Treat Population [179:223]:

A stratification of subjects by disease severity was not performed in this study by SAR symptom categories of mild, moderate, and severe disease (as performed in the pivotal SAR trial C93-013). Nonetheless, comparison of baseline total nasal symptom scores (a.m. and p.m. combined) for the three treatment groups indicated comparable severity of total nasal symptom scores with a mean score of 0.3 for the mometasone treatment group and 0.4 for both the beclomethasone and placebo groups, respectively [180:355]. A comparison of baseline total symptom scores (a.m. and p.m. combined) for the three treatment groups also indicated comparable severity of total symptom scores between the three groups with a mean score of 0.5 for the mometasone treatment group and 0.6 for both the beclomethasone and placebo groups, respectively [180:351]. No statistically significant differences in total nasal and total symptom scores were noted between any of the three treatment groups at baseline.

(D) Subject Discontinuation

A total of 37 subjects (5 treated with Mometasone, 13 treated with Beclomethasone, 19 treated with placebo) discontinued the study prior to scheduled completion. This data is summarized in Table IV. [171:43].

Table IV: Number and Percentage of Randomized Subjects Who Completed Treatment and Number/(%) Who Discontinued the Study with Reasons for Discontinuation

	TREATMENT GROUP			
	Mometasone (n=117)[1]	Beclomethasone (n=116)	Placebo (n=116)	Total (n=349)
Number (%) Completed	110 (96%)	103 (89%)	97 (84%)	312 (89%)
Reason for Discontinuation				
–Adverse event	1 (1%)	5 (4%)	4 (3%)	10 (3%)
–Treatment Failure	2 (2%)	1 (1%)	8 (7%)	4 (1%)
–Noncompliance with Protocol	0	4 (3%)	1 (1%)	5 (1%)
–Lost to follow-up	0	0	1 (1%)	1 (<1%)
–Did not wish to continue	1 (1%)	3 (3%)	3 (3%)	7 (2%)
–Did not meet protocol eligibility	1 (1%)	0	2 (2%)	3 (1%)
TOTAL # (%) DISCONTINUED	5 (4%)	13 (11%)	19 (16%)	37 (11%)

[1] n=number of randomized subjects at the time of study initiation

Reviewer's Note: With the exception of the mometasone treatment group, > 10 % of subjects discontinued treatment in the other two treatment arms. Because of these relatively high discontinuation rates (especially for the placebo group), the overall percentage of subjects discontinuing treatment for the entire study population was 11%.

(E) Subject Validity

A total of 22 subjects (8 treated with mometasone, 9 treated with beclomethasone, and 5 treated with placebo) valid for efficacy had data invalidated for some visits. These subjects and the reasons for invalidation are summarized in Table 9 of the NDA submission [179:45, 48, 155-162]. Review of reasons for subject invalidation consisted of concurrent illness, non-compliance with medication dosing, and unacceptable concomitant medication use and were overall appropriate reasons for subject exclusion.

(F) Pollen Counts [179:165-204]

A review of ragweed pollen counts across the 9 centers participating in this

study revealed an abrupt onset and offset of the pollen season in 7 of the 9 centers with significant elevation of the ragweed count, the exception being study centers C93-215-05 and -07 where mild ragweed pollen seasons were evident [179:179, 181]. Interestingly, the corresponding symptom scores at these 2 study sites did not differ significantly from the other 7 study sites [179:247, 249]. Overall, the onset of the ragweed pollen season occurred > 21 days for 8 of the 9 study centers with the majority of study centers having pollen season onset occurring at approximately day 27-30. Only one center (C93-215-09) had onset of its pollen season at day 16 post-initiation of study medication [179:173]. Hence, the mean duration of the prophylactic period for this study across all centers combined was 26 days (i.e. similar in duration to the anticipated study prophylaxis period).

8.9.4.2. EFFICACY ENDPOINT OUTCOMES:

(1) Primary Efficacy Variable (ITT Population) [179:223]:

Analysis of the mean proportion of minimal symptom days during the ragweed pollen season was based on the intent-to-treat population for the ragweed season interval (n=115 for mometasone, n=112 for beclomethasone, and n=109 for placebo; which was decreased from the ITT population distribution during the prophylaxis period: n=116 for mometasone, n=116 for beclomethasone, and n=115 for placebo, due to subject drop-outs) [179:223]. For this primary efficacy endpoint both active treatment groups--mometasone and beclomethasone, were significantly more effective than placebo ($p<.01$) [179:223]. The mometasone treatment group showed a numerical advantage (proportion of minimal symptom days=0.84 or 84%) over the beclomethasone treatment group (proportion of minimal symptom days=0.79 or 79%), although these differences were not statistically significant ($p=0.17$). Because of study design and underpowering to detect a difference between these 2 groups, no conclusion can be made regarding the true meaning of a p-value of 0.17 in this context. A summary of the primary efficacy variable results for all 3 treatment groups is provided in Table V.

Reviewer's Note: Of note, the primary efficacy variable results for the efficacy evaluable population was approximately the same as that for the intent-to-treat population [179:51, 207]. For certain secondary and supplementary endpoints, intent-to-treat population data was not provided by the sponsor. In these situations, given the similarity of the efficacy-evaluable population to the ITT, the efficacy evaluable population was substituted for data analysis.

Of note, as discussed under 'Supplementary Efficacy Variables' (Table V.), the mometasone treatment group was noted to have a numerical advantage in increasing the number of minimal symptom days during the prophylaxis period, as compared with placebo, which was statistically significant ($p=0.01$) [179:223] and which could impact on efficacy findings during the ragweed

period. While the prophylaxis period could not be treated as a covariate for a post-hoc analysis of the primary efficacy variable because treatment *periods* cannot used statistically as covariates (per discussion with Dr. Jim Gebert, Biostatistics); subtraction of total nasal symptom scores for the prophylaxis period from the total nasal symptom scores for the ragweed season did not change the trend in values for the mometasone treatment group compared with the placebo group, thus supporting a numerical advantage of mometasone in reducing total nasal symptom scores over placebo. Because this was a post-hoc analysis, p-values were not assigned for this comparison.

Because of the definition of the primary efficacy variable as being a composite of a.m. and p.m. subject diary total nasal symptom scores, separate analysis of a.m. and p.m. scores was not possible, and more importantly, not logical for this composite study parameter. Subset analysis by age, gender, and race for the primary efficacy variable in the efficacy evaluable population [179:226] overall revealed similar efficacy results for the 3 age subgroups (12-17, 18-64, >64 years of age), and in males vs. females. Because the number of subjects in the age 12-17 years or age >64 years subgroups were small, no meaningful conclusions regarding efficacy could be made for these populations. Regarding race, the majority of subjects for this study were Caucasian and efficacy results observed in this racial subgroup were similar to the overall population.

A review of the treatment-by-center interaction for the 9 centers indicates that for the efficacy evaluable population (ITT population data not available in the NDA submission for further analysis), while each of the 9 centers had approximately the same number of subjects enrolled, the statistical significance of the primary efficacy variable was primarily influenced by 2 of the 9 study centers: center C93-215-03 and C93-215-06 [179:211, 214]. Of note, the other 7 study centers did not demonstrate a statistically significant effect of the mometasone treatment group over placebo in increasing the proportion of 'minimal nasal symptom days' [179:207-217], however a numerically superior difference over placebo in increasing the proportion of 'minimal symptom days' was demonstrable at most study centers for the mometasone treatment group. An evaluation of the proportion of 'minimal nasal symptom days' in subjects of study center C93-215-09, where the SAR prophylaxis period was approximately 16 days, did not show a significant difference in the two active treatment groups, compared to placebo, however the study was not designed to compare individual study sites.

Reviewer's Note: One fundamental study design flaw for study C93-215 which limits assessment of how great a difference prophylaxis really makes in decreasing the symptoms of SAR compared with mometasone use at the time of allergy season onset (and which would affect all efficacy variables) is the lack of an active comparator mometasone group where subjects did not receive prophylaxis prior to the onset of the pollen season but received mometasone with the onset of the ragweed season. Presence of such a study

arm would allow comparative analysis between use of mometasone at the start of the pollen season vs. prophylaxis with mometasone prior to the onset of the pollen season in decreasing symptoms of SAR.

Alternatively, one might utilize a cross-study comparison of the two pivotal SAR studies (C93-013 and C93-215) to compare the prophylaxis mometasone arm of study C93-215 with the non-prophylaxis mometasone arm of C93-013. Because the total nasal symptom scores at the time of the allergy season were so markedly different for these 2 studies with significantly higher total nasal symptom scores in all treatment arms of study C93-013 that cannot be explained by higher pollen counts for the allergy season of study C93-013, it is difficult if not altogether impossible to compare these 2 study populations.

(II) Secondary Efficacy Variables (ITT population except where otherwise noted):

(1) **The proportion of minimal symptom days (total nasal symptom score ≤ 2) during the first week of the pollen season** [179:219] (Table V., Efficacy evaluable population, ITT population data not available):

A review of the proportion of subjects with minimal symptom days during the first week of the ragweed pollen season confirmed findings seen in the primary efficacy variable (as pooled across all study centers), namely that both active treatment groups (mometasone and beclomethasone) had a significantly greater proportion of minimal symptom days (92% and 89%, respectively, $p < .01$) than the placebo group (79%). Again, the findings for the 2 active treatment groups were not statistically significantly different from one another ($p=0.23$), although the mometasone treatment group had a numerical advantage of a greater proportion of minimal symptom days than the beclomethasone treatment group.

(2) **The proportion of minimal symptom days (total nasal symptom score ≤ 2) for the entire treatment period** (ITT Population) [179:223] (Table V.):

A review of the proportion of subjects with minimal symptom days in each of the 3 treatment groups during the entire treatment period (entire study) was very similar to that of the first week of the pollen season. The 2 active treatment groups had a significantly greater proportion of minimal symptom days (89% and 85%, respectively, $p <.01$) than the placebo group (75%) but did not statistically differ significantly from one another ($p=0.15$). Interestingly, during the portion of the study prior to the ragweed season (prophylaxis period, refer to supplementary efficacy variable, Table V), subjects treated with mometasone recorded minimal symptoms for 95% of days, compared to 93% of days in the beclomethasone group and 88% of days in the placebo group, respectively [179:223]. As

compared with placebo, these differences were statistically significant for the mometasone treatment group (p=.01) and marginally statistically significant for the beclomethasone treatment group (p=.06). For all 3 treatment groups, the proportion of minimal symptom days during the prophylaxis period was slightly higher than during the onset of the ragweed season.

In summary, the two active treatments were more effective in decreasing total nasal symptoms of SAR than placebo from both the start of the pollen season and from the start of treatment to study completion. While decreased relative to placebo, the onset of total nasal symptoms of SAR was not completely abrogated with mometasone use.

(3) **The proportion of days during the pollen season when the total nasal symptom score =0** [179:221] (the proportion of symptom-free days, efficacy evaluable population, ITT population data not available, Table VI.):

Analysis of the secondary efficacy variable (the proportion--the number of days during the pollen season when subjects experienced no nasal symptoms/total number of days in the pollen season) for the 3 treatment groups is compared with the supplementary efficacy variables of the proportion of days with total nasal symptoms of SAR=0 during the prophylaxis period and the entire treatment period and is presented in Table VI. During the prophylaxis period, 67% of subjects in the mometasone treatment group, 59% of subjects in the beclomethasone treatment group, and 53% of subjects in the placebo group recorded no nasal symptoms. Only the difference in proportions between the mometasone and placebo group was statistically significant during the prophylaxis period ($p < .01$). During the pollen season, subjects treated with mometasone recorded no symptoms for 46% of days, compared with 40% of beclomethasone subjects, and 26% of placebo group subjects. The two active treatments were more effective in decreasing total nasal SAR symptoms than placebo ($p < .01$). For the entire treatment period, subjects treated with mometasone recorded no symptoms for 55% of days, compared with 39% of beclomethasone subjects, and 34% of placebo group subjects. Once again, the two active treatments were more effective in decreasing total nasal SAR symptoms than placebo for the entire study duration ($p < .01$) but did not completely abrogate or prevent onset of nasal SAR symptoms.

(4) **The number of days from the start of the pollen season to the first occurrence of a non-minimal symptom day** [182:1044-1055] (total nasal symptom score > 2, efficacy evaluable population, ITT population data not available).

An analysis of the number of days from the start of the pollen season to the first occurrence of a symptomatic day (i.e. total nasal symptom score > 2) for the three study treatments showed that the median number of days to the first

symptomatic day was 26.5 days for subjects in the mometasone treatment group, 27.0 days for the beclomethasone treatment group, and 10.5 days for the placebo treatment group. Comparisons between both the mometasone and beclomethasone treatment group with the placebo group using the Wilcoxon test and log rank test showed a statistical difference between the two active treatments and placebo with a slight numerical advantage of the mometasone treatment group over the beclomethasone treatment group with respect to time to delaying onset of 'symptomatic days' ($p < .01$) [182:1045].

Using these survival analysis methods, a Kaplan-Meier plot of time from the start of treatment to the first occurrence of a symptomatic day was generated [179:54, 182: 1045] and is presented in Figure 1.

(5) **The number of days from the start of treatment to the first occurrence of a non-minimal symptom day** (total nasal symptom score > 2, efficacy evaluable population, ITT population data not available).

An analysis of the number of days from the start of treatment (i.e. Baseline visit or Visit 2) to the first occurrence of a symptomatic day for the three study treatments showed that the median number of days to the first symptomatic day was 48.5 days for subjects in the mometasone treatment group, 43.0 days for the beclomethasone treatment group, and 30.0 days for the placebo group ($p < .01$) [182:1057]. Again, pairwise comparisons of mometasone vs. placebo and beclomethasone vs. placebo showed both active treatments to be statistically significantly different from placebo, with a numerically greater time to onset of 'symptomatic days' with mometasone treatment than beclomethasone treatment.

Using survival analysis methods, a Kaplan-Meier plot of time from the start of treatment to the first occurrence of a symptomatic day was generated [182: 1057] and is presented in Figure 2.

APPEARS THIS WAY

Table V.

Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Prophylactic Treatment of SAR: Primary and Secondary Efficacy Variables--Proportion of Days with Total Nasal Symptom Score ≤ 2

Intent-to-Treat (ITT) POPULATION* [179 219, 223]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARI A-B	A-C	
EVALUATION	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-
Primary Efficacy Variable: POLLEN (RAGWEED) SEASON																
-am & pm nasal	115	0.84	0.25	112	0 79	0.29	109	0.63	0.36	0.29	<.01	<.01	0.02	0.17	<.01	
Secondary Efficacy Variable: FIRST WEEK OF POLLEN SEASON (*Efficacy population)																
am & pm nasal	114	0 92	0 21	112	0 89	0 26	104	0 79	0 31	0 25	< 01	< 01	0 01	0 23	< 01	
Secondary Efficacy Variable: ENTIRE STUDY																
- am & pm nasal	116	0 89	0 19	116	0 85	0 22	115	0 75	0.26	0 22	< 01	< 01	0.19	0 15	< 01	
Supplementary Efficacy Variable: PROPHYLAXIS PERIOD (Prior to Pollen Season)																
- am & pm nasal	116	0 95	0 16	116	0 93	0 17	115	0 88	0.23	0 19	0.02	<.01	0.9	0 35	0 01	

* Exception is the First Week of the Pollen (Ragweed) Season where the Efficacy Population was analyzed.
SD= Standard Deviation T X I = Treatment by Investigator interaction
# P Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

POLLEN (RAGWEED) SEASON= Pooled diary data from the start of the pollen (ragweed) season to study completion.
ENTIRE STUDY=Pooled diary data from the start of the treatment to study completion.
PROPHYLAXIS PERIOD=Pooled diary data from the start of the treatment to the pollen (ragweed) season.

Table VI.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Prophylactic Treatment of SAR:
Secondary Efficacy Variable:
Proportion of 'Symptom-Free' Days (i.e. Proportion of Days with Total Nasal Symptom Score= 0)
Efficacy Evaluable POPULATION [179,221]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS A-B	A-C	B-
EVALUATION	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-
Secondary Efficacy Variable: POLLEN (RAGWEED) SEASON																
--am & pm nasal	114	0.46	0.34	112	0.40	0.36	104	0.26	0.32	0.33	<.01	<.01	0.41	0.21	<.01	
Supplementary Efficacy Variable: ENTIRE STUDY																
--am & pm nasal	114	0.55	0.32	112	0.48	0.34	104	0.37	0.28	0.30	<.01	<.01	0.71	0.14	<.01	
Supplementary Efficacy Variable: PROPHYLAXIS PERIOD (Prior to Pollen Season)																
--am & pm nasal	114	0.67	0.34	112	0.59	0.39	104	0.53	0.35	0.32	0.01	<.01	0.5	0.09	<.01	

SD= Standard Deviation T X I = Treatment by Investigator interaction
# P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

POLLEN (RAGWEED) SEASON= Pooled diary data from the start of the pollen (ragweed) season to study completion.
ENTIRE STUDY=Pooled diary data from the start of the treatment to study completion.
PROPHYLAXIS PERIOD=Pooled diary data from the start of the treatment to the pollen (ragweed) season.

Figure 1. [179:54, 182:1045]

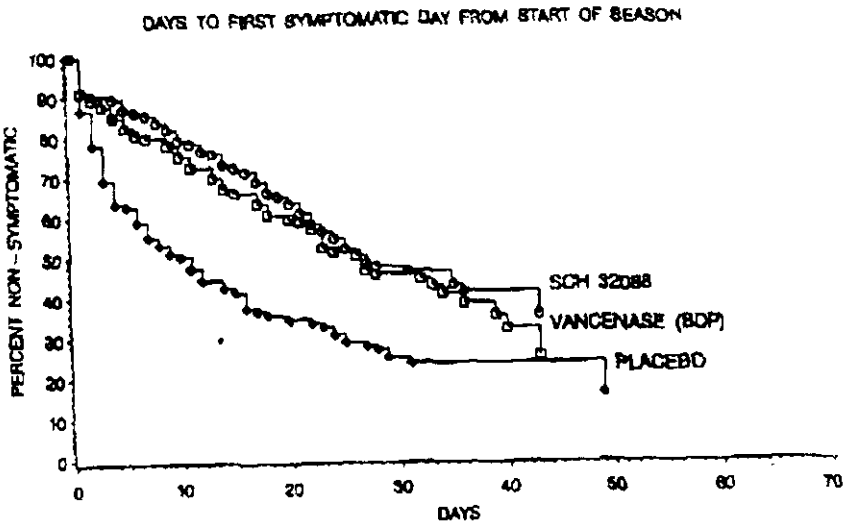
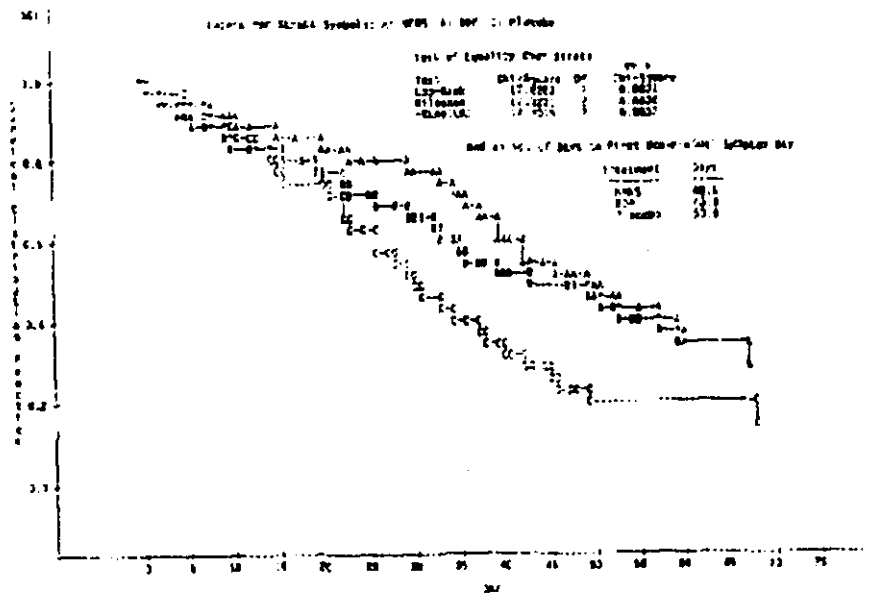


Figure 2. [182:1057]



(III) Supplementary Efficacy Variables:

(1) **Mean change from baseline in subject evaluated total nasal symptom scores during the ragweed season (a.m. and p.m. combined), for days 1-15 (with days 1-7 and days 8-15 analyzed separately), days 16-30, days 31-45, days 46-61, days 61-71, and the endpoint visit (ITT population, Tables VII.-XI., SAS Datafiles). Refer to Attachment 1 for line listings.**

A review of the combined (a.m. and p.m. combined) mean change in the **total nasal symptom** scores as compiled from the SAS datafiles for the ITT population for all time intervals of study C93-215, indicates that at all 15 day time intervals after the start of the pollen season, with the exception of the day 31-45 and day 61-71 time intervals (which because of study design and a small subject number at these latter two time points, were non-estimable (N/E)), the mometasone treatment group demonstrated a statistically less significant increase in total nasal symptoms than the placebo treatment group ($p < .01$). Of note, the mometasone treatment group also demonstrated a statistically less significant increase in total nasal symptoms than the placebo treatment group (total nasal symptom score mometasone group=0.4, total nasal symptom score placebo group=0.7, $p<.01$; mean change in nasal score, mometasone group=0.1 (66%), mean change in nasal score, placebo group=0.3 (97.9%), $p=0.04$) during the prophylaxis period (Table VII.). The reason for this discrepancy is unclear, and although the 3 treatment populations were noted to have a similar severity of seasonal allergic rhinitis symptoms at baseline, the difference of the total nasal symptom scores between the mometasone group and placebo group was marginally statistically significant ($p=0.07$). Whether or not some subjects had underlying perennial rhinitis despite careful exclusion criteria to avoid enrolling subjects with active or anticipated active perennial rhinitis is also unclear. In summary, the mean scores increased in all treatment groups both before (the prophylaxis period) and after onset of the pollen season, however, for all 3 treatment groups, total nasal symptom scores were significantly greater after the onset of the pollen season.

Comparing the two active treatments, while not statistically significant, the mometasone treatment group demonstrated a numerically smaller increase in total nasal symptoms than the beclomethasone treatment group at all 15 day time intervals (Tables VII., VIII., IX., X., and XI.). For all 3 treatment groups and for all time periods, the standard deviation in the percent change in total nasal symptom scores was high, attesting to the high variability in subject nasal symptom scores.

Regarding the day 1-15 interval, the percent increase in total nasal symptoms in the mometasone treatment group was numerically smaller (total nasal symptom score=0.7, mean change in total nasal score=0.4 (86.6%) than the beclomethasone treatment group (total nasal symptom score=1.0, mean change in total nasal score=0.6 (216%), or the placebo group (total nasal symptom

score=2.0, mean change in total nasal score=1.6 (367%). In other words, mometasone pre-treated subjects had less severe worsening of SAR allergic symptoms during onset of the allergy season than did the other 2 treatment groups which was statistically significantly less severe when compared with placebo subjects but not when compared with beclomethasone subjects. Evaluation of subject diary scores for the day 1-15 interval separately for the a.m. and p.m. in order to assess duration of drug effect, failed to show a significant difference in raw total nasal symptom scores for either of the two active treatments but did show a greater change (% increase) in symptom scores during the p.m. in the mometasone treatment group (also noted for the beclomethasone group). These findings suggest that during the active ragweed season, no significant waning of effect of mometasone in decreasing SAR symptoms appears evident by 24 hours (mometasone group: 0.8=a.m. score (47.9% change) vs. 0.7=p.m. score (68% change). These results are summarized in Table VIII. of the review.

A separation of the day 1-15 interval into weekly intervals of day 1-7 and day 8-15 is presented in Tables IX. and X. of the review. Notable by week 2 of the pollen season (day 8-15), as compared with week 1, is a continued increase in total nasal symptoms for all 3 treatment groups. Nonetheless, the total nasal symptom score and mean change in total nasal symptom score for the mometasone treatment group was lower than the other 2 treatment groups (mometasone group: total nasal symptom score=0.9 and mean change in total nasal symptom score=0.5 (+125%)), and was statistically significantly lower than the placebo group. For the mometasone group per se, no significant difference in raw total nasal symptom scores was noted for the a.m. vs. p.m. scores during week 2 of treatment, although the p.m. score showed a slight increase in the percent change (week 2: a.m.= +75.4%, p.m.= +97.9% change).

Analysis of the day 16-30 interval during the ragweed season continued to demonstrate the greater efficacy of mometasone treatment in decreasing subject evaluated total nasal symptoms, as compared with the beclomethasone treatment group and placebo group, ((mometasone group: total nasal symptom score=1.2 and mean change in total nasal symptom score=0.8 (+184%), beclomethasone group (total nasal symptom score=1.4 and mean change in total nasal symptom score=1.0 (+225%), and placebo group, (total nasal symptom score=2.4 and mean change in total nasal symptom score=1.9 (+442%), $p < 0.01$ for mometasone vs. placebo and mometasone vs. beclomethasone for both raw total nasal symptom scores and the mean change in total nasal symptom score)).

Further analysis for days 31-45 and days 46-61 of the ragweed season required accounting for subject dropout at these later study timepoints, hence making it impossible to comment on the statistical significance of these findings. Nonetheless, the total nasal symptom scores for these two time intervals support conclusions for the day 1-15 and day 16-30 time points; namely that the mometasone treatment group had a smaller increase in total nasal symptoms as the ragweed season continued than either the beclomethasone treatment group or placebo (mometasone group: day 31-45: total nasal symptom score=1.4, mean

change in total nasal symptom score=1.0 (+173% increase), day 46-61: total nasal symptom score=1.4, mean change in total nasal symptom score=1.0 (+281%)). Total nasal symptom scores for the endpoint visit for all 3 treatment groups were similar to that of the day 16-30 interval. Of note, the total nasal symptom scores, the mean change in total nasal symptom scores, and the percent increase in scores did not uniformly increase for all treatment groups (namely, the mometasone group and placebo group) as the ragweed season advanced. The clinical implications of these findings are unclear but given the large standard deviation in subject symptom scores (refer to Table XI.), these findings most likely reflect large inter-subject and possibly intra-subject variability of symptom recording. A summary of the findings for these timepoints is provided in Table XI.

Reviewer's Note: As noted for the SAR studies of this NDA submission, the a.m. and p.m. scoring system represents an integration of the subject's symptoms over the previous 12 hours and does not represent a 'snap-shot' of the subject's clinical status at the particular time of symptom recording.

The majority of subjects in this study received mometasone prophylaxis for 4 weeks, however, of those who did not (primarily subjects at study sites -02 and -09, who received from 14-21 days of pre-treatment with mometasone (a total of 30 subjects) or one of the other treatments), shorter duration of pre-treatment with mometasone did not appear to change the trend in decreasing total nasal symptom scores (statistical comparison was not performed on these subjects because of low subject number and underpowering) [Response to FDA Request on Prophylaxis Studies, Schering Plough, Inc., 05/21/97, p. 58-84].

Furthermore, noted throughout this study for all supplementary efficacy variables was a significant decrease in study subject numbers (visit n values) for the % change in subject number (=n) for all subject evaluated symptom scores as the study progressed (total SAR, total nasal, total non-nasal, and individual nasal and non-nasal symptom scores). This decrease in subject number (=n) represented subjects who had 0 as a given symptom score with a resultant inability to compute the % change based on a denominator of 0. Acknowledging that the primary and secondary efficacy variables support the efficacy of mometasone in the prophylaxis of subjects with SAR, nonetheless the lack of incorporation of these subjects as data points into the supplementary efficacy variable analysis represents a study flaw which does not address symptom scores for all efficacy evaluable subjects.

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Table VII.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Subject Evaluated Total Nasal Symptom Scores
Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION, [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS A-B	A-C	B-
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	
BASELINE																
--am & pm nasal	116	0.3	0.5	115	0.4	0.5	115	0.4	0.5	0.4	0.19	<.01	0.48	0.41	0.07	
--am nasal	116	0.4	0.5	115	0.5	0.6	115	0.5	0.6	0.5	0.49	< 01	0.34	0.39	0 25	
--pm nasal	116	0.3	0.5	115	0.3	0.4	115	0.4	0.6	0.6	0.08	< 01	0.67	0.53	0.03	
PROPHYLAXIS PERIOD																
--am & pm nasal																
RAW	116	0.4	0.7	115	0.6	1.0	115	0.7	0.9	0.8	0.01	< .01	0.66	0.13	< .01	
CHG	116	0.1	0.6	115	0.2	1.0	115	0.3	0.8	0.6	0.12	< .01	0.32	0.29	0.04	
%CHG	66	14.0	127	65	56.6	206	65	97.9	234							
-am nasal																
RAW	116	0 5	0 8	115	0 6	1 0	115	0 8	0 9	0 8	0.02	< .01	0.56	0.16	< .01	
CHG	116	0 1	0 7	115	0 2	1 1	115	0 3	0 9	0.8	0.09	< .01	0.2	0.37	0 03	
%CHG	63	2 4	124	57	0 5	140	60	106	272							
pm nasal																
RAW	116	0 4	0 7	115	0 5	1 0	115	0 7	0 9	0 8	0 01	< .01	0.7	0.13	< .01	
CHG	116	0 1	0 6	115	0 2	1 0	115	0 3	0 8	0 8	0 23	0 03	0 47	0 26	0 09	
%CHG	43	1 1	135	43	54 9	161	52	87 0	227							

SD= Standard Deviation CHG=Change T X I = Treatment by Investigator interaction
# P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

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Table VIII.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Subject Evaluated Total Nasal Symptom Scores
Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS(A-B A-C		
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-(
BASELINE																
--am & pm nasal	116	0.3	0.5	115	0.4	0.5	115	0.4	0.5	0.4	0.19	<.01	0.48	0.41	0.07	
--am nasal	116	0.4	0.5	115	0.5	0.6	115	0.5	0.6	0.5	0.49	<.01	0.34	0.39	0.25	
--pm nasal	116	0.3	0.5	115	0.3	0.4	115	0.4	0.6	0.6	0.08	<.01	0.67	0.53	0.03	
DAYS 1-15 POLLEN (RAGWEED) SEASON																
--am & pm nasal																
RAW	114	0.7	1.0	111	1.0	1.3	109	2.0	2.0	1.4	<.01	<.01	<.01	0.12	<.01	
CHG	114	0.4	0.9	111	0.6	1.4	109	1.6	2.0	1.4	<.01	<.01	<.01	0.2	<.01	
%CHG	65	86.6	237	63	216	432	59	367	713							
--am nasal																
RAW	114	0.8	1.0	111	1.0	1.4	109	2.0	2.0	1.4	<.01	<.01	0.01	0.16	<.01	
CHG	114	0.4	0.9	111	0.6	1.4	109	1.5	2.1	1.5	<.01	<.01	<.01	0.26	<.01	
%CHG	62	47.9	174	55	115	355	55	307	622							
pm nasal																
RAW	114	0.7	1.0	111	1.0	1.4	109	2.0	2.1	1.4	<.01	<.01	<.01	0.11	<.01	
CHG	114	0.4	1.0	111	0.7	1.4	109	1.6	2.1	1.5	<.01	0.01	<.01	0.17	<.01	
%CHG	42	68.0	203	42	168	382	47	282	511							

SD= Standard Deviation CHG=Change T X I = Treatment by investigator interaction
# P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table IX.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Weekly Analysis of the Subject Evaluated Total Nasal Symptom Score: Supplementary Efficacy Variable--WEEK 1
Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS A-B	A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-
BASELINE																
--am & pm nasal	116	0.3	0.5	115	0.4	0.5	115	0.4	0.5	0.4	0.19	<.01	0.48	0.41	0.07	
--am nasal	116	0.4	0.5	115	0.5	0.6	115	0.5	0.6	0.5	0.49	<.01	0.34	0.39	0.25	
--pm nasal	116	0.3	0.5	115	0.3	0.5	115	0.4	0.6	0.5	0.08	<.01	.67	0.53	0.03	
DAYS 1-7 POLLEN (RAGWEED) SEASON																
--am & pm nasal																
RAW	114	0.6	0.8	111	0.8	1.3	109	1.6	1.8	1.3	<.01	<.01	<.01	0.13	<.01	
CHG	114	0.2	0.8	111	0.4	1.3	109	1.2	1.9	1.3	<.01	<.01	<.01	0.19	<.01	
%CHG	65	42.9	197	63	173	3979	59	285	579							
--am nasal																
RAW	114	0.6	0.9	111	0.9	1.3	109	1.6	1.8	1.3	<.01	<.01	0.03	0.14	<.01	
CHG	114	0.2	0.8	111	0.4	1.3	109	1.1	1.9	1.4	<.01	<.01	.01	0.24	<.01	
%CHG	62	16.7	160	55	65.6	236	55	224	523							
--pm nasal																
RAW	114	0.5	0.8	111	0.8	1.3	109	1.6	1.9	1.3	<.01	<.01	.01	0.11	<.01	
CHG	114	0.3	0.8	111	0.5	1.3	109	1.2	2.0	1.3	<.01	<.01	<.01	0.11	<.01	
%CHG	42	34.6	183	42	117	329	47	232	513							

SD= Standard Deviation CHG=Change T X I = Treatment by Investigator interaction
# P Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table X.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Weekly Analysis of the Total Nasal Symptom Score: Supplementary Efficacy Variable--WEEK 2
Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS A-B	A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A C	B
BASELINE																
--am & pm nasal	116	0 3	0.5	115	0.4	0.5	115	0.4	0.5	0.4	0.19	<.01	0.48	0.41	0.07	
- am nasal	116	0 4	0 5	115	0 5	0 6	115	0 5	0.6	0.5	0.49	<.01	0.34	0.39	0.25	
--pm nasal	116	0 3	0 5	115	0 3	0 5	115	0 4	0.6	0.5	0 08	<.01	.67	0.53	0.03	
DAYS 8-15 POLLEN (RAGWEED) SEASON																
--am & pm nasal																
RAW	114	0.9	1.2	108	1.2	1.5	105	2.2	2.3	1.8	<.01	<.01	<.01	0.16	<.01	
CHG	114	0.5	1.2	111	0.4	1.3	109	1.2	1.9	1.3	<.01	<.01	<.01	0.25	<.01	
%CHG	65	125	291	61	264	547	59	443	885							
- am nasal																
RAW	114	0 9	1 3	108	1 1	1 5	105	2 2	2 2	1 6	<.01	<.01	<.01	0.25	<.01	
CHG	114	0 5	1 2	108	0 7	1 5	105	1 7	2 3	1 6	<.01	<.01	<.01	0.34	<.01	
%CHG	62	75 4	211	53	166	510	55	380	734							
pm nasal																
RAW	114	0 9	1 2	108	1 2	1 6	105	2 2	2 4	1 7	<.01	<.01	<.01	0.15	<.01	
CHG	114	0 6	1 3	108	0 8	1 7	105	1 8	2 5	1 7	<.01	<.01	<.01	0 2	<.01	
%CHG	42	97 9	243	40	231	542	47	327	545							

SD - Standard Deviation CHG=Change T X I = Treatment by Investigator interaction
P Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table XI.

Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Subject Evaluated Total Nasal Symptom Scores
Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS(		
														A-B	A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-(
BASELINE																
--am & pm nasal	116	0.3	0.5	115	0.4	0.5	115	0.4	0.5	0.4	0.19	<.01	0.48	0.41	0.07	
DAYS 16-30 POLLEN (RAGWEED) SEASON, am & pm nasal																
--am & pm nasal																
RAW	114	1.2	1.3	107	1.4	1.7	103	2.4	2.3	1.7	<.01	.003	0.04	0.21	<.01	
CHG	114	0.8	1.3	107	1.0	1.8	103	1.9	2.3	1.8	<.01	<.01	0.02	0.27	<.01	
%CHG	65	184	322	60	225	369	58	442	656							
DAYS 31-45 POLLEN (RAGWEED) SEASON, am & pm nasal																
RAW	76	1.4	2.0	67	1.7	2.2	61	2.4	2.3	2.2	< .01	0.54	0.54	N/E	N/E	N/
CHG	76	1.0	2.0	67	1.3	2.3	61	2.0	2.4	2.2	< .01	0.04	0.49	N/E	N/E	N/
%CHG	40	173	361	33	223	611	30	404	880							
DAYS 46-61 POLLEN (RAGWEED) SEASON, am & pm nasal																
RAW	18	1.4	1.5	14	2.0	2.8	13	1.8	1.9	2.2	0.69	0.83	0.7	0.5	N/E	N/
CHG	18	1.0	1.5	14	1.7	2.9	13	1.6	2.0	2.2	0.53	0.62	0.62	0.38	N/E	N/
%CHG	11	281	384	8	602	1267	4	118	281							
ENDPOINT VISIT POLLEN (RAGWEED) SEASON, am & pm nasal																
RAW	116	1.2	1.7	115	1.5	1.9	115	2.6	2.5	2.0	< .01	0.02	0.06	0.26	< .01	
CHG	116	0.9	1.7	115	1.1	2.0	115	2.1	2.5	2.0	< .01	< .01	0.06	0.35	< 01	
%CHG	66	184	344	65	256	573	65	507	906							

SD= St[illegible] Deviation CHG=Change T X I = Treatment by Investigator interaction *E=Non-estimable (due to small subject number)
# P-Va from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustm[illegible] verall α level).

(III) Supplementary Efficacy Variables-cont:

(2) **Mean change from baseline ('baseline' defined as mean of the a.m. and p.m. symptom score from the subject diary for day 1/Visit 2 of the study plus the 3 prior consecutive days [179:35]) in total symptom scores during the ragweed season, as obtained from subject diaries (a.m. and p.m. combined) for: days 1-15 (with further separation into days 1-7 and days 8-15), days 16-30, days 31-45, days 46-61, and the endpoint visit. (ITT population, Tables XII.-XVI.). Refer to Attachment 1 for line listings.**

A review of the combined (a.m. and p.m. combined) mean change in the **total (nasal plus non-nasal) subject evaluated symptom** scores using the ITT population compiled from SAS datafiles for all time intervals of study C93-215, indicates that for all 15 day time intervals from the onset of the pollen season, with the exception of the prophylaxis period and the day 31-45 and day 61-71 time intervals (which because of study design and a small subject number at these latter two time points, were non-estimable (NE)), the mometasone treatment group demonstrated a statistically less significant increase in total symptoms than the placebo treatment group ($p < .01$). As was noted for the supplementary efficacy variable of the total nasal symptom score, the mean total symptom scores increased (as compared to baseline) in all treatment groups both before (the prophylaxis period) and after onset of the pollen season, with higher mean symptom score values recorded after the onset of the pollen season (Table XIII.). Again noted for the total symptom score during the prophylaxis period, and as discussed previously for the total nasal symptom score (prophylaxis period) was the numerically slightly smaller total symptom score for mometasone treatment subjects, as compared with the active treatment group and the placebo group. For the comparison of mometasone vs. the placebo group, these raw scores were statistically significant ($p=0.03$) but the mean differences were not ($p=0.2$).

Comparing the two active treatments, while not statistically significant, the mometasone treatment group demonstrated a numerically smaller increase in total symptom scores than the beclomethasone treatment group at all 15 day time intervals (Tables XIII.- XVI.). Evaluation of the first 15 day interval on a weekly basis revealed a numerically smaller increase in total symptom scores in the mometasone treatment group for week 1 (days 1-7) but not week 2 (days 8-15) of treatment.

Regarding the day 1-15 interval, the total SAR symptom score values and percent increase in total symptoms for the mometasone treatment group was numerically smaller (total SAR score=1.3, mean change=0.8 (208%) than the beclomethasone treatment group (total SAR score=1.7, mean change=1.1 (327%), and statistically significantly smaller than the placebo group (total SAR score=3.0, mean change=2.4 (428%), $p<.01$). Evaluation of subject diary scores for the day 1-15 interval separately for the a.m. and p.m. (Table XIII.) in order to assess

duration of drug effect, failed to show a significant difference in raw total symptom scores for either of the two active treatments but did show a greater change (% increase) in symptom scores during the p.m. in the mometasone treatment group (also noted for the beclomethasone group). Similar findings were demonstrated during analysis of the a.m. and p.m. scores for total nasal symptoms and again suggest that during the active ragweed season, no significant waning of effect of mometasone in decreasing total SAR symptoms appears evident by 24 hours post-dosing (mometasone group: 0.8=a.m. score (125% change) vs. 0.9=p.m. (95.2% change).

Separation of the day 1-15 interval into weekly intervals of day 1-7 and day 8-15 is presented in Tables XIV. and XV. of the review. Notable by week 2 of the pollen season (day 8-15), as compared with week 1, was a continued increase in total symptoms (a.m. and p.m. combined) for the mometasone treatment group, but no consistent increase in total symptoms for the beclomethasone or placebo treatment group. The clinical implications of this study finding are unclear, especially given the large standard deviations for each treatment group.

The raw total symptom score and percent change in symptom score for the mometasone treatment group was lower than the beclomethasone and placebo treatment groups for the first week of the ragweed season (mometasone group; raw score=1.0, mean change=0.5, % change=102% vs. the beclomethasone group; raw score=0.8, mean change=0.8, % change=267, and vs. the placebo group; raw score=2.3, mean change=1.8, % change=331; $p<.01$ for the mometasone group vs. placebo (Table XIV)). The raw total symptom score but not the percent change in symptom score for the mometasone treatment group was likewise lower than the beclomethasone and placebo treatment groups during the second week of the ragweed season ($p<.01$ for the mometasone group vs. placebo).

Analysis of the day 16-30 interval during the ragweed season demonstrated the continued greater efficacy of mometasone treatment in decreasing subject evaluated total symptoms, as compared with the beclomethasone treatment group and placebo group (mometasone group: total SAR symptom score=2.0, mean change=1.5 (279% increase in total symptoms), beclomethasone group: total SAR symptom score=2.5, mean change=2.0 (391% increase in total symptoms) and placebo group: total SAR symptom score=3.7, mean change=3.1, (574% increase in total symptoms (Table XVI)), $p<.01$ for mometasone vs. placebo and mometasone vs. beclomethasone)).

Analysis of the day 31-45 and day 46-61 study intervals reveal a mild steady increase in total SAR symptoms for the mometasone and beclomethasone treatment groups and a comparable plateauing of total SAR symptoms for the placebo group by day 31-45 (Table XVI.). Numerically, the total SAR symptom score was lower and % change in the total SAR symptom score for the mometasone group was smaller than that of the placebo or the beclomethasone groups, however, no conclusion could be based on these findings given the smaller number of subjects at these study points (i.e. study underpowering to derive a conclusion for these 2 time intervals). As was noted for the total nasal symptom

score, the total score for all three treatment groups at the endpoint visit was most similar to the day 16-30 interval.

(3) Mean change from baseline ('baseline' defined as mean of the a.m. and p.m. symptom score from the subject diary for day 1/Visit 2 of the study plus the 3 prior consecutive days [179:35]) in total non-nasal symptom scores during the ragweed season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit (ITT population, Tables XVII.-XIX.). Refer to Attachment 1 for line listings.

Review of the combined (a.m. and p.m. combined) mean change in the **total non-nasal symptom** scores for the ITT population (using the primary SAS datafiles) for all time intervals of study C93-215, indicates that at all 15 day time intervals after onset of the pollen season (with the exception of the baseline period ($p=0.22$), the prophylaxis period ($p=0.96$) and the day 31-45 and 61-71 intervals--the latter secondary to a non-estimable p-value), the mometasone treatment group demonstrated a less statistically significant increase in total non-nasal symptoms than the placebo treatment group as noted in both the raw symptom score and the percent change from baseline in the total non-nasal score ($p<.01$).

Comparing the two active treatments, while not statistically significant, the mometasone treatment group demonstrated a numerically smaller increase in total non-nasal symptom scores than the beclomethasone treatment group at all 15 day intervals with the exception of the prophylaxis period (Tables XVII.-XIX.). Once again, for all 3 treatment groups and for all time periods, the large standard deviation in the percent change in the total nasal symptom score appears to confirm previous implications that subject SAR symptom scores have high variability.

In terms of the day 1-15 interval, the raw total non-nasal symptom score, the mean change in total non-nasal symptoms and the percent change in total non-nasal symptoms in the mometasone treatment group was statistically significantly smaller ($p<.01$) than the placebo group, but not so when compared with the beclomethasone group ($p=0.56$ for raw symptom score or $p=0.66$ for mean change in raw non-nasal symptom score). Evaluation of subject diary scores for the day 1-15 interval separately for the a.m. and the p.m. to assess duration of drug effect, failed to show a signficant difference in the raw non-nasal symptom score for the mometasone treatment group (mometasone group; raw score: a.m.=0.6 and p.m.=0.6, mean change in score: a.m.=0.4, p.m.=0.5). Similar findings of lack of waning of a duration effect on total non-nasal SAR symptoms were likewise noted for the beclomethasone treatment group and the placebo group for study C93-215 (Table XVIII.). Separation of the day 1-15 interval into weekly intervals of day 1-7 and day 8-15 in order to assess subject response from week 1 to week 2 of the ragweed season was not performed for the supplementary efficacy endpoint of total non-nasal symptoms.

Analysis of the day 16-30 interval (a.m. and p.m. scores combined) during the ragweed season demonstrated greater efficacy of the mometasone treatment group in decreasing total non-nasal symptom scores compared with placebo ($p=0.01$) and numerically (though not statistically) greater efficacy when compared with the beclomethasone treatment group (raw score comparison of mometasone vs. beclomethasone, $p=0.17$, comparison of the mean change in non-nasal symptom score for mometasone vs. beclomethasone, $p=0.2$).

Having taken into account subject dropouts, evaluation of the day 31-45 and day 46-61 interval of the ragweed pollen season nonetheless revealed a lower mean total non-nasal symptom score and smaller mean change in the non-nasal score in the mometasone group, as compared with placebo and the beclomethasone active control (Table XIX.). These findings are similar to those noted for subject total nasal and total SAR symptom scores. Total non-nasal symptom scores for the endpoint visit for all 3 treatment groups were similar to that of the day 16-30 interval. For the most part, the raw total non-nasal symptom scores and the percent increase in scores mildly but steadily increased for all treatment groups as the ragweed season advanced. Similar trends in data were noted for the prior 2 supplementary efficacy variables of total nasal and total SAR symptoms discussed previously. Given that the ragweed pollen counts were likely decreasing in at least several study centers (C93-215-02, -03, and -06) approximately 1 month after onset of the pollen season [179:175-183], the etiology of the increasing symptom scores in at least some study subjects (e.g. study site -02: subject 005, 017, 019, 020 (mometasone treatment group); study site -06: subject 041, study site -03 excluded because most subjects did not complete treatment beyond 30 days post-initiation of the ragweed season (efficacy evaluable population [179:122-123, 124-125, 130-131]): is not readily explained, although similar trends were observed for individual subjects in the beclomethasone and placebo treatment groups as well.

A summary of the statistical response of total nasal, total non-nasal, and total SAR (nasal plus non-nasal) seasonal allergic rhinitis symptoms for all 15 day study intervals is provided in Table XX. below.

Table XII.

Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Subject Evaluated Total Sympton: Scores
Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS		
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-
BASELINE																
--am & pm total	116	0.5	0.6	115	0.6	0.8	115	0.6	0.8	0.7	0.18	<.01	0.14	0.4	0.06	
--am total	116	0.6	0.7	115	0.7	0.9	115	0.7	0.9	0.7	0.54	<.01	0.14	0.42	0.29	
--pm total	116	0.4	0.6	115	0.5	0.8	115	0.6	0.9	0.7	0.05	<.01	0.31	0.46	0.02	
PROPHYLAXIS PERIOD																
--am & pm total symptom score																
RAW	116	0.7	1.0	115	0.9	1.6	115	1.1	1.3	1.3	0.09	<.01	0.49	0.25	0.03	
CHG	116	0.2	0.9	115	0.3	1.7	116	0.4	1.1	1.2	0.44	<.01	0.22	0.47	0.2	
%CHG	72	39.3	157	68	106	325	70	95.3	244							
--am total symptom score																
RAW	116	0.8	1.1	115	0.9	1.7	115	1.1	1.4	1.3	0.09	<.01	0.51	0.3	0.03	
CHG	116	0.2	1.0	115	0.3	1.8	115	0.5	1.2	1.3	0.26	<.01	0.2	0.54	0.1	
%CHG	70	25.6	148	61	19.1	133	63	120	297							
pm total symptom score																
RAW	116	0.6	0.9	115	0.8	1.6	115	1.0	1.2	1.2	0.09	<.01	0.45	0.22	0.03	
CHG	116	0.2	1.6	115	0.3	1.7	115	0.4	1.1	1.3	0.65	0.01	0.27	0.42	0.42	
%CHG	50	23.8	67.8	50	67.8	189	58	74.4	217							

SD= Standard Deviation CHG=Change T X I = Treatment by Investigator interaction
# P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table XIII.

Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:

Subject Evaluated Total Symptom Scores

Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARISC A-B	A-C	E
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-(
BASELINE																
--am & pm total	116	0.5	0.6	115	0.8	0.8	115	0.6	0.8	0.7	0.18	<.01	0.14	0.4	0.06	
--am total	116	0.6	0.7	115	0.7	0.9	115	0.7	0.9	0.7	0.54	<.01	0.14	0.42	0.29	
--pm total	116	0.4	0.6	115	0.5	0.8	115	0.6	0.9	0.7	0.05	<.01	0.31	0.46	0.02	
DAYS 1-15 POLLEN (RAGWEED) SEASON																
--am & pm total																
RAW	114	1.3	1.5	111	1.7	2.2	109	3.0	3.3	2.3	<.01	<.01	0.01	0.23	<.01	
CHG	114	0.8	1.5	111	1.1	2.2	109	2.4	3.3	2.3	<.01	<.01	<.01	0.12	<.01	
%CHG	71	208	542	65	327	539	84	486	1085							
--am total symptom score																
RAW	114	1.4	1.6	111	1.7	2.2	109	3.0	3.2	2.3	<.01	<.01	0.02	0.28	<.01	
CHG	114	0.8	1.5	111	1.0	2.3	109	2.4	3.3	2.3	<.01	<.01	0.01	0.39	<.01	
%CHG	69	125	296	58	191	400	58	459	938							
pm total symptom score																
RAW	114	1.3	1.6	111	1.7	2.2	109	3.0	3.4	2.4	<.01	<.01	<.01	0.19	<.01	
CHG	114	0.9	1.6	111	1.2	2.2	109	2.5	3.4	2.4	<.01	<.01	<.01	0.27	<.01	
%CHG	49	95.2	176	49	229	432	52	307	572							

SD= Standard Deviation CHG=Change T X I = Treatment by Investigator interaction

P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table XIV.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Subject Evaluated Total Symptom Scores
Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS A-B	A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B
BASELINE																
--am & pm total	116	0.5	0.6	115	0.6	0.8	115	0.6	0.8	0.7	0.18	<.01	0.14	0.4	0.06	
--am total	116	0.6	0.7	115	0.7	0.9	115	0.7	0.9	0.7	0.54	< 01	0.14	0.42	0.29	
--pm total	116	0.4	0.6	115	0.5	0.8	115	0.6	0.9	0.7	0.05	< 01	0.31	0.46	0.02	
DAYS 1-7 POLLEN (RAGWEED) SEASON																
--am & pm total symptom score																
RAW	114	1.0	1.3	111	1.3	2.1	109	2.3	2.9	2.1	<.01	0.03	0.01	0.25	<.01	
CHG	114	0.6	1.3	111	0.8	2.1	109	1.8	3.0	2.1	<.01	0.02	0.01	0.36	<.01	
%CHG	71	102	270	65	267	503	64	331	760							
--am total symptom score																
RAW	114	1 1	1 3	111	1 3	2 1	109	2 3	2 9	2.1	< 01	0.04	0.11	0.3	< 01	
CHG	114	0 5	1 3	111	0 7	2 1	109	1 7	2.9	2.1	< 01	0.02	0.02	0.42	< 01	
%CHG	69	61 2	199	58	133	312	58	291	644							
pm total symptom score																
RAW	114	1 0	1 3	111	1 3	2 1	109	2 4	3 1	2.2	< 01	0.02	0.01	0.22	< 01	
CHG	114	0 6	1 3	111	0 8	2 1	109	1 8	3 2	2.2	< 01	0.02	<.01	0.32	<.01	
%CHG	49	50 2	169	49	172	427	52	226	503							

SD - Standard Deviation CHG=Change T X I = Treatment by Investigator interaction
P values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table XV.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Subject Evaluated Total Symptom Scores
Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS A-B	A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B
BASELINE																
--am & pm total	116	0.5	0.6	115	0.6	0.8	115	0.6	0.8	0.7	0.18	<.01	0.14	0.4	0.06	
--am total	116	0.6	0.7	115	0.7	0.9	115	0.7	0.9	0.7	0.54	<.01	0.14	0.42	0.29	
--pm total	116	0.4	0.6	115	0.5	0.8	115	0.6	0.9	0.7	0.05	<.01	0.31	0.46	0.02	
DAYS 8-15 POLLEN (RAGWEED) SEASON																
--am & pm total symptom score																
RAW	114	1.6	2.0	108	2.0	2.5	105	2.3	2.9	2.1	<.01	0.03	0.03	0.25	<.01	
CHG	114	1.1	2.0	108	0.8	2.1	105	1.8	3.0	2.1	<.01	0.02	0.01	0.36	<.01	
%CHG	71	298	876	65	287	503	64	331	750							
--am total symptom score																
RAW	114	1.6	2.0	108	1.9	2.4	105	3.4	3.9	2.7	<.01	<.01	<.01	0.35	<.01	
CHG	114	1.1	2.0	108	1.3	2.5	105	2.8	4.0	2.7	<.01	<.01	<.01	0.43	<.01	
%CHG	69	181	468	56	248	514	58	607	1248							
--pm total symptom score																
RAW	114	1.6	2.0	108	2.0	2.6	105	3.5	4.2	2.9	<.01	<.01	<.01	0.2	<.01	
CHG	114	1.2	2.1	108	1.5	2.6	105	3.0	4.3	2.9	<.01	<.01	<.01	0.27	<.01	
%CHG	49	136	215	47	291	496	52	226	503							

SD= Standard Deviation CHG=Change T X I = Treatment by Investigator interaction
# P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table XVI.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Subject Evaluated Total Symptom Scores
Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS A-B	A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B
BASELINE																
--am & pm total	116	0.5	0.8	115	0.6	0.8	115	0.6	0.8	0.7	0.18	<.01	0.14	0.4	0.06	
DAYS 16-30 POLLEN (RAGWEED) SEASON, am & pm total symptom scores																
RAW	114	2.0	2.3	107	2.6	3.1	103	3.7	4.0	3.1	<.01	<.01	0.08	0.16	<.01	
CHG	114	1.5	2.3	107	2.0	3.2	103	3.1	4.0	3.1	<.01	<.01	0.04	0.19	<.01	
%CHG	71	279	464	62	391	642	63	574	959							
DAYS 31-45 POLLEN (RAGWEED) SEASON, am & pm total symptom scores																
RAW	76	2.3	3.5	67	2.9	4.0	61	3.6	4.2	3.9	0.02	0.19	0.72	N/E	N/E	N
CHG	76	1.8	3.5	67	2.4	4.2	61	3.0	4.1	3.9	0.04	0.02	0.8	N/E	N/E	N
%CHG	45	184	329	35	333	638	34	712	1716							
DAYS 46-61 POLLEN (RAGWEED) SEASON, am & pm total symptom scores																
RAW	18	2.4	2.8	14	2.9	5.8	13	2.5	2.6	4.0	0.77	0.8	0.57	0.63	N/E	N
CHG	18	1.8	2.8	14	3.5	5.8	13	2.2	2.6	4.0	0.58	0.59	0.53	0.47	N/E	N
%CHG	12	351	453	9	768	967	6	660	1200							
ENDPOINT VISIT POLLEN (RAGWEED) SEASON, am & pm total symptom scores																
RAW	116	2.0	3.0	115	2.6	3.5	115	3.9	4.3	3.5	<.01	<.01	0.06	0.16	<.01	
CHG	116	1.5	3.0	115	2.0	3.6	115	3.3	4.3	3.5	<.01	<.01	0.06	0.21	<.01	
%CHG	72	260	462	68	403	684	70	771	1582							

SD= Standard Deviation CHG=Change T X I = Treatment by Investigator interaction N/E=Non-estimable (due to small subject number)
# P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table XVII.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Subject Evaluated Total Non-Nasal Symptom Scores
Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARISO A-B	A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-(
BASELINE																
--am & pm non-nasal	116	0.1	0.3	115	0.2	0.4	115	0.2	0.4	0.4	0.47	<.01	0.07	0.8	0.22	
--am non-nasal	116	0.1	0.3	115	0.2	0.4	115	0.2	0.4	0.4	0.85	<.01	0.04	0.66	0.59	
--pm non-nasal	116	0.1	0.3	115	0.2	0.4	115	0.2	0.5	0.4	0.21	<.01	0.2	0.57	0.08	
PROPHYLAXIS																
--am & pm non-nasal																
RAW	116	0.3	0.4	115	0.3	0.8	115	0.3	0.6	0.6	0.78	<.01	0.58	0.87	0.49	
CHG	116	0.1	0.4	115	0.1	0.8	115	0.1	0.4	0.6	0.99	<.01	0.43	0.91	0.96	
%CHG	33	132	423	26	91.1	264	37	207	384							
--am non-nasal																
RAW	116	0.3	0.5	115	0.3	0.8	115	0.3	0.7	0.6	0.73	<.01	0.64	0.75	0.44	
CHG	116	0.1	0.4	115	0.1	0.8	115	0.2	0.5	0.6	0.87	<.01	45	0.95	0.62	
%CHG	29	28.4	161	26	-30	81.0	29	22.0	140							
--pm non-nasal																
RAW	116	0.2	0.4	115	0.3	0.8	115	0.3	0.5	0.6	0.82	<.01	0.46	0.59	0.58	
CHG	116	0.1	0.4	115	0.1	0.9	115	0.1	0.5	0.6	0.73	0.02	0.42	0.88	0.55	
%CHG	21	-1.2	111	19	-43	58.3	32	-15	117							

SD = Standard Deviation CHG=Change T X I = Treatment by Investigator interaction
# P Values are from 2-way analysis of variance and LSMeans pairwise comparisons ,no adjustment for overall α level)

Table XVIII.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Subject Evaluated Total Non-Nasal Symptom Scores
Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS(A-B	A-C	B-(
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	
BASELINE																
-am & pm non-nasal	116	0.1	0.3	115	0.2	0.4	115	0.2	0.4	0.4	0.47	<.01	0.07	0.8	0.22	
am non-nasal	116	0.1	0.3	115	0.2	0.4	115	0.2	0.4	0.4	0.85	< 01	0 04	0 66	0 59	
pm non-nasal	116	0.1	0.3	115	0.2	0.4	115	0.2	0.5	0.4	0.21	< 01	0.2	0 57	0.08	
DAYS 1-15 POLLEN (RAGWEED) SEASON																
-am & pm non-nasal																
RAW	114	0.6	0.8	111	0.7	1.0	109	1.0	1.5	1.1	<.01	0.04	0.1	0.56	< 1(	
CHG	114	0.4	0.9	111	0.5	1.0	109	0.9	1.5	1.1	<.01	0.01	0.8	0.66	<.01	
%CHG	33	132	423	26	91.1	264	37	207	384							
-am non nasal																
RAW	114	0 6	0.9		0 6	1.0	109	1.0	1.5	1.1	0.01	0.09	0.16	0.67	< 01	
CHG	114	0 4	0 9	111	0 5	1 0	109	0 9	1.40	1.1	<.01	0.03	0.05	0.75	<.01	
%CHG	29	71 8	256	24	35 9	187	25	149	358							
pm non-nasal																
RAW	114	0 6	0 9	111	0 7	1 1	109	1.1	1.5	1.1	<.01	0.01	0.06	0.46	<.01	
CHG	114	0 5	0 9	111	0 5	1 1	109	0 9	1 5	1 1	0.01	<.01	0.08	0 58	<.01	
%CHG	21	-3 3	98 9	19	47 5	148	27	136	295							

SD = Standard Deviation CHG=Change T X I = Treatment by Investigator interaction
# P Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table XIX.

Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of SAR:
Subject Evaluated Total Non-nasal Symptom Scores
Supplementary Efficacy Variable--Intent-to-Treat (ITT) POPULATION [SAS Datafiles for NDA 20-762, Attachment 1]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARIS(A-B	A-C	
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-(
BASELINE																
-am & pm non-nasal	116	0.1	0.3	115	0.2	0.4	115	0.2	0.4	0.4	0.47	<.01	0.07	0.8	0.22	
DAYS 16-30 POLLEN (RAGWEED) SEASON, am & pm total non-nasal symptom scores																
RAW	114	0.8	1.3	107	1.1	1.7	103	1.3	2.0	1.6	0.03	0.01	0.09	0.17	0.01	
CHG	114	0.7	1.3	107	0.9	1.7	103	1.2	1.9	1.6	0.04	<.01	0.08	0.2	0.01	
%CHG	33	130	267	25	137	383	37	207	384							
DAYS 31-45 POLLEN (RAGWEED) SEASON, am & pm total non-nasal symptom scores																
RAW	76	0 9	1 7	67	1 2	2 0	61	1 2	2 1	1.9	0.26	0.06	0 91	N/E	N/E	N/
CHG	76	0 8	1 8	67	1 1	2 1	61	1.0	2 0	1.9	0 41	0 01	0.96	N/E	N/E	N/
%CHG	26	143	300	18	203	490	22	280	560							
DAYS 46-61 POLLEN (RAGWEED) SEASON, am & pm total non-nasal symptom scores																
RAW	18	1 0	1 5	14	1 9	3 1	13	0 7	1 0	2.1	1.9	0.26	0.06	0.91	N/E	N/
CHG	18	0 8	1 5	14	1 8	3 0	13	0 7	1.0	2.0	0.69	0.6	0.37	0.63	N/E	N/
%CHG	7	349	749	3	802	756	3	294	460							
ENDPOINT VISIT POLLEN (RAGWEED) SEASON, am & pm total non-nasal symptom scores																
RAW	116	0 8	1 5	115	1 1	1 8	115	1.4	2 1	1.8	0.04	<.01	0.06	0.13	0 01	
CHG	116	0 6	1 5	115	0 9	1 9	115	1 2	2 0	1.7	0.06	<.01	0.08	0.16	0 02	
%CHG	33	176	438	28	150	440	42	239	430							

SD= Standard Deviation CHG=Change T X I = Treatment by Investigator interaction N/E=Non-estimable (due to small subject number)
# P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table XX. Summary of Change in SAR Symptoms (a.m. and p.m. combined) with Mometasone Treatment

[SAS Datafiles for NDA 20-762, Attachment 1]

SAR SYMPTOM	*Statistical Response: Prophylaxis Period (Yes=Y/No=N)	*Statistical Response$_{DAY\ 1-15}$ (Yes=Y/No=N)	Statistical Response$_{DAY\ 16-30}$ (Y/N)	Statistical Response$_{DAY\ 31-45,\ DAY\ 46-61}$ (Y/N)	Statistical Response$_{Endpoint}$ (Y/N)
Total symptoms	No (^{2}p=0.2)	Yes	Yes	N/E	Yes
Total nasal symptoms	Yes	Yes	Yes	N/E	Yes
Total non-nasal symptoms	No (p=0.96)	Yes	Yes	N/E	Yes

* Statistical Response= Statistical response of mometasone treatment group, as compared with placebo
N/E = Not estimable based on inadequate subject numbers to maintain a power of 90%
P values were calculated based on the change in symptom score from baseline.

(III) Supplementary Efficacy Variables-cont

(4) Mean change from baseline ('baseline' defined as mean of the a.m. and p.m. symptom score from the subject diary for day 1/Visit 2 of the study plus the 3 prior consecutive days [179:35]) in individual nasal symptom scores during the ragweed season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit (ITT population). Refer to Attachment 1 for line listings.

Analysis of subject evaluated individual nasal symptom scores for each 15 day study interval subsequent to the onset of the pollen season included the following four nasal symptoms: rhinorrhea (nasal discharge), sneezing, nasal congestion, and nasal itch. Of note, the day 1-15 interval for the individual nasal symptom scores was not sub-analyzed by week 1 and week 2.

Evaluation of subject **rhinorrhea** (a.m. and p.m. combined) revealed that the mometasone treatment group had a lower mean rhinorrhea score than the placebo group at all 15 day time points with the marginal exception of the prophylaxis period (prophylaxis period rhinorrhea (raw) score: mometasone vs. placebo, p=0.03, mean change in score: mometasone vs. placebo, p=0.25) and which was statistically significant at day 1-15 (rhinorrhea score: mometasone group=0.2, % change=-1.6; rhinorrhea score: placebo=0.5, % change=55.2; p<.01 for both raw score and mean change) and day 16-30 (rhinorrhea score: mometasone group=0.3, % change=66.7; rhinorrhea score: placebo=0.6, % change=119; p<.01 for both raw score and mean change). While the mean rhinorrhea score for the mometasone group was numerically lower than that of the placebo group for the endpoint visit (rhinorrhea score: mometasone group=0.3, % change=84.0; rhinorrhea score: placebo=0.7, % change=74.0; p<.01 for both raw score and mean change), the mean % change in rhinorrhea increased for mometasone subjects. Rhinorrhea scores at day 31-45 and day 46-61 were lower for the mometasone treatment group than placebo but statistical significance was not assigned to these values because of study underpowering. Comparison of the mometasone treatment group with the active comparator, beclomethasone on this clinical endpoint revealed that in general, the mometasone treatment group had rhinorrhea scores numerically lower than or equal to the rhinorrhea scores of the beclomethasone treatment group for all 15 day study intervals. These differences were not statistically significant at any of the 15 day study intervals. Evaluation of rhinorrhea scores for the mometasone treatment group for the a.m. vs. the p.m. showed no significant difference in the rhinorrhea score at any of the 15 day intervals (including the prophylaxis period) when the a.m. score was compared to the p.m. score. Post-hoc analysis of the a.m. vs. the p.m. scores was not performed, thus a significance level was not obtained for these values.

Evaluation of subject evaluated **sneezing** scores for the mometasone treatment group vs. placebo for all 15 day study intervals with the marginal

exception of the prophylaxis period (prophylaxis period sneezing (raw) score mometasone vs. placebo, p=0.04, mean change in score: mometasone vs. placebo=0.2), revealed that sneezing scores and mean change in sneezing scores were statistically lower for the mometasone group than the placebo group ((day 1-15: sneezing score: mometasone group=0.2, % change=1.9; sneezing score: placebo=0.5, % change=120; p<.01 for both raw score and mean change and day 16-30: sneezing score: mometasone group=0.2, % change=62.6; sneezing score: placebo=0.5, % change=136; p<.01 for both the raw score and mean change)). While the mean sneezing score for the mometasone group was numerically lower than that of the placebo group for the endpoint visit (sneezing score: mometasone group=0.3, % change=120; sneezing score: placebo=0.6, % change=93.4; p<.01 for both the raw score and mean change), the mean % change in sneezing increased for mometasone subjects. Again, sneezing scores at day 31-45 and day 46-61 intervals were lower for the mometasone treatment group than placebo but statistical significance was not assigned to these values because of study underpowering. Comparison of the mometasone treatment group with the active comparator, beclomethasone with regard to the sneezing score revealed that in general, the mometasone treatment group had sneezing scores numerically lower than or equal to the sneezing scores of the beclomethasone treatment group for all 15 day study intervals. These differences were not statistically significant at any of the 15 day study intervals. Evaluation of sneezing scores for the mometasone treatment group for the a.m. vs. the p.m. showed no significant difference in the sneezing score at any of the 15 day intervals (including the prophylaxis period) when the a.m. score was compared to the p.m. score.

Evaluation of subject evaluated **nasal congestion** scores for the mometasone treatment group vs. placebo for all 15 day study intervals, and including the prophylaxis period (prophylaxis period nasal congestion (raw) score: mometasone vs. placebo, p=0.01, mean change in score: mometasone vs. placebo, p=0.05), revealed that the nasal congestion scores and mean change in nasal congestion scores were statistically lower for the mometasone group than the placebo group (day 1-15: nasal congestion score: mometasone group=0.3, % change=19.0; nasal congestion score: placebo=0.7, % change=116; p<.01 and day 16-30: nasal congestion score: mometasone group=0.4, % change=46.9; sneezing score: placebo=0.8, % change=146; p<.01 for both raw score and mean change. While the mean nasal congestion score for the mometasone group was numerically lower than that of the placebo group for the endpoint visit: (nasal congestion score: mometasone group=0.3, % change=120; nasal congestion score: placebo=0.6, % change=93.4; p<.01 for both raw score and mean change), the mean % change in nasal congestion increased for mometasone subjects. Again, nasal congestion scores at day 31-45 and day 46-61 were lower for the mometasone treatment group compared with placebo but statistical significance was not assigned to these values because of study underpowering. Comparison of the mometasone treatment group with the active comparator, beclomethasone with regard to the nasal congestion score revealed that in general, the mometasone

treatment group had nasal congestion scores numerically lower than or equal to the nasal congestion scores of the beclomethasone treatment group for all 15 day study intervals. These differences were not statistically significant at any of the 15 day study intervals. Evaluation of nasal congestion scores for the mometasone treatment group for the a.m. vs. the p.m. showed no significant difference in the nasal congestion score at any of the 15 day intervals (including the prophylaxis period) when the a.m. score was compared to the p.m. score.

Finally, evaluation of subject evaluated **nasal itch** scores for the mometasone treatment group vs. placebo for all 15 day study intervals, including the prophylaxis period (prophylaxis period nasal itch (raw) score: mometasone vs. placebo, p=0.01, mean change in score: mometasone vs. placebo=0.04), revealed that nasal itch scores and the mean change in nasal itch scores were statistically lower for the mometasone group than placebo ((day 1-15: nasal itch score: mometasone group=0.1, % change=10.1; nasal itch score: placebo=0.4, % change=73.1; p<.01 for both raw score and mean change; day 16-30: nasal itch score: mometasone group=0.2, % change=37.2; sneezing score: placebo=0.5, % change=126; p<.01 for both raw score and mean change, and the endpoint visit: nasal itch score: mometasone group=0.2, % change=22.3; nasal itch score: placebo=0.5, % change=160; p<.01 for both raw score and mean change) (again, nasal itch scores at day 31-4[illegible]nd day 46-61 were lower for the mometasone treatment group than placebo but statistical significance was not assigned to these values because of study underpowering). Comparison of the mometasone treatment group with the active comparator, beclomethasone, with regard to the nasal itch score revealed that in general, the mometasone treatment group had nasal itch scores numerically lower than or equal to the nasal itch scores of the beclomethasone treatment group for all 15 day study intervals, although these differences were not statistically significant at any of the 15 day study intervals. Evaluation of nasal itch scores for the mometasone treatment group for the a.m. vs. the p.m. showed no significant difference in the nasal itch score at any of the 15 day intervals (including the prophylaxis period) when the a.m. score was compared to the p.m. score.

In summary, review of the four nasal symptom scores showed that no single symptom disproportionately influenced the overall total nasal symptom score, although the nasal congestion score was higher for all treatment groups than either of the other 3 nasal symptoms analyzed in study C93-215. In contrast to the SAR pivotal trial C93-013 where a statistically significant decrease at all study intervals was only noted for the nasal congestion endpoint, prophylaxis with mometasone (also with beclomethasone) appeared to decrease all 4 nasal SAR symptoms in comparison with placebo. This may imply that prophylaxis with mometasone prior to onset of the pollen season may reduce nasal SAR symptoms to a greater degree than initiation of mometasone at the start of the pollen season but without head-to-head comparisons of a mometasone prophylaxis group vs. a mometasone treatment group where administration of drug began at the start of the pollen season (no prophylaxis), no firm conclusions can be made with regard to

the comparability of both treatment strategies in decreasing SAR symptoms. Furthermore, the clinical response from mometasone pretreatment may be indicative of a more general finding that applies to many, if not all nasal steroids when used prophylactically to treat SAR symptoms prior to onset of the allergy season.

No evidence of waning of mometasone action was noted for any of the 4 nasal symptoms over 24 hours, as noted in the a.m. vs. p.m. comparisons of drug efficacy. These findings support once a day dosing of mometasone for the prophylaxis of SAR symptoms in allergic subjects.

(5) **Mean change from baseline ('baseline' defined as mean of the a.m. and p.m. symptom score from the subject diary for day 1/Visit 2 of the study plus the 3 prior consecutive days [179:35]) in individual non-nasal symptom scores during the ragweed season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit (ITT population). Refer to Attachment 1 for line listings.**

Analysis of subject evaluated **individual non-nasal symptom** scores for each 15 day study interval included the following four non-nasal symptoms: eye tearing, eye redness, eye itch, and ear/palatal itch. Of note, the day 1-15 interval for individual non-nasal symptom scores was not sub-analyzed by week 1 and week 2.

Evaluation of subject **eye tear** scores (a.m. and p.m. combined) revealed that the mometasone treatment group had statistically lower mean eye tear scores than the placebo group only at the day 1-15 interval (eye tear score: mometasone group=0.1, % change=-35; eye tear score: placebo=0.2, % change=19.7; p=.04 for both raw score and mean change) but had marginally statistically significantly lower eye tear scores at the day 16-30 interval (eye tear score: mometasone group=0.2, % change=47.6; eye tear score: placebo=0.3, % change=125; p=0.05 for raw score comparison between mometasone and placebo, p=0.06 for mean change in eye tear score for mometasone vs. placebo) and the endpoint interval (eye tear score: mometasone group=0.2, % change=70.2; eye tear score: placebo=0.3, % change=89.3; p=.07 for the raw eye tear score comparison of mometasone vs. placebo, p=0.1 for mean change in the eye tear score of mometasone vs. placebo). Eye tear scores at day 31-45 and day 46-61 intervals were similar between the mometasone and placebo group but were not consistently lower for the mometasone treatment group as compared with placebo (statistical significance was not assigned to these values because of study underpowering). Comparison of the mometasone t[illegible]atment group with the active comparator, beclomethasone, on this clinical endpoint revealed that in general, the mometasone treatment group h[illegible]eye tear scores numerically lower than the eye tear scores of the beclomethasone treatment group for all 15 day study intervals with the exception of the prophylaxis period. These differences were not statistically

significant at any of the 15 day study intervals. Evaluation of eye tear scores for the mometasone treatment group for the a.m. vs. the p.m. showed no significant difference in the eye tear score for any of the 15 day intervals (including the prophylaxis period) when the a.m. score was compared to the p.m. score. As discussed in the analysis of individual nasal symptoms above, post-hoc analysis of the a.m. vs. the p.m. scores was not performed, and thus a significance level was not obtained for these values.

Evaluation of subject **eye redness** scores (a.m. and p.m. combined) revealed that the mometasone treatment group had lower mean eye redness scores than the placebo group at all 15 day time points with the exception of the prophylaxis period (eye redness (raw) score: mometasone vs. placebo, p=0.16, mean change in score: mometasone vs. placebo, p=0.34) and which were statistically significant at the day 1-15 (eye redness score: mometasone group=0.1, % change=-17; eye redness score: placebo=0.3, % change=12.3; p<.01 for both raw score and mean change comparisons between mometasone and placebo), the day 16-30 interval (eye redness score: mometasone group=0.2, % change=-22; eye redness score: placebo=0.3, % change=55.1; p=.03 for the raw score comparison between mometasone and placebo and p=0.02 for the mean change comparison between mometasone and placebo), and the endpoint visit (eye redness score: mometasone group=0.2, % change=-28; eye redness score: placebo=0.3, % change=42.7; p=.03 for the raw score comparison between mometasone and placebo and p=0.05 for the mean change comparison between mometasone and placebo). Eye redness scores for the mometasone group at day 31-45 and day 46-61 were lower than or equal to that of the placebo group, however statistical significance again was not assigned to these values because of study underpowering. Comparison of the mometasone treatment group with the active comparator, beclomethasone, with regard to eye redness, revealed that in general, the mometasone treatment group had eye redness scores numerically lower than or equal to the eye redness scores of the beclomethasone treatment group for all 15 day study intervals. These differences were not statistically significant at any of the 15 day study intervals. Evaluation of eye redness scores for the mometasone treatment group for the a.m. vs. the p.m. showed no significant difference in the eye redness score at any of the 15 day intervals (including the prophylaxis period) when the a.m. score was compared to the p.m. score.

Evaluation of subject **eye itch** scores (a.m. and p.m. combined) revealed that the mometasone treatment group had statistically lower mean eye itch scores than the placebo group only at the day 1-15 interval (eye itch score: mometasone group=0.2, % change=-1.4; eye itch score: placebo=0.3, % change=22.6; p=.02 for the raw score comparison and p=0.04 for the mean change comparison in eye itch scores between mometasone and placebo) and the day 16-30 interval (eye itch score: mometasone group=0.3, % change=7.4; eye itch score: placebo=0.4, % change=22.9; p=0.03 for the raw score comparison, p=0.05 for mean change comparison between mometasone and placebo). Numerically lower but marginally statistically significantly lower eye itch scores were noted at the endpoint visit (eye

itch score: mometasone group=0.3, % change=-2.1; eye itch score: placebo=0.4, % change=29.6; p=.07 for the raw eye itch score comparison of mometasone vs. placebo, p=0.13 for mean change in the eye itch score of the mometasone group vs. placebo). Eye itch scores at the day 31-45 and day 46-61 intervals were the same for the mometasone and placebo group. Comparison of the mometasone treatment group with the active comparator, beclomethasone, with regard to eye redness revealed that the mometasone treatment group had eye itch scores numerically lower than the eye itch scores of the beclomethasone treatment group for all 15 day study intervals with the exception of the prophylaxis period. These differences were not statistically significant at any of the 15 day study intervals. Evaluation of eye itch scores for the mometasone treatment group for the a.m. vs. the p.m. showed no significant difference in the eye itch score for any of the 15 day intervals (including the prophylaxis period) when the a.m. score was compared to the p.m. score.

Evaluation of subject **ear/palatal itch** scores (a.m. and p.m. combined) revealed that the mometasone treatment group had lower mean ear itch scores than the placebo group at all 15 day time points with the exception of the prophylaxis period (prophylaxis period ear/palatal itch (raw) score: mometasone vs. placebo, p=0.41, mean change in score: mometasone vs. placebo, p=0.98). Ear/palatal itch scores were statistically significantly lower for the mometasone group as compared with placebo at the day 1-15 interval (ear/palatal itch score: mometasone group=0.1, % change=-55; ear/palatal itch score: placebo=0.2, % change=64.2; p<.01 for both the raw score and mean change comparison in the ear/palatal itch scores between mometasone and placebo), the day 16-30 interval (ear/palatal itch score: mometasone group=0.1, % change=-16; ear/palatal itch score: placebo=0.3, % change=159; p<.01 for the raw score comparison between mometasone and placebo and p=0.01 for the mean change comparison in ear/palatal itch scores between mometasone and placebo), and the endpoint visit (ear/palatal itch score: mometasone group=0.1, % change=40.9; ear/palatal itch score: placebo=0.3, % change=124; p<.01 for the raw score comparison between mometasone and placebo and p=0.01 for the mean change comparison between mometasone and placebo). Ear/palatal itch scores for the mometasone group at day 31-45 and day 46-61 were lower than or equal to that of the placebo group, however statistical significance again was not assigned to these values because of study underpowering. Comparison of the mometasone treatment group with the active comparator, beclomethasone, with regard to ear/palatal itch, revealed that in general, the mometasone treatment group had ear/palatal itch scores numerically lower than or equal to the ear/palatal itch scores of the beclomethasone treatment group for all 15 day study intervals. These differences were not statistically significant at any of the 15 day study intervals. Evaluation of ear/palatal itch scores for the mometasone treatment group for the a.m. vs. the p.m. showed no significant difference in the ear/palatal itch score at any of the 15 day intervals (including the prophylaxis period) when the a.m. score was compared to the p.m. score.

Review of the four non-nasal symptom scores showed that no single symptom disproportionately influenced the overall total non-nasal symptom score, and in general, the numerical values for the non-nasal symptom scores were small and did not impact greatly on the total SAR score for study subjects. Importantly, in contrast to the SAR pivotal trial C93-013 where no statistically significant decrease in any non-nasal symptom score with mometasone treatment was noted at any study endpoint (day 1-15, day 16-30 and the endpoint visit), prophylaxis with mometasone (also with beclomethasone for some time intervals) appeared to decrease all 4 non-nasal SAR symptoms in comparison with placebo for the day 1-15 and day 16-30 interval. It should be noted however, that overall these symptom score differences, while statistically significant, were numerically very small (i.e. a 0.1-0.2 change in symptom scores) and unclear how relevant clinically. The non-nasal symptoms of eye redness and ear/palatal itching also appeared statistically significantly lower for the mometasone treatment group as compared with placebo for the endpoint visit. This was not the case for the symptoms of eye itching or eye tearing. Also of note, no statistically significant response of the mometasone treatment group compared with placebo for any of the 4 non-nasal symptoms was noted during the prophylaxis period. The efficacy results for both individual nasal and non-nasal SAR symptoms for study C93-215 are summarized in Table XXI.

No evidence of waning of mometasone action was noted for any of the individual (4) non-nasal symptoms over 24 hours, as noted in the a.m. vs. p.m. comparisons of drug efficacy. These findings support once a day dosing of mometasone for the prophylaxis of SAR symptoms in allergic subjects.

Table XXI. Change in Individual SAR Symptoms (a.m. and p.m. combined) with Mometasone Treatment

[SAS Datafiles for NDA 20-762, Attachment 1]

SAR SYMPTOM	*Statistical Response Prophylaxis Period (Yes=Y/No=N)	Statistical Response DAY 1-15 (Yes=Y/No=N)	Statistical Response DAY 16-30 (Y/N)	Statistical Response DAY 15-45, DAY 46-61 (Y/N)	Statistical Response Endpoint (Y/N)
Nasal					
--Rhinorrhea	No ([2]p=0.25)	Yes	Yes	N/E	Yes
--Congestion	Yes (p=0.05)	Yes	Yes	N/E	Yes
--Itching	Yes	Yes	No (p=0.09)	N/E	Yes
--Sneezing	No (p=0.2)	Yes	No (p=0.11)	N/E	Yes
NON-Nasal					
--Eye Itching	No (p=0.52)	Yes	Yes (p=0.05)	N/E	No (p=0.13)
--Eye Tearing	No (p=0.67)	Yes	Yes	N/E	No (p=0.1)
--Eye Redness	No (p=0.34)	Yes	Yes	N/E	Yes (p=0.05)
--Ear/palate itching	No (p=0.98)	Yes	Yes	N/E	Yes

* Statistical Response= Statistical response of mometasone treatment group, as compared with placebo
N/E=non-estimable, based on inadequate subject numbers to maintain a power of 90%
[2] p values were calculated based on the change in symptom score from baseline.

III. Supplementary Efficacy Variables-cont.

(6) All total (total SAR, total nasal, total non-nasal) and individual symptom scores, as determined by the physician (physician evaluations, ITT population) for study visits 3-9 (day 8, day 22, day 29, day 36, day 50, day 57, day 71, and the endpoint visit [180:389-403].

An evaluation of total SAR, total nasal, total non-nasal symptom scores along with individual nasal and non-nasal symptom scores was performed at each study center visit by the principal investigator or designated study coordinator in order to provide an additional efficacy endpoint of subject response to mometasone treatment during both the prophylaxis (day 8, 22, 29) period and ragweed onset period (day 36, 50, 57, and 71).

Review of physician evaluated **total symptom scores** [180:389] for the three treatment groups showed that the mometasone treated subjects had statistically significantly lower total SAR symptoms compared with placebo at days 29, 36, 50, 57, and the endpoint visit ($p<.01$ for all study visits) and numerically lower but only marginally statistically significantly lower total SAR symptoms compared with the placebo group at day 22 (mometasone total SAR score=1.1 vs. placebo group total SAR score=1.6 ($p=0.05$); mometasone mean change in total SAR score=0.7 (35.4%) vs. placebo mean change in total SAR score=1.0 (64.9%), ($p=0.21$)), and day 71 ((mometasone total SAR score=3.0 vs. placebo group total SAR score=5.1 ($p=0.11$); mometasone mean change in total SAR score=2.3 (112%) vs. placebo mean change in total SAR score=4.5 (369%), ($p=0.09$)). No statistically significant differences were noted between the two active comparator groups, however the total SAR symptom scores for the mometasone group were numerically smaller than or equal to those of the beclomethasone group. Based on these pooled results, subjects treated with mometasone were found to experience less severe total SAR symptoms than the placebo group for much of the study duration, including at least part of the prophylaxis period.

Review of physician evaluated **total nasal symptom scores** [180:390] for the three treatment groups showed that, similar to the findings noted above for total SAR symptoms, the mometasone treated subjects had statistically significantly lower total nasal symptoms compared with the placebo group at days 29, 36, 50, 57, and the endpoint visit ($p<.01$ for all study visits) and numerically lower but only marginally statistically significantly lower total nasal symptoms compared with the placebo group at day 22 (mometasone total nasal score=0.7 vs. placebo group total nasal score=1.1 ($p=0.02$); mometasone mean change in total nasal score=0.4 (-14%) vs. placebo mean change in total nasal score=0.8 (-3.0%), ($p=0.07$)), and day 71 ((mometasone total nasal score=2.0 vs. placebo group total nasal score=3.5 ($p=0.04$); mometasone mean change in total nasal score=1.6 (11.1%) vs. placebo mean change in total nasal score=3.1 (250%), ($p=0.06$)). Additionally, some efficacy of mometasone in reducing the total nasal symptom

score was noted by day 8 (visit 3) of the study where the mometasone treatment group demonstrated a numerically smaller total symptom score compared with placebo which approached statistical significance (p=0.08) but whose mean change in total nasal score did not (p=0.42). Again, no statistically significant differences were noted between the two active comparator groups, however the total nasal symptom scores for the mometasone group were numerically smaller than or equal to those of the beclomethasone group. Based on these pooled results, subjects treated with mometasone were found to experience less severe total nasal symptoms than the placebo group for much of the study duration, including at least part of the prophylaxis period (day 29 and perhaps day 8 and day 22).

Interestingly, review of physician evaluated **total non-nasal symptom scores** [180:393] for the three treatment groups showed that the mometasone treated subjects did not have a statistically significantly lower total non-nasal symptom score compared with the placebo group at any study visit with the exception of the day 50 visit (mometasone total non-nasal symptom score=1.2 vs. placebo group total non-nasal symptom score=2.0 (p=0.01); mometasone mean change in total non-nasal symptom score=1.1 (15.8%) vs. placebo mean change in total non-nasal symptom score=1.8 (198%), (p=0.02)) and marginally, at the endpoint visit ((mometasone total non-nasal symptom score=0.9 vs. placebo group total non-nasal symptom score=1.5 (p=0.03); mometasone mean change in total non-nasal symptom score=0.8 19.2%) vs. placebo mean change in total non-nasal symptom score=1.3 (87.5%), (p=0.06)). No statistically significant differences were noted between the two active comparator groups. The total non-nasal symptom scores for the mometasone group were numerically smaller than or equal to that of the beclomethasone group. Nonetheless, based on these pooled physician evaluated scores, one may not conclude statistically that subjects treated with mometasone experienced less severe total non-nasal symptoms than the placebo group for most of the study duration, with the exception of perhaps day 50 (visit 7) and the endpoint visit, although the overall trend in non-nasal symptom scores was for the mometasone treatment group to have numerically smaller non-nasal symptom scores than the placebo group at all study visits.

Evaluation of physician evaluated **individual nasal symptom scores** for all subject study visits indicates that for the 4 nasal symptoms of rhinorrhea, sneezing, nasal congestion, and nasal itch, subject symptom scores for the mometasone treated group were statistically smaller than those of the placebo group at the day 29, 36, 50, 57, and the endpoint visit [180:395-398]. Again, no statistically significant differences were noted for any of these 4 endpoints between the mometasone treatment group and the active comparator, beclomethasone.

Evaluation of physician evaluated **individual non-nasal symptom scores** for all subject study visits indicates that for the 4 non-nasal symptoms of eye tearing, eye redness, eye itch, and ear/palatal itch [180:395-403], the only statistically significant difference in symptoms between the mometasone group and placebo was noted for **eye tearing** at the endpoint visit (p=0.02 for the raw score comparison of mometasone vs. placebo or p=0.01 for the mean change in eye

tearing for mometasone vs. placebo), **eye itch** at the day 50 visit ($p=0.04$ for the raw score comparison of mometasone vs. placebo or $p=0.05$ for the mean change in eye itch for mometasone vs. placebo), and **ear/palatal itching** at the day 29 and day 50 visits ($p \leq .01$). These inconsistent responses for non-nasal symptoms as evaluated by physician visits contrast with those of subject evaluated (diary) non-nasal symptom scores.

(7) The proportion of minimal symptom days (total nasal symptom score ≤ 2) during the prophylaxis period (Table V., ITT population) [179:223].

An analysis of the proportion of minimal symptom days during the prophylaxis period was conducted in order to ascertain that the majority of study subjects for all three treatment groups were minimally symptomatic with regard to their SAR symptoms and thereby improve the likelihood of detecting a true effect of the study drug mometasone in prophylaxing subjects against ragweed pollen effects compared with placebo. As shown in Table V., 95% of mometasone subjects were minimally symptomatic during the prophylaxis period, compared with 93% of beclomethasone subjects, and 88% of placebo subjects. The difference in the proportion of minimally symptomatic subjects between the mometasone and placebo group was statistically significant ($p=0.01$) and marginally statistically significant between the beclomethasone and placebo group ($p=0.06$). These findings suggest that all three groups were not equally symptomatic during the prophylaxis period, with the placebo group either having more SAR symptoms during this time interval than the other two groups, the three treatment groups having a component of PAR symptoms which for the two steroid treatment groups (but not placebo group) were receiving active treatment via intranasal steroids, or lastly, that the ragweed season began prematurely (prior to 1 month after initiation of treatment) for a number of study subjects and was only actively treated in the two steroid groups. Any of these three possibilities make it more difficult to quantify mometasone's effect on prophylaxis of SAR such as that due to ragweed allergen but actually represent a more 'real-life' situation of allergic disease and the possibility of overlap of SAR and PAR symptoms in any one individual.

(8) The proportion of days during the prophylaxis period when the total nasal symptom score=0 (i.e. the proportion of symptom-free days), Table VI., efficacy evaluable population [179:221].

Similar to (7) above, an analysis of the proportion of 'asymptomatic' symptom days during the prophylaxis period was conducted in order to ascertain that the majority of study subjects for all three treatment groups were not only minimally symptomatic but actually asymptomatic with regard to their SAR symptoms and thereby again, improve the likelihood of detecting a true effect of

the study drug mometasone in prophylaxing subjects against ragweed pollen effects compared with placebo.

As shown in Table VI., 67% of mometasone subjects were asymptomatic during the prophylaxis period, compared with 59% of beclomethasone subjects, and 53% of placebo subjects. The difference in the proportion of asymptomatic subjects between the mometasone and placebo group was statistically significant (p=0.01) and marginally statistically significant between the beclomethasone and placebo group (p=0.12). Interestingly, the difference in the proportion of asymptomatic days between the two active comparators, mometasone and beclomethasone, was also marginally statistically significant (p=0.09). Based on these findings, one may conclude that the three treatment groups were not equally symptomatic during the prophylaxis period of study C93-215, thus making any conclusions about the efficacy of mometasone in decreasing SAR symptoms (compared to the baseline) for any of the study endpoints potentially biased. As discussed in section 8.10.4.2 of this review ('Primary Efficacy Variable'), while it is not possible to include the prophylaxis period as a covariate for the analysis of the different time periods, subtraction of raw scores for the prophylaxis period was not noted to change the numerical advantage of mometasone treatment of placebo. Nonetheless, this discrepancy during the prophylaxis period between the different study groups must be considered when making concluding statements about the degree of efficacy of mometasone in SAR prophylaxis.

(9) **The proportion of days during the <u>entire study</u> when the total nasal symptom score=0 (i.e. proportion of symptom-free days), Table VI, efficacy evaluable population [179:221].**

The sponsor provided an analysis of the proportion of days during the entire study duration (from the onset of the prophylaxis period to the completion of the study) during which subjects reported being 'asymptomatic' with respect to their SAR symptoms. The purpose of this efficacy endpoint, while interesting perhaps in showing that the majority of mometasone subjects (55%) indeed were asymptomatic for the entire study duration, is of limited utility as a study endpoint. As shown in Table VI., 55% of mometasone subjects were asymptomatic for the entire study duration, compared with 48% of beclomethasone subjects, and 37% of placebo subjects. Both active drug groups had statistically significant differences in the proportion of asymptomatic days in terms of SAR symptoms, as compared to the placebo group (p<.01). A baseline proportion of asymptomatic days for each treatment group was not provided by the sponsor, hence it is more difficult to conclude that these differences are entirely due to active drug treatment with either mometasone or beclomethasone. Nonetheless, as noted in the reviewer's prior discussion of subject distribution by SAR severity at baseline (Section 8.10.4.1.C. of this review), similar baseline SAR scores would suggest that indeed the three study populations had a similar severity of total nasal and total SAR symptoms with a small but numerically greater symptom score for the beclomethasone and

placebo groups at baseline, when compared with the mometasone group

Reviewer's Note: Summary of Efficacy Findings

Overall, mometasone was found to be effective in increasing the proportion of minimal symptom days during onset of the ragweed pollen season at a dose of 200 µg po qd, as related to prophylaxis of seasonal allergic rhinitis symptoms over the course of all study intervals. Mometasone administered at a dose of 200 µg po qd (once daily) was also found to statistically decrease total nasal symptom scores, total SAR scores and total non-nasal symptom scores, as compared to placebo. This effect of mometasone on decreasing non-nasal SAR symptoms was in contrast to those found in the SAR studies (e.g. C93-013) where mometasone was not administered prophylactically. Of note, this effect was also seen when the active comparator drug, beclomethasone, was administered prophylactically to study subjects, hence this effect may represent one which may be attributable to other nasal steroid preparations.

Mometasone did not demonstrate a significant waning of clinical efficacy based on separate a.m. and p.m. scoring of symptoms in subject diaries, a finding which supports once a day (qd) dosing of mometasone.

In terms of the primary efficacy variable, subset analysis by age, gender, and race revealed that mometasone treatment demonstrated similar efficacy in subjects age 12-17, 18-64, and > 64 years of age, and in males and females. Because the majority of study subjects for protocol C93-215 were Caucasian, no statistical conclusion can be reached regarding efficacy of mometasone in the small number of non-Caucasian subjects, however no significant difference in response was noted for non-Caucasian subjects compared with Caucasian subjects.

In summary, given a reasonable study design (and despite some study flaws which were previously addressed) to assess a therapeutic response in the treatment of seasonal allergic rhinitis when mometasone is given prophylactically before the onset of the pollen season, and reasonable clinical efficacy results, mometasone was found to be effective in decreasing the symptoms of SAR when used prophylactically, compared with placebo. Without a mometasone treatment arm in this study where subjects would have received mometasone at the onset of the pollen season, the additional degree of SAR symptom relief achieved by prophylaxis in contrast to initiation of treatment at the onset of the pollen season cannot be assessed.

Summary tables of all efficacy endpoints for study C93-215 (primary, secondary, and supplementary) are provided below (Table XXII., XXIII., and XXIV).

Table XXII. Primary Efficacy Variable of SAR and Treatment with Mometasone [179:223]

1° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1	Proportion of minimal sx days during the pollen season (total nasal sx score ≤ 2)	*Yes

sx=Symptom

* Note Statistically significant response for 1° efficacy variable carried by 2 of the 9 study centers (i.e. 7/9 centers had a statistically non-significant response

Table XXIII. Secondary Efficacy Variables of SAR and Treatment with Mometasone [179:219, 223]

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1	Proportion of minimal sx days during the first week of the pollen season (total nasal sx score ≤ 2)	Yes
2	Proportion of minimal sx days for the entire treatment period (total nasal sx score ≤ 2)	Yes
3	Proportion of asymptomatic days during the pollen season (total nasal sx score =0)	Yes
4	# of days from the start of the pollen season to the first occurrence of a non-minimal sx day (total nasal sx score > 2)	Yes
5	# of days from the start of treatment to the first occurrence of a non-minimal sx day (total nasal sx score > 2)	Yes

sx=Symptom, #=Number

Table XXIV. Supplementary Efficacy Variables of SAR and Treatment with Mometasone [179.221, 223, 180.389-403, SAS Datafiles, Attachment I]

Supplementary EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)	
1	Subject evaluated mean Δ in Total Nasal Sx Score DAY 1-15 DAY16-30 DAY 31-45 DAY 46-61 Endpoint Visit	Yes:	Day 1-15, Day 16-30, Endpoint Visit
		*N/E:	Day 31-45, Day 46-61
2	Subject evaluated mean Δ in Total SAR Sx DAY 1-15 DAY16-30 DAY 31-45 DAY 46-61 Endpoint Visit	Yes:	Day 1-15, Day 16-30, Endpoint Visit
		N/E:	Day 31-45, Day 46-61
3	Subject evaluated mean Δ in Total Non-nasal Sx DAY 1-15 DAY16-30 DAY 31-45 DAY 46-61 Endpoint Visit	Yes:	Day 1-15, Day 16-30, Endpoint Visit
		N/E:	Day 31-45, Day 46-61
4	Subject evaluated individual nasal Sx DAY 1-15 DAY16-30 DAY 31-45 DAY 46-61 Endpoint Visit	Yes:	All 4 nasal sx: Day 1-15, Day 16-30, Endpoint Visit
		N/E:	All 4 nasal sx: Day 31-45, Day 46-61
5	Subject evaluated individual non-nasal Sx DAY 1-15 DAY16-30 DAY 31-45 DAY 46-61 Endpoint Visit	Yes:	Eye Tearing: Day 1-15 Eye Redness: Day 1-15, Day 16-30, Endpoint visit Eye Itch: Day 1-15, Day 16-30 Ear/Palatal Itch: Day 1-15, Day 16-30, Endpoint Visit
		N/E:	Eye Redness: Day 31-45, Day 46-61 Ear/Palatal Itch: Day 31-45, Day 46-61
6	Physician evaluated total SAR, total nasal, total non-nasal, individual nasal and individual non-nasal sx	Yes:	Total SAR: Day 29, 36, 50, 57, Endpoint Visit Total Nasal: Day 29, 36, 50, 57, Endpoint Visit Total Non-nasal: Day 50 Individual Nasal (all 4 sxs responded to mometasone): Day 29, 36, 50, 57, Endpoint Visit Individual Non-nasal: Eye tearing: Endpoint Visit Eye Itch: Day 50 Ear/Palatal Itch: Day 29, 50
7	Proportion of minimal sx days during the prophylaxis period	Yes	
8	Proportion of asymptomatic days during the prophylaxis period	Yes	
9	Proportion of asymptomatic days during the entire study	Yes	

Δ=Change, Sx=Symptom, Rx=Treatment

*N/E (Non-estimable) denotes numerically greater decrease in sx noted for the mometasone treatment group compared with placebo but p-value is non-estimable due to study underpowering

8.9.4.3. SAFETY ANALYSIS

A review of safety data was performed on the safety (intent-to-treat) population which consisted of all randomized subjects who received at least one post-baseline evaluation. For the safety population, 116 subjects each were treated with mometasone or beclomethasone and 115 subjects were treated with placebo.

Safety data consisted of clinical adverse events (further characterized as treatment emergent [179:67-71], treatment related (severe and non-severe) [179:75, 72-73], and treatment unrelated [183:3587-3829]), laboratory test values, vital signs, and pertinent physical exam findings such as nasal septal perforation or nasal candidiasis. A review of all safety parameters submitted by the sponsor by line listings was performed and those laboratory results, vital sign abnormalities, physical exam findings, and adverse events deemed by the medical reviewer to be clinically significant or pertinent negative results, are discussed in the sections below.

Overall, analysis of the safety data for protocol C93-215 indicates that mometasone was safe and well tolerated by subjects. Adverse events were similar to those observed with beclomethasone and in general, similar to those seen with nasal corticosteroid use. Unlike most studies reviewed in this NDA submission, the incidence of adverse events was found to be highest in the mometasone treatment group. No significant difference in adverse event rates was found based on age, gender, or race.

Adverse events were reported by 63% of subjects treated with mometasone, compared to 51% [illegible]ubjects treated with beclomethasone, and 52% of subjects treated with placebo. The most frequently reported adverse events are summarized in Table 17 of the NDA submission (see below) [179:67]. For a complete listing of adverse events, please refer to [180:406-412].

Table 11 Incidence of Patients Reporting Frequent Treatment-Emergent Adverse Events[a] Safety Population (Protocol No. C93.215)

	Number (%) of Patients[a]		
	MFNS (n = 116)	BDP (n = 116)	Placebo (n = 115)
Body As a Whole - General Disorders			
fatigue	1 (1)	0	3 (3)
headache	42 (36)	25 (22)	27 (23)
influenza-like symptoms	2 (2)	3 (3)	1 (1)
Central and Peripheral Nervous System Disorders			
dizziness	1 (1)	1 (1)	3 (3)
Cardiovascular System Disorders			
syncope	2 (2)	0	3 (3)
Musculo-skeletal System Disorders			
musculoskeletal pain	3 (3)	1 (1)	4 (3)
myalgia	2 (2)	4 (3)	3 (3)
Psychiatric Disorders			
insomnia	3 (3)	1 (1)	2 (2)
Reproductive Disorders, Female[b]			
dysmenorrhea	4 (6)	0	4 (8)
Respiratory Mechanism Disorders			
infection, viral	3 (3)	7 (6)	3 (3)
Respiratory System Disorders			
coughing	3 (3)	3 (3)	5 (4)
epistaxis	5 (4)	3 (3)	5 (4)
nasal burning	3 (3)	1 (1)	2 (2)
nasal irritation	1 (1)	1 (1)	3 (3)
pharyngitis	7 (6)	12 (10)	6 (5)
rhinitis	1 (1)	1 (1)	4 (3)
sinusitis	2 (2)	3 (3)	2 (2)
sneezing	2 (2)	0	4 (3)
upper respiratory tract infection	7 (6)	5 (5)	1 (1)
Skin and Appendages Disorders			
ingrown hair	0	0	3 (3)
Special Senses Other, Disorders			
taste perversion	1 (1)	3 (3)	1 (1)

Headache was reported as the most frequent adverse event and was found to be present in 36% of subjects treated with mometasone, 22% of subjects treated with beclomethasone, and 23% of subjects treated with placebo [180:406]. All other adverse events were present in less than or equal to 10% of study subjects in either of the 3 treatment arms. The second most frequent adverse event was pharyngitis [180:410] (present in 6% of mometasone subjects, 10% of beclomethasone subjects, and 5% of placebo subjects), interestingly followed by dysmenorrhea [180:409, 183:3634-3635] (present in 6% of the mometasone group's female subjects, no beclomethasone subjects, and 8% of the placebo group's female subjects). Epistaxis, frequently cited as one of the more common adverse events in the SAR studies in this NDA submission was mild or moderate in severity, intermittent, and of short duration in all treatment groups. Epistaxis was recorded in 4% of mometasone and placebo subjects, respectively, and 3% of beclomethasone subjects [180:410]. No cases of nasal septal perforation or nasal ulceration were reported in any of the three treatment groups in this study [184:4450-4507]. One case of cataract formation in the left eye was reported in a subject in the beclomethasone treatment group who was struck by lightening (see below, C93-215-05, #26) and this was felt by the principal investigator to be unrelated to treatment [180:412, 183:3724, 3739]. No subject deaths were reported in this study [179:76], although a 22 year old male subject in the

beclomethasone treatment group (C93-215-05 #26) was struck by lightening and suffered a respiratory arrest with eventual full recovery and discharge from the hospital 4 days after the initial event [179:77, 183:3724].

Regarding associated infections, 6% of subjects treated with mometasone reported an upper respiratory tract infection, in contrast to 3% of subjects in the beclomethasone treatment group and 1% of subjects in the placebo group [180:410, 183:3728-3729, 3640-3641, 3658-3660, 3707-3709, 3796, 3820]. No cases of nasal or oral candidiasis were reported in any of the three treatment groups in this study [184:4450-4507]. One case of herpes simplex labialis in a 27 year old female (C93-215-05, #2) was reported for the mometasone treatment group during visits 6 and 7 of the study which was moderate in severity and thought to be unrelated to treatment by the investigator [180:409, 183:3636] along with one case of herpes zoster, reported in a 38 year old female (C93-215-01, #33) in the mometasone treatment group during visit 9 which was moderate in severity and also thought to be unrelated to treatment by the investigator [180:409, 183:3637]. In summary, the most frequent adverse events cited were symptoms known to be associated with seasonal allergic rhinitis itself, and not necessarily related to drug use per se.

Regarding significant laboratory tests abnormalities, one case of an elevated SGOT to 113 U/L (normal range 11-36 U/L) and SGPT to 75 U/L (normal range 6-43 U/L) was reported in a 28 year old male (subject C93-215-01 #043) during Visit 8 of the study, with repeat liver function tests measured 6 days later within normal range. The subject's presumed liver function test elevations were considered by the principal investigator to be a result of muscle damage from a 50 mile run 3 days prior to the Visit 8 blood test, and unrelated to study medication [179:76, 183:3624]. No other clinically relevant abnormal laboratory test results were reported in this study. Although there were scattered laboratory test values outside the normal ranges for several subjects, as assessed by shift tables, none were remarkable.

No clinically relevant changes in mean values from pretreatment were noted in any of the subjects' vital signs or body weight. Shift tables were similar among all 3 treatment groups. ECGs performed pretreatment and at endpoint failed to reveal any relevant abnormal findings.

Gender, race and age subgroup analyses of vital signs, body weight, laboratory data, and ECGs failed to reveal any differences between any of these subgroups and the overall subject population, although the number of non-Caucasian subjects and subjects between 12-17 years or > 64 years of age was too small to draw meaningful conclusions concerning these subgroups.

Regarding subject drop-outs due to adverse events, a total of 10 subjects (1 treated with mometasone, 5 treated with beclomethasone, and 4 treated with placebo) discontinued treatment because of adverse events [179:145-147]. The reason for discontinuation in the study for one subject in the mometasone treatment group (C93-215-06, #16) was bronchitis and sinusitis rated as moderate in severity and which was felt to be unrelated to treatment by the principal

investigator [179:76, 151]. Overall, for the 3 treatment groups, most subjects who discontinued treatment (7/10 subjects) did so for reasons 'unrelated' to the study drug [179:76, 149-153].

8.9.5. **Reviewer's Conclusion of Study Results**:

In this prophylaxis of SAR trial, 116 subjects received mometasone treatment, 116 subjects received the active comparator beclomethasone, and 115 subjects received placebo treatment.

With the exception of a greater percentage of subjects in the mometasone treatment group who were female, all 3 treatment arms were otherwise similar in demographic and clinical characteristics, including subject self-rated severity of SAR symptoms at baseline (0-3 score). The majority of subjects in this study received mometasone prophylaxis for 4 weeks, however, of those who did not (primarily subjects at study sites -02 and -09, who received from 14-21 days of pre-treatment with mometasone or one of the other treatments), shorter duration of pre-treatment with mometasone did not appear to change the trend in decreasing total nasal symptom scores (statistical comparison was not performed on these subjects because of low subject number and underpowering) [Response to FDA Request on Prophylaxis Studies, Schering Plough, Inc., 05/21/97, p. 58-84].

Results that Support Approval:

Mometasone administered at a dose of 200 µg qd intranasally was statistically better than placebo in increasing the proportion of minimal total nasal symptom days (based on subject self-rated total nasal symptom scores that were a composite of rhinorrhea, sneezing, nasal congestion, and nasal itch scores and were defined as being ≤ 2 to qualify as a 'minimal' symptom day) during the ragweed pollen season. Mometasone treatment increased the proportion of minimal symptom days to 84%, compared to a respective 63% increase in the proportion of minimal symptom days in the placebo treatment group (and as compared with a 79% increase in the beclomethasone treatment group). This statistically significant decrease in symptomatic days in mometasone treated subjects was likewise noted during the prophylaxis period, the first week of the pollen season, and more broadly, for the entire study treatment period, when compared to placebo. Mometasone treated subjects were statistically more likely to have a greater proportion of 'no' nasal symptoms ('asymptomatic' days) during the prophylaxis period, the pollen season and even the entire treatment period than the placebo treatment group. Additionally, the number of days from the start of treatment or start of the pollen season to the onset of a non-minimal nasal symptom day was more likely to be statistically significantly longer in subjects who were treated with mometasone than those receiving placebo.

Based on subject self-rated total SAR, total nasal, total non-nasal, and individual nasal and non-nasal symptom scores, mometasone treated subjects demonstrated statistically significantly lower symptom scores and a smaller

increase of symptoms with onset of the pollen season than the placebo treatment group. Because this relative decrease in symptoms in the mometasone treatment group already occurred during the prophylaxis period (a 4 week period), onset of action of mometasone in the prophylaxis setting appeared to occur sooner than 4 weeks, however based on the data provided by the sponsor, the approximate week of onset of action of mometasone cannot be more specifically defined. The physician evaluated subject symptom scores indicate that for almost all study parameters, treatment for at least 3-4 weeks (day 29 visit) was required before a statistically significant difference in symptoms was evident in mometasone treated subjects vs. placebo treated subjects.

Interestingly, and in contrast to the SAR studies reviewed in this NDA submission, the total and individual subject evaluated non-nasal symptom scores were found to be statistically significantly lower in the mometasone treatment group, as compared with placebo. This observation was likewise noted in the beclomethasone treatment group and implies that pretreatment with nasal steroids prior to onset of the pollen season in subjects with SAR may afford greater efficacy in decreasing other symptoms of SAR (non-nasal) in addition to nasal symptoms. Without a fourth study arm comparing mometasone pretreatment prior to onset of the pollen season with mometasone treatment at the onset of the pollen season, this question cannot be addressed definitively. Thus, based on the study design and efficacy results of trial C93-215, mometasone treatment appears to decrease SAR symptoms compared to placebo, however, it is not clear and not conclusive that pretreatment (prior to pollen season onset) with mometasone will statistically significantly decrease SAR symptoms compared with initiation of mometasone treatment at the time of pollen season onset.

Finally, physician rated subject total SAR, total nasal, total non-nasal, and individual nasal and non-nasal symptom scores indicate that for most study visits (exceptions noted below in the 'Results that did not support Approval' section), mometasone treated subjects had statistically better symptom scores than those subjects treated with placebo. A summary of all efficacy endpoints evaluated in study C93-215 is provided in Tables XXII.-XXIV.

Results that did not Support Approval:

Very few results from study C93-215 do not support approval of mometasone for the treatment of SAR. For the primary efficacy endpoint, one must note that only 2 of the 9 study centers had statistically significant differences between mometasone treatment and placebo and 3 additional centers (-01, [179:209], -04 [179:212], -07 [179:215]) approached statistical significance. In addition, several of the non-nasal symptoms were found to have a less consistent response in mometasone treated subjects, as compared with placebo. Notably, subject evaluated eye tearing scores on day 16-30 of the study were not found to be statistically different between the mometasone and placebo treated subjects. Of physician evaluated scores, the total and individual non-nasal symptom scores of mometasone treated subjects were overall not found to be consistently better than

those of placebo subjects. Given the lesser importance of non-nasal symptom scores in the assessment of SAR; these findings, while noted, are less critical in determining efficacy of mometasone treatment than nasal symptom scores.

Other Results:

Mometasone (200 µg qd) appeared to exert its effect at decreasing SAR symptoms (nasal and non-nasal) throughout the day, with similar subject self-rated total SAR, total nasal, total non-nasal, and individual nasal and non-nasal symptom scores achieved during the a.m. and p.m. measurements. Hence, mometasone administered as a 200 µg dose once a day demonstrated a reasonable 24 hour duration of effect in this study.

Safety:

Overall, mometasone was safe and well-tolerated administered as a once a day, 200 µg dose. No serious adverse events occurred in subjects treated with mometasone, nor were any deaths reported. Similar to placebo and similar to the SAR studies in this NDA submission, headache was the most common adverse event associated with mometasone use, followed by pharyngitis. The third most common adverse event, uniquely noted in this study, was dysmenorrhea in female subjects; however more female subjects comprised the mometasone treatment group, compared with the other two study arms. No nasal septal perforations or cases of nasal candidiasis were reported. While one case of cataract formation was reported in a beclomethasone treated subject, a scientific link between the subject's lightening strike and cataract formation was not provided by the sponsor. Because of study duration, this study did not specifically evaluate posterior subcapsular cataract formation or hypothalamic-pituitary-adrenal (HPA) axis suppression.

Summary:

Based on results of the seasonal allergic rhinitis prophylaxis trial C93-215, mometasone demonstrated adequate evidence of efficacy and safety compared with placebo in the treatment of symptoms of SAR. Based on study design, however, one cannot conclude that mometasone prophylaxis demonstrates superior efficacy in the treatment of SAR symptoms compared to mometasone treatment given at the time of onset of the allergy season.

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM & PM AVERAGED NASAL SYMPTOM SCORE - POOLED DIARY DATA

DAYS		(A) MFNS N	(A) MFNS MEAN	(A) MFNS SD	(B) VANCENASE N	(B) VANCENASE MEAN	(B) VANCENASE SD	(C) PLACEBO N	(C) PLACEBO MEAN	(C) PLACEBO SD	POOLED SD	ANOVA P-VALUES # TRT	ANOVA P-VALUES # INV	ANOVA P-VALUES # T X I	PAIRWISE COMPARISONS # A-B	PAIRWISE COMPARISONS # A-C	PAIRWISE COMPARISONS # B-C
BASELINE		116	0.3	0.5	115	0.4	0.5	115	0.4	0.5	0.4	0.19	<.01	0.48	0.41	0.07	0.32
PRE	RAW	116	0.4	0.7	115	0.6	1.0	115	0.7	0.9	0.8	0.01	<.01	0.65	0.13	<.01	0.13
	CHG	116	0.1	0.6	115	0.2	1.0	115	0.3	0.8	0.8	0.12	<.01	0.32	0.29	0.04	0.32
	%CHG	66	14.0	127	65	58.6	206	65	97.9	234							
1-7	RAW	114	0.6	0.8	111	0.8	1.3	109	1.6	1.8	1.3	<.01	<.01	<.01	0.12	<.01	<.01
	CHG	114	0.2	0.8	111	0.4	1.3	109	1.2	1.9	1.3	<.01	<.01	<.01	0.19	<.01	<.01
	%CHG	65	42.9	197	63	173	397	59	285	579							
8-15	RAW	114	0.9	1.2	108	1.2	1.5	105	2.2	2.3	1.6	<.01	<.01	<.01	0.18	<.01	<.01
	CHG	114	0.5	1.2	108	0.8	1.6	105	1.8	2.3	1.6	<.01	<.01	<.01	0.25	<.01	<.01
	%CHG	65	125	291	61	264	547	59	443	885							
16-45	RAW	114	1.2	1.4	107	1.5	1.8	103	2.4	2.3	1.8	<.01	0.02	0.07	0.2	<.01	<.01
	CHG	114	0.8	1.4	107	1.1	1.8	103	2.0	2.3	1.8	<.01	<.01	0.05	0.26	<.01	<.01
	%CHG	65	287	330	60	243	426	58	466	689							
46-61	RAW	18	1.4	1.5	14	2.0	2.8	13	1.8	1.9	2.2	0.69	0.83	0.7	0.5	M/E	M/E
	CHG	18	1.0	1.5	14	1.7	2.9	13	1.6	2.0	2.2	0.53	0.62	0.62	0.34	M/E	M/E
	%CHG	11	281	384	8	602	1267	4	118	201							
ENDPT	RAW	116	1.2	1.4	115	1.6	1.9	115	2.6	2.4	1.9	<.01	0.01	0.03	0.11	<.01	<.01
	CHG	116	0.8	1.4	115	1.2	2.0	115	2.1	2.5	1.9	<.01	<.01	0.02	0.17	<.01	<.01
	%CHG	66	191	339	65	294	631	65	497	911							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION M/E = NON-ESTIMABLE
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
PRE : PRE-SEASON TREATMENT INTERVAL -- OTHERS ARE DAYS POST-ONSET OF SEASON
@ SUM OF THE 4 NASAL SYMPTOMS FROM THE AVERAGED AM & PM DIARIES - *RUNNY NOSE, STUFFINESS, SNEEZING AND ITCH*
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM & PM DIARY BASELINE VALUES
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

NOTE: Data generated from SAS datafiles for ITT population (Dr. Jim Gebert, Biostatistics, HFD-570).

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM NASAL SYMPTOM SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES @			PAIRWISE COMPARISONS @		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.4	0.5	115	0.5	0.6	115	0.5	0.6	0.5	0.49	<.01	0.34	0.39	0.25	0.77
PRE	RAW	116	0.5	0.8	115	0.6	1.0	115	0.8	0.9	0.8	0.02	<.01	0.56	0.16	<.01	0.14
	CHG	116	0.1	0.7	115	0.2	1.1	115	0.3	0.9	0.8	0.09	<.01	0.2	0.37	0.03	0.19
	%CHG	63	2.4	124	57	0.5	140	60	106	272							
1-7	RAW	114	0.6	0.9	111	0.9	1.3	109	1.6	1.8	1.3	<.01	<.01	0.03	0.14	<.01	<.01
	CHG	114	0.2	0.8	111	0.4	1.3	109	1.1	1.9	1.4	<.01	<.01	0.01	0.24	<.01	<.01
	%CHG	62	16.7	160	55	65.6	236	55	224	523							
8-15	RAW	114	0.9	1.3	108	1.1	1.5	105	2.2	2.2	1.6	<.01	<.01	<.01	0.25	<.01	<.01
	CHG	114	0.5	1.2	108	0.7	1.6	105	1.7	2.3	1.6	<.01	<.01	<.01	0.34	<.01	<.01
	%CHG	62	75.4	211	53	166	510	55	380	734							
16-45	RAW	114	1.2	1.4	107	1.5	1.8	103	2.4	2.3	1.8	<.01	0.01	0.1	0.18	<.01	<.01
	CHG	114	0.8	1.4	107	1.1	1.9	103	2.0	2.4	1.8	<.01	<.01	0.06	0.25	<.01	<.01
	%CHG	62	120	255	52	113	264	54	399	727							
46-61	RAW	18	1.4	1.6	14	2.2	3.1	13	1.8	2.1	2.4	0.58	0.8	0.57	0.41	N/E	N/E
	CHG	18	0.9	1.5	14	1.8	3.2	13	1.5	2.2	2.4	0.4	0.63	0.46	0.29	N/E	N/E
	%CHG	11	170	319	6	474	762	4	19.7	147							
ENDPT	RAW	116	1.2	1.4	115	1.6	2.0	115	2.6	2.4	1.9	<.01	<.01	0.06	0.1	<.01	<.01
	CHG	116	0.8	1.4	115	1.1	2.1	115	2.1	2.5	2.0	<.01	<.01	0.05	0.16	<.01	<.01
	%CHG	63	123	261	57	177	508	60	406	753							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
@ P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 4 NASAL SYMPTOMS FROM THE AM DIARY - RUNNY NOSE, STU FFINESS, SNEEZING AND ITCH
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 4 AM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO AND INCLUDING DAY 1
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

PM NASAL SYMPTOM SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.3	0.5	115	0.3	0.5	115	0.4	0.6	0.5	0.08	<.01	0.67	0.53	0.03	0.12
PRE	RAW	116	0.4	0.7	115	0.5	1.0	115	0.7	0.9	0.8	0.01	<.01	0.7	0.13	<.01	0.14
	CHG	116	0.1	0.6	115	0.2	1.0	115	0.3	0.8	0.8	0.23	0.03	0.47	0.26	0.09	0.58
	%CHG	43	1.1	135	43	54.9	161	52	87.0	227							
1-7	RAW	114	0.5	0.8	111	0.8	1.3	109	1.6	1.9	1.3	<.01	<.01	<.01	0.11	<.01	<.01
	CHG	114	0.3	0.8	111	0.5	1.3	109	1.2	2.0	1.3	<.01	0.01	<.01	0.18	<.01	<.01
	%CHG	42	34.6	183	42	117	329	47	232	513							
8-15	RAW	114	0.9	1.2	108	1.2	1.6	105	2.2	2.4	1.7	<.01	<.01	<.01	0.15	<.01	<.01
	CHG	114	0.6	1.3	108	0.8	1.7	105	1.8	2.5	1.7	<.01	<.01	<.01	0.2	<.01	<.01
	%CHG	42	97.9	243	40	231	542	47	327	545							
16-45	RAW	114	1.2	1.4	107	1.5	1.7	103	2.4	2.4	1.8	<.01	0.84	0.06	0.23	<.01	<.01
	CHG	114	0.9	1.4	107	1.1	1.8	103	2.0	2.4	1.8	<.01	<.01	0.05	0.29	<.01	<.01
	%CHG	42	185	348	39	182	354	47	395	572							
46-61	RAW	18	1.4	1.4	14	1.8	2.6	13	1.7	1.9	2.1	0.83	0.73	0.86	0.62	N/E	N/E
	CHG	18	1.1	1.5	14	1.6	2.7	13	1.6	2.0	2.1	0.71	0.52	0.8	0.53	N/E	N/E
	%CHG	7	340	569	5	90.0	236	3	423	847							
ENDPT	RAW	116	1.2	1.4	115	1.5	1.9	115	2.6	2.5	1.9	<.01	0.02	0.02	0.14	<.01	<.01
	CHG	116	0.9	1.4	115	1.2	2.0	115	2.2	2.5	2.0	<.01	<.01	0.01	0.2	<.01	<.01
	%CHG	43	185	366	43	232	526	52	342	495							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LEHMANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 4 NASAL SYMPTOMS FROM THE AM DIARY - RUNNY NOSE, STU FFINESS, SNEEZING AND ITCH
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 3 PM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO BUT NOT INCL.DING DAY 1
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM & PM AVERAGED TOTAL SYMPTOM SCORE - POOLED DIARY DATA

	(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES @			PAIRWISE COMPARISONS @		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	116	0.5	0.6	115	0.6	0.8	115	0.6	0.8	0.7	0.28	<.01	0.14	0.4	0.06	0.3
PRE RAW	116	0.7	1.0	115	0.9	1.6	115	1.1	1.3	1.3	0.09	<.01	0.48	0.25	0.03	0.28
CHG	116	0.2	0.9	115	0.3	1.7	115	0.4	1.1	1.2	0.44	<.01	0.22	0.67	0.2	0.58
%CHG	72	39.3	157	68	106	325	70	95.3	244							
1-15 RAW	114	2.3	3.5	111	1.7	2.2	109	3.0	3.3	2.3	<.01	<.01	0.01	0.23	<.01	<.01
CHG	114	0.8	1.5	111	1.1	2.2	109	2.4	3.3	2.3	<.01	<.01	<.01	0.32	<.01	<.01
%CHG	71	208	542	65	327	539	64	486	1085							
16-30 RAW	114	2.0	2.3	107	2.5	3.1	103	3.7	4.0	3.1	<.01	0.01	0.05	0.15	<.01	<.01
CHG	114	1.5	2.3	107	2.0	3.2	103	3.1	4.0	3.1	<.01	<.01	0.04	0.19	<.01	<.01
%CHG	72	279	464	62	391	642	63	574	959							
31-45 RAW	76	2.3	3.5	67	2.9	4.0	61	3.6	4.2	3.9	0.02	0.19	0.72	M/E	M/E	M/E
CHG	76	1.8	3.5	67	2.4	4.2	61	3.0	4.1	3.9	0.04	0.02	0.8	M/E	M/E	M/E
CHG	45	184	329	35	333	638	34	712	1716							
46-61 RAW	18	2.4	2.8	14	3.9	5.8	13	2.5	2.6	4.0	0.77	0.8	0.67	0.63	M/E	M/E
CHG	18	1.8	2.8	14	3.5	5.8	13	2.2	2.6	4.0	0.58	0.59	0.53	0.47	M/E	M/E
%CHG	12	351	453	9	760	967	6	660	1200							
ENDPT RAW	116	2.0	3.0	115	2.6	3.5	115	3.9	4.3	3.5	<.01	<.01	0.06	0.16	<.01	<.01
CHG	116	1.5	3.0	115	2.0	3.6	115	3.3	4.3	3.5	<.01	<.01	0.06	0.21	<.01	0.01
CHG	72	260	462	68	403	684	70	771	1582							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION M/E = NON-ESTIMABLE
@ P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LEHMANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
# SUM OF THE 8 TOTAL SYMPTOMS FROM THE AVERAGED AM & PM DIARIES
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM & PM DIARY BASELINE VALUES
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM TOTAL SYMPTOM SCORE - POOLED DIARY DATA

		(A) *MFNS*			(B) VANCENASE			(C) PLACEBO			*POOLED*	ANOVA P-VALUES @			PAIRWISE COMPARISONS @		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.6	0.7	115	0.7	0.9	115	0.7	0.9	0.7	*0.56*	<.01	0.14	0.42	0.29	0.8
PRE	RAW	116	0.8	1.1	115	0.9	1.7	115	1.1	1.4	1.3	0.09	<.01	0.51	0.3	0.03	0.25
	CHG	116	0.2	1.0	115	0.3	1.8	115	0.5	1.2	1.3	0.26	<.01	0.2	0.54	0.1	0.3
	%CHG	70	25.6	148	61	19.1	133	63	120	297							
1-15	RAW	114	1.4	2.6	111	1.7	2.2	109	3.0	3.2	2.3	<.01	<.01	0.02	0.28	<.01	<.01
	CHG	114	0.8	1.5	111	1.0	2.3	109	2.4	3.3	2.3	<.01	<.01	0.01	0.39	<.01	<.01
	%CHG	69	125	296	58	191	400	58	459	938							
16-30	RAW	114	2.0	2.4	107	2.6	3.1	103	3.7	4.0	3.1	<.01	0.01	0.04	0.12	<.01	<.01
	CHG	114	1.4	2.3	107	1.9	3.3	103	3.1	4.0	3.1	<.01	<.01	0.03	0.16	<.01	<.01
	%CHG	69	202	369	55	219	413	57	656	1348							
31-45	RAW	76	2.4	3.6	67	3.1	4.2	61	3.6	4.0	3.9	0.03	0.14	0.75	N/E	N/E	N/E
	CHG	76	1.7	3.6	67	2.4	4.4	61	2.9	3.9	3.9	0.05	0.01	0.01	N/E	N/E	N/E
	%CHG	45	139	277	33	218	406	30	366	757							
46-61	RAW	18	2.4	2.8	14	4.2	6.2	13	2.6	2.6	4.3	0.77	0.82	0.63	0.59	N/E	N/E
	CHG	18	1.6	2.8	14	3.7	6.3	13	2.1	2.7	4.2	0.57	0.61	0.5	0.43	N/E	N/E
	%CHG	12	256	413	7	707	649	5	91.0	199							
ENDPT	RAW	116	2.1	3.1	115	2.7	3.6	115	3.9	4.2	3.5	<.01	<.01	0.06	0.12	<.01	0.01
	CHG	116	1.5	3.0	115	2.1	3.9	115	3.3	4.2	3.5	<.01	<.01	*0.06*	*0.16*	<.01	0.02
	%CHG	70	192	371	61	232	428	63	613	1283							

SD = *STANDARD DEVIATION* T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
@ P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS *PAIRWISE COMPARISONS* (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 8 TOTAL SYMPTOMS FROM THE AM DIARY
BASELINE FOR *EACH SUBJECT* WAS THE AVERAGE OF 4 AM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO *AND INCLUDING* DAY 1
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

C93-213

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

PM TOTAL SYMPTOM SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES @			PAIRWISE COMPARISONS @		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.4	0.6	115	0.5	0.8	115	0.6	0.9	0.7	0.05	<.01	0.31	0.46	0.02	0.09
PRE	RAW	116	0.6	0.9	115	0.8	1.6	115	1.0	1.2	1.2	0.09	<.01	0.45	0.22	0.03	0.34
	CHG	116	0.2	0.9	115	0.3	1.7	115	0.4	1.1	1.3	0.65	0.01	0.27	0.42	0.42	>.99
	%CHG	50	23.8	147	50	67.8	189	58	74.4	217							
1-15	RAW	116	1.3	1.6	111	1.7	2.2	109	3.0	3.4	2.4	<.01	<.01	<.01	0.19	<.01	<.01
	CHG	114	0.9	1.6	111	1.2	2.2	109	2.5	3.4	2.4	<.01	<.01	<.01	0.27	<.01	<.01
	%CHG	49	95.2	176	49	229	432	52	307	572							
16-30	RAW	114	2.0	2.3	107	2.5	3.1	103	3.7	4.2	3.1	<.01	0.01	0.06	0.19	<.01	<.01
	CHG	114	1.6	2.4	107	2.0	3.2	103	3.1	4.1	3.1	<.01	<.01	0.06	0.24	<.01	0.01
	%CHG	49	221	297	46	252	424	52	445	690							
31-45	RAW	67	2.4	3.6	56	3.2	4.1	54	3.5	4.4	4.0	0.3	0.24	0.96	M/E	M/E	M/E
	CHG	67	1.9	3.6	56	2.7	4.3	54	2.9	4.4	4.0	0.42	0.03	0.94	M/E	M/E	M/E
	%CHG	27	229	345	23	319	661	28	696	1347							
46-61	RAW	18	2.4	2.8	14	3.6	5.4	13	2.6	2.6	3.9	0.77	0.74	0.72	0.67	M/E	M/E
	CHG	18	1.9	2.8	14	3.3	5.4	13	2.4	2.6	3.8	0.6	0.53	0.57	0.89	M/E	M/E
	%CHG	8	359	553	6	485	587	5	552	632							
ENDPT	RAW	116	2.0	2.9	115	2.6	3.4	115	3.9	4.4	3.5	<.01	<.01	0.09	0.2	<.01	<.01
	CHG	116	1.6	2.9	115	2.1	3.5	115	3.3	4.3	3.5	<.01	<.01	0.12	0.27	<.01	0.01
	%CHG	50	239	367	50	290	528	58	519	976							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION M/E = NON-ESTIMABLE
@ P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 8 TOTAL SYMPTOMS FROM THE PM DIARY
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 3 PM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO BUT NOT INCLUDING DAY 1
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

ATTACHMENT 1

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM & PM AVERAGED TOTAL SYMPTOM SCORE - POOLED DIARY DATA

DAYS		(A) MFNS N	(A) MFNS MEAN	(A) MFNS SD	(B) VANCENASE N	(B) VANCENASE MEAN	(B) VANCENASE SD	(C) PLACEBO N	(C) PLACEBO MEAN	(C) PLACEBO SD	POOLED SD	ANOVA P-VALUES @ TRT	ANOVA P-VALUES @ INV	ANOVA P-VALUES @ T X I	PAIRWISE COMPARISONS @ A-B	PAIRWISE COMPARISONS @ A-C	PAIRWISE COMPARISONS @ B-C
BASELINE		116	0.5	0.6	115	0.6	0.8	115	0.6	0.8	0.7	0.18	<.01	0.14	0.4	0.06	0.3
PRE	RAW	116	0.7	1.0	115	0.9	1.6	115	1.1	1.3	1.3	0.09	<.01	0.49	0.25	0.03	0.28
	CHG	116	0.2	0.9	115	0.3	1.7	115	0.4	1.1	1.2	0.44	<.01	0.22	0.47	0.2	0.58
	%CHG	72	39.3	157	68	106	325	70	95.3	244							
1-7	RAW	114	1.0	1.3	111	1.3	2.1	109	2.3	2.9	2.1	<.01	0.03	0.03	0.25	<.01	<.01
	CHG	114	0.5	1.3	111	0.8	2.1	109	1.8	3.0	2.1	<.01	0.02	0.01	0.35	<.01	<.01
	%CHG	71	102	270	65	267	503	64	331	750							
8-15	RAW	114	1.6	2.0	108	2.0	2.5	105	3.5	4.1	2.7	<.01	<.01	<.01	0.26	<.01	<.01
	CHG	114	1.1	2.0	108	1.4	2.5	105	2.9	4.1	2.7	<.01	<.01	<.01	0.33	<.01	<.01
	%CHG	71	298	876	63	391	630	64	628	1522							
16-45	RAW	114	2.0	2.5	107	2.6	3.2	103	3.8	4.1	3.2	<.01	<.01	0.09	0.14	<.01	<.01
	CHG	114	1.5	2.5	107	2.0	3.4	103	3.2	4.0	3.2	<.01	<.01	0.07	0.18	<.01	0.01
	%CHG	71	278	498	62	407	850	63	635	1051							
46-61	RAW	18	2.4	2.8	14	3.9	5.8	13	2.5	2.6	4.0	0.77	0.8	0.67	0.63	N/E	N/E
	CHG	18	1.8	2.8	14	3.5	5.8	13	2.2	2.6	4.0	0.58	0.59	0.53	0.47	N/E	N/E
	%CHG	12	351	453	9	968	967	6	660	1200							
ENDPT	RAW	116	2.0	2.5	115	2.7	3.4	115	4.0	4.1	3.2	<.01	<.01	0.01	0.08	<.01	<.01
	CHG	116	1.5	2.5	115	2.1	3.6	115	3.3	4.1	3.3	<.01	<.01	0.01	0.12	<.01	0.01
	%CHG	72	288	474	68	424	687	70	743	1542							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
@ P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 6 TOTAL SYMPTOMS FROM THE AVERAGED AM & PM DIARIES
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM & PM DIARY BASELINE VALUES
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
%CHG PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
'DPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

C91-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM TOTAL SYMPTOM SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.6	0.7	115	0.7	0.9	115	0.7	0.9	0.7	0.56	<.01	0.14	0.42	0.25	0.8
PRE	RAW	116	0.8	1.1	115	0.9	1.7	115	1.1	1.4	1.3	0.09	<.01	0.51	0.3	0.03	0.25
	CHG	116	0.2	1.0	115	0.3	1.6	115	0.5	1.2	1.3	0.26	<.01	0.2	0.54	0.1	0.3
	%CHG	70	25.5	148	61	19.1	133	63	120	297							
1-7	RAW	114	1.1	1.3	111	1.3	2.1	109	2.3	2.8	2.1	<.01	0.04	0.11	0.3	<.01	<.01
	CHG	114	0.5	1.3	111	0.7	2.1	109	1.7	2.9	2.1	<.01	0.02	0.02	0.42	<.01	<.01
	%CHG	69	61.2	193	58	134	312	58	291	644							
8-15	RAW	114	1.6	2.0	108	1.9	2.4	105	3.4	3.9	2.7	<.01	<.01	<.01	0.35	<.01	<.01
	CHG	114	1.1	2.0	108	1.3	2.5	105	2.8	4.0	2.7	<.01	<.01	<.01	0.43	<.01	<.01
	%CHG	69	181	468	56	248	514	58	607	1248							
16-45	RAW	114	2.0	2.5	107	2.7	3.3	103	3.8	4.0	3.2	<.01	<.01	0.09	0.11	<.01	0.01
	CHG	114	1.5	2.5	107	2.0	3.5	103	3.2	4.0	3.2	<.01	<.01	0.07	0.15	<.01	0.01
	%CHG	69	202	367	55	231	415	57	665	1342							
46-61	RAW	18	2.4	2.8	14	4.2	6.2	13	2.4	2.6	4.3	0.77	0.82	0.63	0.59	N/E	N/E
	CHG	18	1.6	2.8	14	3.7	6.3	13	2.1	2.7	4.2	0.57	0.61	0.5	0.43	N/E	N/E
	%CHG	12	256	413	7	707	649	5	91.8	199							
ENDPT	RAW	116	2.0	2.5	115	2.8	3.5	115	4.0	4.1	3.3	<.01	<.01	0.01	0.06	<.01	0.01
	CHG	116	1.4	2.5	115	2.1	3.7	115	3.3	4.1	3.3	<.01	<.01	0.01	0.09	<.01	0.01
	%CHG	70	208	372	61	269	494	63	664	1391							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 8 TOTAL SYMPTOMS FROM THE AM DIARY
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 4 AM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO AND INCLUDING DAY 1
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
%CHG PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
/DPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

ATTACHMENT 1

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

FN TOTAL SYMPTOM SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.4	0.6	115	0.5	0.8	115	0.6	0.9	0.7	0.05	<.01	0.31	0.46	0.02	0.09
PRE	RAW	116	0.6	0.9	115	0.8	1.6	115	1.0	1.2	1.2	0.09	<.01	0.65	0.22	0.03	0.34
	CHG	116	0.2	0.9	115	0.3	1.7	115	0.4	1.1	1.3	0.65	0.01	0.27	0.42	0.41	> .99
	%CHG	50	23.8	147	50	67.8	189	58	74.4	217							
1-7	RAW	114	1.0	1.3	111	1.3	2.1	109	2.4	3.1	2.2	<.01	0.02	0.01	0.22	<.01	<.01
	CHG	114	0.6	1.3	111	0.8	2.1	109	1.8	3.2	2.2	<.01	0.02	<.01	0.32	<.01	<.01
	%CHG	49	50.2	169	49	172	427	52	226	503							
8-15	RAW	114	1.6	2.0	108	2.0	2.6	105	3.5	4.3	2.9	<.01	<.01	<.01	0.2	<.01	<.01
	CHG	114	1.2	2.1	108	1.5	2.6	105	3.0	4.3	2.9	<.01	<.01	<.01	0.27	<.01	<.01
	%CHG	49	136	215	47	291	496	52	378	694							
16-45	RAW	114	2.0	2.5	107	2.6	3.2	103	3.8	4.2	3.2	<.01	0.01	0.1	0.18	<.01	<.01
	CHG	114	1.6	2.5	107	2.1	3.3	103	3.2	4.1	3.2	<.01	<.01	0.1	0.23	<.01	0.01
	%CHG	49	227	308	46	283	460	52	498	768							
46-61	RAW	18	2.4	2.5	14	3.6	5.4	13	2.6	2.6	3.8	0.77	0.74	0.72	0.67	N/E	N/E
	CHG	18	1.9	2.8	14	3.3	5.4	13	2.4	2.6	3.8	0.6	0.53	0.57	0.53	N/E	N/E
	%CHG	8	359	553	6	485	587	5	552	632							
ENDPT	RAW	116	2.0	2.5	115	2.6	3.4	115	4.0	4.3	3.3	<.01	<.01	0.01	0.12	<.01	<.01
	CHG	116	1.6	2.5	115	2.1	3.5	115	3.4	4.2	3.3	<.01	<.01	0.01	0.17	<.01	0.01
	%CHG	50	232	369	50	302	523	58	428	680							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 6 TOTAL SYMPTOMS FROM THE FN DIARY
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 3 FN DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO BUT NOT INCLUDING DAY 1
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
ONE PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

CB3-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

PM NON-NASAL EAR/PALATE ITCHING SCORE - POOLED DIARY DATA

	(A) MOMS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES @			PAIRWISE COMPARISONS @		
AYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	116	0.0	0.1	115	0.0	0.1	115	0.0	0.1	0.1	0.26	0.03	0.03	0.31	0.1	0.54
PPL RAW	116	0.0	0.1	115	0.0	0.2	115	0.1	0.1	0.2	0.67	0.37	0.74	0.61	0.37	0.71
CHG	116	0.0	0.1	115	0.0	0.2	115	0.0	0.1	0.2	0.97	0.55	0.24	0.84	0.0	0.96
%CHG	3	-50	44.3	6	-78	62.9	8	-41	96.2							
.5 RAW	114	0.1	0.2	111	0.1	0.3	109	0.2	0.4	0.3	<.01	0.16	0.05	0.3	<.01	<.01
CHG	114	0.1	0.2	111	0.1	0.3	109	0.2	0.4	0.3	<.01	0.05	0.02	0.5	<.01	<.01
%CHG	3	-47	61.1	6	-58	74.6	7	-7.1	139							
15 30 RAW	114	0.1	0.3	107	0.2	0.5	103	0.3	0.5	0.4	0.02	0.68	0.19	0.32	<.01	0.06
CHG	114	0.1	0.3	107	0.1	0.5	103	0.2	0.5	0.4	0.03	0.54	0.12	0.46	0.01	0.06
%CHG	3	-2.1	100	6	-38	111	7	114	163							
31 45 RAW	67	0.1	0.3	56	0.2	0.5	54	0.3	0.6	0.5	0.14	0.25	0.8	M/E	M/E	M/E
CHG	67	0.1	0.3	56	0.2	0.5	54	0.2	0.6	0.4	0.17	0.19	0.7	M/E	M/E	M/E
%CHG	2	90.0	212	3	-44	62.5	5	139	157							
46-61 RAW	18	0.1	0.4	14	0.3	0.6	13	0.1	0.5	0.5	0.93	0.66	0.96	0.75	M/E	M/E
CHG	18	0.1	0.4	14	0.3	0.6	13	0.1	0.5	0.5	0.9	0.74	0.93	0.71	M/E	M/E
%CHG	2	170	382	2	-100	0.0										
ENDPT RAW	116	0.1	0.3	115	0.2	0.4	115	0.3	0.6	0.5	<.01	0.44	0.33	0.34	< 01	0.02
CHG	116	0.1	0.3	115	0.1	0.4	115	0.3	0.6	0.4	0.01	0.4	0.21	0.46	<.01	0.02
%CHG	3	60.0	312	6	-36	111	8	93.2	155							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION M/E = NON-ESTIMABLE
@ P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 3 PM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO BUT NOT INCLUDING DAY 1
SYMPTOM IS SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM & PM AVERAGED NASAL STUFFINESS SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES @			PAIRWISE COMPARISONS @		
AYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.2	0.3	115	0.2	0.3	115	0.2	0.3	0.3	0.71	<.01	0.54	0.54	0.43	0.85
ME	RAW	116	0.2	0.3	115	0.3	0.4	115	0.3	0.4	0.3	0.02	<.01	0.33	0.03	0.01	0.63
	CHG	116	0.0	0.3	115	0.1	0.3	115	0.1	0.3	0.3	0.1	0.01	0.41	0.1	0.05	0.75
	CHG	65	-17	88.7	67	17.7	100	49	36.5	121							
5	RAW	114	0.3	0.4	111	0.4	0.5	109	0.7	0.6	0.5	<.01	<.01	0.01	0.04	<.01	<.01
	CHG	114	0.1	0.4	111	0.2	0.5	109	0.5	0.6	0.5	<.01	0.17	0.01	0.11	<.01	<.01
	CHG	65	19.0	144	66	78.8	207	65	116	238							
6-30	RAW	114	0.4	0.4	107	0.5	0.6	103	0.8	0.9	0.6	<.01	0.04	0.02	0.10	<.01	<.01
	CHG	114	0.2	0.5	107	0.3	0.6	103	0.6	0.7	0.6	<.01	0.01	0.02	0.25	<.01	<.01
	CHG	65	46.9	166	63	66.7	172	44	146	268							
31-45	RAW	76	0.5	0.6	67	0.6	0.7	61	0.8	0.9	0.7	<.01	0.33	0.34	M/E	M/E	M/E
	CHG	76	0.3	0.6	67	0.5	0.8	61	0.6	0.8	0.7	<.01	0.05	0.27	M/E	M/E	M/E
	CHG	28	66.8	235	23	97.7	207	19	136	279							
46-61	RAW	18	0.3	0.6	14	0.7	0.9	13	0.6	0.7	0.7	0.39	0.49	0.36	0.19	M/E	M/E
	CHG	10	0.3	0.6	14	0.6	0.9	13	0.5	0.7	0.7	0.18	0.8	0.2	0.33	M/E	M/E
	CHG	7	225	399	5	211	241	2	222	346							
ENDPT	RAW	116	0.4	0.5	115	0.6	0.7	115	0.9	0.8	0.7	<.01	0.01	0.3	0.08	<.01	<.01
	CHG	116	0.3	0.6	115	0.4	0.7	115	0.6	0.8	0.7	<.01	<.01	0.28	0.15	<.01	0.01
	CHG	65	52.3	200	67	78.4	189	69	162	253							

SD = STANDARD DEVIATION T x I = TREATMENT BY INVESTIGATOR INTERACTION M/E = NON-ESTIMABLE
@ P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LEHMANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM & PM DIARY BASELINE VALUES
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM NASAL STUFFINESS SYMPTOM SCORE - *POOLED DIARY DATA*

		(A) MOMS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
AVG		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.2	0.3	115	0.2	0.4	115	0.2	0.3	0.3	0.99	<.01	0.6	0.96	0.93	0.89
1-4	RAW	116	0.2	0.3	115	0.3	0.4	115	0.4	0.4	0.3	0.03	<.01	0.43	0.86	0.01	0.47
	CHG	116	-0.0	0.4	115	0.1	0.4	115	0.1	0.4	0.4	0.03	<.01	0.47	0.66	0.01	0.41
	CHG	48	-13	96.3	44	-16	66.2	47	22.9	104							
1-5	RAW	116	0.3	0.4	111	0.4	0.5	109	0.7	0.6	0.5	<.01	<.01	0.05	0.07	<.01	<.01
	CHG	116	0.1	0.4	111	0.2	0.5	109	0.5	0.7	0.5	<.01	0.02	0.05	0.09	<.01	<.01
	CHG	67	-21	60.2	62	31.5	149	66	77.2	167							
6-10	RAW	116	0.4	0.5	107	0.6	0.6	103	0.8	0.7	0.6	<.01	0.01	0.04	0.17	<.01	<.01
	CHG	116	0.2	0.5	107	0.3	0.7	103	0.6	0.7	0.6	<.01	<.01	0.07	0.16	<.01	<.01
	CHG	67	38.5	120	59	12.9	122	63	101	194							
11-45	RAW	76	0.5	0.6	67	0.7	0.8	61	0.8	0.7	0.7	<.01	0.17	0.41	M/E	M/E	M/E
	CHG	76	0.3	0.7	67	0.6	0.8	61	0.6	0.8	0.7	<.01	0.01	0.33	M/E	M/E	M/E
	CHG	30	22.2	134	22	34.0	143	20	62.8	167							
46-90	RAW	18	0.5	0.6	14	0.8	0.9	13	0.6	0.7	0.7	0.27	0.38	0.29	0.13	M/E	M/E
	CHG	18	0.2	0.6	14	0.6	1.0	13	0.5	0.7	0.7	0.09	0.69	0.04	0.07	M/E	M/E
	CHG	8	69.0	105	6	109	243	2	96.5	262							
LWOPT	RAW	116	0.5	0.6	115	0.6	0.7	115	0.9	0.8	0.7	<.01	<.01	0.39	0.06	<.01	<.01
	CHG	116	0.2	0.6	115	0.4	0.7	115	0.6	0.8	0.7	<.01	<.01	0.44	0.1	<.01	0.03
	CHG	48	27.7	133	44	30.7	153	47	96.5	187							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION M/E = NON-ESTIMABLE
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 4 AM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO AND INCLUDING DAY 1
SYMPTOM IS SCORED AS 0=NONE, 1=*MILD*, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
LWOPT = LAST AVAILABLE POST-BASELINE *VALUE* FOR EACH SUBJECT

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL *ALLERGIC RHINITIS* WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

PM NASAL STUFFINESS SYMPTOM SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.1	0.3	115	0.2	0.3	115	0.2	0.3	0.3	0.28	<.01	0.72	0.38	0.11	0.46
PRE	RAW	116	0.2	0.3	115	0.3	0.4	115	0.3	0.3	0.3	0.01	<.01	0.19	0.01	0.01	0.82
	CHG	116	0.0	0.3	115	0.1	0.3	115	0.1	0.3	0.3	0.2	0.16	0.15	0.09	0.2	0.67
	%CHG	24	-45	78.2	31	16.2	65.7	36	3.0	85.4							
1-15	RAW	114	0.3	0.4	111	0.4	0.5	109	0.6	0.6	0.5	<.01	<.01	<.01	0.04	<.01	<.01
	CHG	114	0.1	0.4	111	0.2	0.5	109	0.5	0.6	0.5	<.01	0.39	<.01	0.13	<.01	<.01
	%CHG	24	-28	79.1	30	56.7	149	32	56.6	124							
16-30	RAW	114	0.4	0.4	107	0.5	0.6	103	0.8	0.7	0.6	<.01	0.11	0.02	0.22	<.01	<.01
	CHG	114	0.3	0.5	107	0.4	0.6	103	0.6	0.7	0.6	<.01	0.05	0.01	0.36	<.01	<.01
	%CHG	24	2.0	106	27	57.1	137	32	92.7	152							
31-45	RAW	67	0.5	0.6	56	0.7	0.8	54	0.7	0.7	0.7	0.13	0.75	0.91	N/E	N/E	N/E
	CHG	67	0.3	0.6	56	0.6	0.8	54	0.6	0.8	0.7	0.34	0.35	0.65	N/E	N/E	N/E
	%CHG	11	0.7	119	13	138	204	15	40.8	111							
46-60	RAW	18	0.5	0.6	14	0.6	0.8	13	0.5	0.6	0.7	0.75	0.72	0.63	0.52	N/E	N/E
	CHG	18	0.5	0.7	14	0.6	0.8	13	0.5	0.7	0.7	0.45	0.8	0.3	0.37	N/E	N/E
	%CHG	2	50.0	212	2	200	0.0	1	-30	.							
ENDPT	RAW	116	0.4	0.5	115	0.6	0.7	115	0.8	0.8	0.6	<.01	0.06	0.12	0.09	<.01	<.01
	CHG	116	0.3	0.6	115	0.4	0.7	115	0.6	0.8	0.7	<.01	0.06	0.11	0.23	<.01	0.01
	%CHG	24	-5.3	105	31	78.5	170	36	89.6	168							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 3 PM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO BUT NOT INCLUDING DAY 1
SYMPTOM IS SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM & PM AVERAGED NASAL DISCHARGE SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES @			PAIRWISE COMPARISONS @		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.1	0.2	115	0.1	0.2	115	0.1	0.2	0.2	0.27	<.01	0.76	0.17	0.16	0.88
PRE	RAW	116	0.1	0.2	115	0.1	0.2	115	0.2	0.3	0.2	0.07	<.01	0.94	0.64	0.03	0.09
	CHG	116	0.0	0.2	115	0.0	0.3	115	0.1	0.3	0.2	0.24	<.01	0.78	0.61	0.25	0.1
	%CHG	17	-33	74.2	27	-25	105	26	15.6	149							
1-15	RAW	114	0.2	0.3	111	0.2	0.4	109	0.5	0.6	0.4	<.01	<.01	<.01	0.40	<.01	<.01
	CHG	114	0.1	0.3	111	0.1	0.4	109	0.4	0.6	0.4	<.01	0.01	<.01	0.78	<.01	<.01
	%CHG	17	-1.6	158	25	2.0	148	22	55.2	196							
16-30	RAW	114	0.3	0.4	107	0.4	0.5	103	0.6	0.7	0.5	<.01	0.04	0.03	0.31	<.01	<.01
	CHG	114	0.2	0.4	107	0.3	0.5	103	0.5	0.7	0.5	<.01	0.01	0.04	0.53	<.01	<.01
	%CHG	17	66.7	222	25	56.1	186	27	119	267							
31-45	RAW	76	0.4	0.6	67	0.4	0.6	61	0.7	0.7	0.6	<.01	0.76	0.42	M/E	M/E	M/E
	CHG	76	0.3	0.6	67	0.3	0.6	61	0.6	0.7	0.6	0.01	0.15	0.66	M/E	M/E	M/E
	%CHG	11	76.6	211	16	66.8	205	17	75.8	205							
46-61	RAW	18	0.4	0.5	14	0.5	0.7	13	0.6	0.7	0.7	0.32	0.5	0.44	0.28	M/E	M/E
	CHG	18	0.4	0.5	14	0.5	0.8	13	0.6	0.7	0.7	0.35	0.44	0.45	0.31	M/E	M/E
	%CHG	1	200		3	-6.7	90.2	2	-70	42.4							
ENDPT	RAW	116	0.3	0.5	115	0.4	0.5	115	0.7	0.8	0.6	<.01	0.05	0.04	0.68	<.01	<.01
	CHG	116	0.3	0.5	115	0.3	0.6	115	0.6	0.8	0.6	<.01	0.01	0.04	0.97	<.01	<.01
	%CHG	17	84.0	217	27	54.0	195	26	74.0	221							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION M/E = NON-ESTIMABLE
@ P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM & PM DIARY BASELINE VALUES
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM NASAL DISCHARGE SYMPTOM SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES @			PAIRWISE COMPARISONS @		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.1	0.2	115	0.1	0.2	115	0.1	0.2	0.2	0.19	<.01	0.76	0.08	0.2	0.62
PRE	RAW	116	0.1	0.3	115	0.1	0.2	115	0.2	0.3	0.3	0.04	<.01	0.82	0.77	0.02	0.04
	CHG	116	0.0	0.2	115	-0.0	0.3	115	0.1	0.3	0.3	0.09	0.14	0.34	0.3	0.24	0.03
	%CHG	10	-47	68.9	27	-46	76.6	24	-39	78.2							
1-15	RAW	114	0.2	0.6	111	0.2	0.6	109	0.4	0.6	0.6	<.01	<.01	0.01	0.71	<.01	<.01
	CHG	114	0.1	0.3	111	0.1	0.5	109	0.4	0.6	0.5	<.01	0.04	0.03	0.78	<.01	<.01
	%CHG	10	-28	73.9	25	-0.0	169	21	-8.4	103							
16-30	RAW	114	0.3	0.6	107	0.4	0.5	103	0.6	0.7	0.5	<.01	0.05	0.06	0.36	<.01	<.01
	CHG	114	0.2	0.6	107	0.2	0.6	103	0.5	0.7	0.6	<.01	0.01	0.09	0.77	<.01	<.01
	%CHG	10	4.6	102	25	36.3	155	21	48.0	149							
31-45	RAW	76	0.4	0.6	67	0.4	0.7	61	0.7	0.7	0.7	<.01	0.79	0.43	N/E	N/E	N/E
	CHG	76	0.3	0.6	67	0.3	0.7	61	0.5	0.7	0.7	0.02	0.1	0.72	N/E	N/E	N/E
	%CHG	22	8.1	97.7	15	62.5	229	16	29.0	128							
46-61	RAW	18	0.4	0.6	14	0.6	0.8	12	0.6	0.7	0.7	0.33	0.46	0.43	0.21	N/E	N/E
	CHG	18	0.3	0.5	14	0.6	0.9	13	0.5	0.8	0.7	0.37	0.36	0.43	0.23	N/E	N/E
	%CHG	2	150	70.7	2	35.6	34.6	3	-73	46.2							
ENDPT	RAW	116	0.1	0.6	115	0.4	0.6	115	0.7	0.7	0.6	<.01	0.05	0.05	0.55	<.01	<.01
	CHG	116	0.1	0.5	115	0.3	0.6	115	0.6	0.8	0.6	<.01	<.01	0.06	> 99	<.01	<.01
	%CHG	18	18.5	109	27	44.5	188	24	40.3	138							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
@ P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 4 AM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO AND INCLUDING DAY 1
SYMPTOM IS SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

PM NASAL DISCHARGE SYMPTOM SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES @			PAIRWISE COMPARISONS @		
		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.0	0.2	115	0.0	0.2	115	0.1	0.2	0.2	0.33	<.01	0.75	0.79	0.16	0.25
WK 1	RAW	116	0.1	0.2	115	0.1	0.2	115	0.2	0.3	0.2	0.14	<.01	0.94	0.57	0.05	0.18
	CHG	116	0.1	0.2	115	0.1	0.2	115	0.1	0.3	0.2	0.65	0.11	0.79	0.7	0.36	0.59
	%CHG	9	-35	87.5	12	-3.1	86.2	15	-27	60.8							
WK 5	RAW	114	0.2	0.3	111	0.2	0.4	109	0.5	0.6	0.4	<.01	<.01	<.01	0.33	<.01	<.01
	CHG	114	0.1	0.2	111	0.2	0.4	109	0.4	0.6	0.4	<.01	<.01	<.01	0.36	<.01	<.01
	%CHG	9	-31	109	11	50.0	150	13	36.2	197							
WK 10	RAW	114	0.3	0.4	107	0.4	0.5	103	0.6	0.7	0.5	<.01	0.05	0.02	0.29	<.01	<.01
	CHG	114	0.2	0.4	107	0.3	0.5	103	0.5	0.7	0.5	<.01	0.04	0.02	0.31	<.01	<.01
	%CHG	9	-15	102	11	76.5	153	13	42.3	221							
WK 45	RAW	67	0.4	0.6	56	0.4	0.6	54	0.6	0.8	0.7	0.01	0.85	0.55	N/E	N/E	N/E
	CHG	67	0.3	0.6	56	0.4	0.6	54	0.5	0.8	0.7	0.03	0.23	0.61	N/E	N/E	N/E
	%CHG	6	4.2	82.7	7	64.0	200	8	85.9	301							
WK 61	RAW	18	0.3	0.5	14	0.5	0.7	13	0.5	0.6	0.6	0.58	0.61	0.61	0.44	N/E	N/E
	CHG	18	0.3	0.5	14	0.4	0.7	13	0.5	0.6	0.6	0.62	0.43	0.58	0.5	N/E	N/E
	%CHG	1	200		2	-100	0.0										
ENDPT	RAW	116	0.3	0.5	115	0.3	0.5	115	0.7	0.8	0.6	<.01	0.11	0.08	0.52	<.01	<.01
	CHG	116	0.3	0.5	115	0.3	0.6	115	0.6	0.8	0.6	<.01	0.03	0.05	0.57	<.01	<.01
	%CHG	9	-14	93.0	12	42.2	179	15	50.2	229							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
@ P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 3 PM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO BUT NOT INCLUDING DAY 1
SYMPTOM IS SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

8.10. Trial I93-133. Safety and Efficacy of Mometasone Furoate Nasal Spray in the Prophylactic Treatment of Seasonal Allergic Rhinitis (SAR).

Principal Investigator: Michael A Drouin, M.D.

Participating Centers: 18 international centers (including Canada).

8.10.1. OBJECTIVE:

1. To evaluate the efficacy of a four week course of mometasone aqueous nasal spray 200 µg qd vs. budesonide (Rhinocort Aqua) 400 µg qd, and vs. placebo in the prophylaxis of symptoms of SAR.
2. To evaluate the efficacy and safety of an 8 week course of mometasone aqueous nasal spray in the treatment of symptoms of SAR.

8.10.2. STUDY DESIGN:

This was a Phase III, randomized, multi-center, double-blind, double-dummy, active- and placebo-controlled, parallel group trial in adult subjects with seasonal allergic rhinitis. Study medications were given to SAR subjects for a total duration of 8 weeks, 4 weeks of which were prophylaxis treatment prior to the anticipated onset of the pollen season.

8.10.3. PROTOCOL:

8.10.3.1.a. POPULATION:

Significant entry criteria consisted of the following: (1) age ≥ 12 years [206:14, 208:881], (2) presence of IgE-mediated hypersensitivity to at least one seasonal allergen relevant for the site and duration of the study (i.e. tree, grass, or weed pollen but individual species were not specified in protocol), as documented by a positive skin test within 1 year of study entry via the prick testing method (≥ 3 mm in diameter than diluent control) [206:14, 208:881], and (3) asymptomatic clinical status (total nasal symptom score ≤ 2) and no nasal or non-nasal symptom rated as moderate or severe (i.e. symptom score=2 or 3) on a 0-3 scale at the Screening and Baseline visits [206:14, 208:881]. Subjects symptomatic or anticipated to become symptomatic to a perennial allergen during the study duration (e.g. molds, dust mites, animal dander) were excluded from study enrollment [206:15, 208:882].

8.10.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1. of Trial I93-133 in the NDA submission [206:13, 208:914] and is essentially identical to the study design of SAR prophylaxis study C93-215 with two exceptions [208:888-901]. In contrast to study C93-215, subjects in study I93-133 were assessed by a physician on day 15 and day 43 rather than on day 22 and day 50. Thus, subjects in study I93-133 were evaluated during the following study

visits: screening (Visit 1), baseline (Visit 2), day 8 (Visit 3), day 15 (Visit 4), day 22 (Visit 5), day 29 (Visit 6), day 36 (Visit 7), day 43 (Visit 8), day 57 (Visit 9), and day 71 (Visit 10, if an extra treatment period was necessary because of a delay in the onset of the pollen season) [206:32, 208:889]. Furthermore, subjects were allowed to use loratadine (up to 10 mg po qd) as a rescue medication after the baseline visit for control of 'intolerable' SAR symptoms [206:19, 208:880, 903]. As in all the other SAR trials for this NDA submission, SAR symptoms which consisted of individual and total nasal, non-nasal, and total (nasal + non-nasal) SAR symptoms were rated on a 0-3 symptom scale, reflectively over the previous 12 hours [206:25-26, 208:900-901, 908]. Physical examination (excluding eye exam and intraocular pressure measurements) and laboratory tests (excluding HPA-axis suppression evaluation) were performed on the first (screening) and last visit(s) (visit 9 and/or 10) of the study [206:13, 208:914]. Safety evaluations were completed at each study visit and consisted of a review by the principal investigator of any adverse events experienced by the subject and checking of vital signs of each study subject [208:914].

A double-dummy design was utilized in drug delivery for trial I93-133 using matching placebos for each bottle type, since the mometasone and budesonide medication bottles were not identical in appearance. Although subjects received bottles of differing appearance, they were blinded as to which bottles contained active drug or placebo [208:902]. The three treatment groups consisted of :

(A) Mometasone aqueous nasal spray 200 µg qd		
a.m. dosing:	Bottle 1: Mometasone	Bottle 2: Rhinocort Placebo
(B) Budesonide nasal spray (Rhinocort Aqua) 400 µg qd		
a.m. dosing:	Bottle 1: Mometasone placebo	Bottle 2: Rhinocort
(C) Placebo (0 µg qd)		
a.m. dosing:	Bottle 1: Mometasone placebo	Bottle 2: Rhinocort placebo

Given a similar study design to SAR prophylaxis trial C93-215, the primary, secondary and supplementary efficacy variables were likewise similar.

The primary efficacy variable was defined as the: **The mean proportion of minimal symptom days during the ragweed pollen season for the ITT population**—i.e. the days when the **total nasal symptom score** (defined as: the sum of individual symptom scores of: rhinorrhea, nasal congestion, sneezing, and nasal itch) was ≤ 2 based on the average of the a.m. + p.m. diary scores from the start of the pollen season, through the last day of treatment, day 57 or 71 (depending on the onset of the pollen season). The primary comparison of the study was a comparison of the mometasone treatment group vs. placebo [206:39-40, 208:908-909].

Secondary Efficacy Variables [206:40-41, 208:908-909] were defined as the following endpoints for the efficacy evaluable population (ITT data not included in the application except where otherwise noted):

(1) The proportion of minimal symptom days (total nasal symptom score ≤ 2) for the entire treatment period (ITT population).

(2) The number of days from the start of the pollen season to the first occurrence of a non-minimal symptom day (total nasal symptom score > 2).

(3) The number of days from the start of treatment to the first occurrence of a non-minimal symptom day (total nasal symptom score > 2).

(4) The proportion of minimal symptom days (total nasal symptom score ≤ 2) during the first week of the pollen season.

(5) The proportion of days during the pollen season when the total nasal symptom score=0 (i.e. the proportion of symptom-free days).

Supplementary efficacy endpoints for the efficacy evaluable population (exception (7) below) were defined in this study as the following:

(1) Mean change from baseline (*'baseline'* defined in this study as the mean of the a.m. and p.m. scores from the 7 consecutive days prior to the day of the baseline visit [206:36], 'baseline' not defined in the general study document Vol. 208) in total nasal symptom scores during the pollen season, as obtained from subject diaries (a.m. and p.m. combined) for: days 1-15 (day 1 being the first day of the pollen season), days 16-30, days 31-45, days 46-61, and the endpoint visit.

(2) Mean change from baseline in total symptom scores during the pollen season, as obtained from subject diaries (a.m. and p.m. combined) for: days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.

(3) Mean change from baseline in total non-nasal symptom scores during the pollen season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.

(4) Mean change from baseline in individual nasal symptom scores during the pollen season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.

(5) Mean change from baseline in individual non-nasal symptom scores during the pollen season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.

(6) All total (total SAR, total nasal, total non-nasal) and individual symptom scores, as determined by the physician (physician evaluations).

(7) The proportion of minimal symptom days (total nasal symptom score ≤ 2) during the prophylaxis period (ITT population).

8.10.4. RESULTS

A total of 514 subjects with SAR were enrolled into the study, with 1 subject excluded from all analyses (193-133-14, #013) because he never received study medication. A total of 513 subjects were evaluated for safety in the intent-to-treat population; 168 subjects received mometasone, 172 subjects received budesonide, and 173 subjects received placebo [206:46]. Of the sponsor's efficacy evaluable subjects, 164 subjects received mometasone, 168 subjects received budesonide, and 168 subjects received placebo [206:46].

The treatment groups in this study were comparable with regard to demographic and disease characteristics with the exception of a statistically significant difference among the treatment groups in age (mean age of the mometasone group=31 years vs. mean age of the placebo group=35 years; p=0.01) and duration of condition (mean duration of SAR in the mometasone group=12 years vs. mean duration of SAR in the placebo group=14 years; p=0.03) [206:47]. Despite these differences, additional statistical analyses performed to assess the impact of treatment imbalance at baseline with respect to these two parameters failed to reveal an interaction of either variable with treatment (p>0.38) [209:1109]. Again, for all four treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the treatment groups was approximately equal. Furthermore, no statistically significant treatment group differences at baseline for the supplementary efficacy parameters of total symptom, total nasal and total non-nasal symptom scores [206:268, 308, 314] were detected.

An evaluation of the pollen count records (tree, grass or both) for the 18 participating centers in this study was, for the most part, consistent with findings in many of the other SAR studies of this NDA submission. One of the 18 centers (center 193-133-016) reported pollen counts for tree (cohort #02) [206:226], weed (cohort #03) [206:227], and grass (cohort #04) [206:228] which were not significantly elevated relative to baseline for at least part of the study duration. An additional problem noted in a significant number of study centers (center -06 (trees), -09 (tree/grass and weed), -12 (tree and grass), -13 (tree/grass/weed), -14 (grass), -15 (grass), -16 (weed and platanus) was that of inappropriate definition of the onset and/or peak onset and offset and/or peak offset of the pollen season where pollen counts did not correlate with the expected timepoint of the pollen season [206:208, 212-213, 216-217, 218, 221, 223, 227, and 229]. At many centers, pollen counts did not appear to be collected after the peak offset of the pollen season, consequently with the offset of the pollen season either not provided in the NDA submission or inappropriately defined [206: 205, 206, 212, 213, 214, 215, 216, 217, 221, 223, 224, 228, 229, 230, 231]. These potentially confounding issues in the NDA submission are not addressed (except in one section of the NDA where exploratory analyses were performed excluding study centers -09 and -016 [209:1110]) and given the possibility of inappropriate definition of pollen onset/offset at some study centers; make extrapolation of efficacy results across all

centers more difficult. The onset of the pollen season for any cohort at all centers was calculated to occur on average 26 days after the initiation of treatment (range 12-47 days) [206:51 and NDA 20-762, Response to FDA request on Prophylaxis studies, Schering Plough, Inc., 05/21/97, p. 2].

Analysis of the primary efficacy variable for the ITT population (the proportion of days during the 'pollen season' where the a.m. and p.m. mean total nasal symptom score ≤ 2) revealed that subjects in the mometasone treatment group had 84% of days with minimal total nasal symptoms, compared with 87% of minimal symptom days experienced by budesonide subjects, and 65% of minimal symptom days experienced by placebo subjects ($p<.01$ for mometasone vs. placebo and budesonide vs. placebo) [206:257]. While some subjects demonstrated a clinical response already during the prophylaxis period (a problem noted in study C93-215), the Sponsor used exploratory analysis to assess the impact of subjects with symptoms during the prophylaxis period by repeating the analysis of the primary efficacy variable using 2-way ANOVA but excluding those subjects who had non-minimal symptoms on at least 20%, 30%, 40% and 50% of days during the prophylaxis period [209:1110]. Results of this analysis failed to demonstrate a difference in the primary efficacy variable, with mometasone treated subjects still having a statistically greater proportion of minimal symptom days as compared with placebo ($p<.01$ for all 4 analyses) [209:1144-1148]. The Sponsor also performed exploratory analysis on the primary efficacy variable excluding 2 study centers (-09 and -016) because of possible ambiguity in the definition of the onset of the pollen season which may have led to misclassification of subjects with respect to cohort type (i.e. tree, grass, weed) [209:1110]. Results of this analysis also failed to demonstrate a difference in the primary efficacy variable with regard to clinical efficacy of mometasone in changing the proportion of minimal symptom days in subjects with SAR [209:1148].

A post-hoc analysis of the primary efficacy endpoint in subjects (n=32) receiving < 15 days of mometasone prophylaxis to determine the onset of action of mometasone revealed that even with 15 days of mometasone treatment, subjects had a statistically significantly greater proportion of 'minimal symptom days' (82%) than the placebo (n=27) group (60%, $p<.01$) [NDA 20,762, Response to FDA Request on Prophylaxis Studies, Schering, Inc., 05/21/97, p. 1-3]. Similar findings were noted for the active comparator, budesonide (n=28), in which budesonide treated subjects experienced 87% of days with minimal total nasal symptoms compared with the placebo group, [$p<.01$, Schering Response to FDA Request on Prophylaxis Studies, p. 1].

Findings for the secondary efficacy variables support those noted with the primary efficacy variable, namely that both active treatment groups displayed a greater proportion of 'minimal' or 'no symptom' days and/or a longer duration of time prior to onset of nasal symptoms, as compared with placebo [206:257, 264, 266, 209:1129,-1140, 1141-1142].

For the supplementary efficacy variables, results in general were similar to those noted in the pivotal SAR prophylaxis study C93-215. Subject symptom

scores tended to be in the same numerical range as those in study C93-215, and subjects in the 2 active treatment groups (mometasone and budesonide) demonstrated a statistically significant difference in subject evaluated total SAR, total nasal, and total non-nasal symptom scores throughout the study duration as compared with placebo. In terms of the subject rated total nasal symptom score for the day 1-15 interval of the pollen season (a.m. and p.m. combined), mometasone treated subjects exhibited a 0.3 unit increase in total nasal symptoms (a 149% increase from the prophylaxis period), compared with a 1.8 unit increase in total nasal symptoms (a 230% increase from the prophylaxis period). This difference between the mometasone treatment group and placebo was statistically significant at a p-value of <.01 [206:268]. Again, clinical efficacy of mometasone treatment (as compared with placebo) was more variable with regard to subject evaluated individual non-nasal symptoms or physician evaluated total and individual non-nasal symptoms. Nonetheless, during at least some study endpoints for each supplementary variable, mometasone treated subjects demonstrated statistically greater efficacy than the placebo group (See Table III.). While not statistically significantly different, the mean decrease in the individual non-nasal symptom scores from subject diaries and physician assessments were numerically greater for the mometasone treatment group than for placebo at some study endpoints [206:337-351] which would support prior clinical efficacy findings for mometasone.

One problem noted in study I93-133, similar to study C93-215 was again the issue of a significant decrease in study subject numbers (visit n values) for the % change in subject number (=n) for all subject evaluated symptom scores as the study progressed (total SAR, total nasal, total non-nasal, and individual nasal and non-nasal symptom scores). This decrease in subject number (=n) represented subjects who had 0 as a given symptom score with a resultant inability to compute the % change based on a denominator of 0. Acknowledging that the primary and secondary efficacy variables support the efficacy of mometasone in the prophylaxis of subjects with SAR, nonetheless the lack of incorporation of these subjects as data points into the supplementary efficacy variable analysis represents a study flaw which does not address symptom scores for all efficacy evaluable subjects.

Review of rescue medication use between the 3 treatment groups (ITT population) supported less frequent rescue medication use in the 2 active treatment groups. While 100/173 or 57.8% of placebo treated subjects used rescue medication (loratadine) >1 time during the course of the study, 73/168 or 43.5% of mometasone subjects and 54/172 or 31.4% of budesonide treated subjects used rescue medication [207:383]. Furthermore, mometasone and budesonide treated subjects who used rescue medication, tended to use it less often that the placebo group subjects; as supported by the smaller number of mometasone or budesonide subjects in the high frequency rescue medication use group [207:383].

No significant differences between a.m. and p.m. dosing of the treatment groups was detected in this study for total SAR, total nasal, total non-nasal and the individual nasal and non-nasal symptom scores; thus supporting the findings of

previous SAR studies in this NDA submission and confirming efficacy of mometasone as a once a day medication for the treatment of SAR symptoms [206:269-271, 308-310, 314-316, 325-335, 337-351]. Subject subset analysis by age, sex, and race did not reveal any significant differences from the overall subject population for the primary efficacy variable [206:260, 262]. Findings for the primary efficacy variables are summarized in Table I. below. Findings for the secondary and supplementary efficacy variables, respectively are summarized in Tables II. and III. below.

Table I. Primary Efficacy Variable of SAR and Treatment with Mometasone (ITT Population), [206:257]

1° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1	Proportion of minimal sx days during the pollen season (total nasal sx score ≤ 2)	*Yes

sx=Symptom
* Note Statistically significant response for 1° efficacy variable carried by 4 of the 18 study centers per the efficacy evaluable population (i.e. 14/18 centers had a statistically non-significant response [206:238-255]

Table II. Secondary Efficacy Variables of SAR and Treatment with Mometasone (Efficacy evaluable Subjects unless otherwise stated), [206:264, 209:1129, 1141]

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1.	Proportion of minimal sx days for the entire treatment period (ITT) (total nasal sx score ≤ 2)	Yes
2.	# of days from the start of the pollen season to the first occurrence of a non-minimal sx day (total nasal sx score > 2)	Yes
3	# of days from the start of treatment to the first occurrence of a non-minimal sx day (total nasal sx score > 2)	Yes
4	Proportion of minimal sx days during the first week of the pollen season (total nasal sx score ≤ 2)	Yes
5	Proportion of asymptomatic days during the pollen season (total nasal sx score =0)	Yes

sx=Symptom, #=Number
ITT=Intent-to-treat population

Table III. Supplementary Efficacy Variables of SAR and Treatment with Mometasone (Efficacy evaluable subjects, unless otherwise specified). [206:237, 268-271, 272, 308-317, 321-335, 337-35, 358-361

Supplementary EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1	Subject evaluated mean ▲ in Total Nasal Sx Score DAY 1-15, DAY16-30, DAY 31-45, DAY 46-61, Endpoint Visit	Yes:	Day 1-15, Day 16-30, Endpoint Visit	
		*N/E:	Day 31-45, Day 46-61	
2	Subject evaluated mean ▲ in Total SAR Sx DAY 1-15, DAY16-30, DAY 31-45, DAY 46-61, Endpoint Visit	Yes:	Day 1-15, Day 16-30, Endpoint Visit	
		N/E:	Day 31-45, Day 46-61	
3	Subject evaluated mean ▲ in Total Non-nasal Sx DAY 1-15, DAY16-30, DAY 31-45, DAY 46-61, Endpoint Visit	Yes:	Day 1-15, Day 16-30, Endpoint Visit	
		N/E:	Day 31-45, Day 46-61	
4	Subject evaluated individual nasal Sx DAY 1-15, DAY16-30, DAY 31-45, DAY 46-61, Endpoint Visit	Yes:	All 4 nasal sx: Day 1-15, Day 16-30, Endpoint Visit	
		N/E:	All 4 nasal sx: Day 31-45, Day 46-61	
5	Subject evaluated individual non-nasal Sx DAY 1-15, DAY16-30, DAY 31-45, DAY 46-61, Endpoint Visit	Yes:	Eye Tearing:	Day 1-15, Day 16-30, Endpoint visit
			Eye Redness:	Day 16-30, Endpoint visit
			Eye Itch:	Day 16-30, Endpoint visit
			Ear/Palatal Itch:	Day 16-30, Endpoint Visit
		N/E:	All 4 non-nasal sx: Day 31-45, Day 46-61	
6	Physician evaluated total SAR, total nasal, total non-nasal, individual nasal and individual non-nasal sx	Yes:	Total SAR:	Day 15, 22, 36, 43, 57, Endpoint Visit
			Total Nasal:	Day 15, 22, 29, 36, 43, 57, Endpoint Visit
			Total Non-nasal:	Day 57
			Individual Nasal:	Rhinorrhea: Day 22, 36, 43, 57, Endpoint visit. Nasal congestion: Day 15, 22, 43, 57, Endpoint visit. Sneezing: Day 8, 15, 22, 29, 36, 43, 57, Endpoint visit. Nasal itch: Day 15, 22, 29, 36, 43, 57, Endpoint visit. N/E: All 4 nasal sx on Day 71.
			Individual Non-nasal:	All 4 individual non-nasal sx: Day 57
7	Proportion of minimal sx days during the prophylaxis period (ITT)	Yes		

▲=Change, Sx=Symptom, Rx=Treatment, ITT=Intent-to-Treat Population

NOTE: For efficacy variables 1-5, statistical assessment is based on the combined a.m. and p.m. symptom scores.

*N/E (Non-estimable) denotes numerically greater decrease in sx noted for the mometasone treatment group compared with placebo but p-value is non-estimable due to study underpowering

8.10.4.3. ADVERSE EVENTS:

The safety analysis was based on 513 subjects in the ITT population; 168 subjects were treated with mometasone 200 µg qd, 172 subjects were treated with budesonide (Rhinocort) 400 µg qd, and 173 subjects were treated with placebo [206:66]. Adverse events were similar for all three treatment groups, with headache being the most frequently reported treatment-related adverse event.

Overall, adverse events were reported in 57% of subjects in the mometasone treatment group, 54% of subjects in the budesonide treatment group, and 57% of subjects in the placebo group [206:67-68]. Headache was reported in 20% of subjects in the mometasone group, 18% of subjects in the budesonide group, and 21% of subjects in the placebo group [206:67-68, 207:405, 211:3941-3960, 4095-4110, 4233-4249]. Again, as previously noted in the other SAR studies in this NDA submission, headache was followed by pharyngitis and epistaxis in terms of frequency of reporting by subjects [207:410]. Pharyngitis was reported in 9% of subjects in the mometasone group, 13% of subjects in the budesonide group, and 10% of placebo subjects [206:67-68]. Epistaxis was reported by 9% of subjects in the mometasone group, 12% of subjects in the loratadine group, and 9% of placebo subjects [206:67-68].

There were no reports of nasal septal perforation in either the mometasone or placebo treatment group however one subject in the budesonide treatment group (subject I93-133-08, #025) was found to have a 1 cm perforation of the anterior nasal septum and posterior margins which per biopsy report 07/27/94 revealed 'inflammatory perforation of the septum with reactive hyperplasia and squamous metaplasia of adjacent epithelium' [206:77-78, 207:476]. In addition, nasal ulcers were not reported in the mometasone treatment group however nasal ulcers were reported in the other 2 treatment groups as follows:

(1) budesonide group: reports in 5 subjects (2 subjects on Visit 9, 3 subjects on Visit 10) [211:4199, 212:5156, 5231, 5232, 5251, 5322],

(2) placebo: reports in 2 subjects (on Visit 9), [212:5162, 5256].

Glaucoma and/or cataract formation via eye examination were not specifically evaluated in this study, nor were any assessments of HPA-axis performed. No deaths were reported in any of the three treatment groups.

In terms of infection, 10% of subjects in the mometasone group reported viral infection, while 7% and 12% of subjects reported viral infection in the budesonide and placebo group, respectively [206:70, 207:460]. One subject in the mometasone treatment group (subject I93-133-08, #018) and one subject in the placebo group reported herpes simplex labialis [207:409, 211:4003, 211:4283]. In this trial, one subject in the placebo treatment group (subject I93-133-18, #011) was noted by the examining physician to have moniliasis (i.e. oral candidiasis) on study Visit 9 [207:409, 460, 211:4296]. No subjects in either of the two active treatment groups were found to have moniliasis and no subjects in either of the three treatment groups were reported to have nasal candidiasis on any clinic visits [207:5141-5334].

A total of 10 subjects discontinued treatment because of adverse events but

none of these subjects were in the mometasone treatment group (5 in the budesonide group, and 5 placebo subjects) [206:77].

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the three treatment groups. One mometasone group subject was reported to have an elevated alkaline phosphatase at screening ... ..hich were not fe... be ... to ... (lab ... 343 U/L and 293 U/L, respectively at these visits) [207:479]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change with the exception of a significant decrease in the peripheral blood eosinophil count for subjects receiving either of the two active treatments [207:490, 519, 575,604, 661]. Adverse events did not appear to differ significantly based on age, sex, or race except that headache appeared to have a higher prevalence in male than female subjects for all three treatment groups, and in Caucasian subjects compared with other racial groups [207:429-471, 441, 449, 456, 465, 466, 468].

8.10.5. CONCLU...IONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of seasonal allergic rhinitis, as compared with placebo. Prophylaxis of subjects with mometasone 2-4 weeks prior to the onset of the pollen season resulted in a statistically significant increase in the proportion of minimal symptom days (total nasal symptom ≤ 2) compared with prophylaxis with placebo for the same period of time. Because the study was not designed to evaluate mometasone treatment at the time of onset of the allergy season as compared with prophylaxis with mometasone prior to onset of the allergy s...on and cross-study comparisons were not possible because of baseline differenc... in subject symptom scores for the respective studies, no comm...nt can be ... as to how mome...one treatment at t... start of t... ...ller... ...son would compare with mometasone prophylaxis in terms of clinical e...icacy.
2. The other active treatment, budesonide also showed statistically gre... efficacy in the treatment of symptoms of SAR, as compared with pla...

8.11. Trial C92-280: Controlled, Pivotal Study of Mometasone for the Treatment of Perennial Allergic Rhinitis (PAR)

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Participating Centers: 19 U.S. centers

8.11.1. OBJECTIVE

The objective of this study was to investigate the safety and efficacy of mometasone furoate in the treatment of symptoms of perennial allergic rhinitis (PAR).

8.11.2. STUDY DESIGN

The study was a phase III, randomized, multi-center, double-blind, active- and placebo-controlled study to determine the safety and efficacy of mometasone furoate 200 µg administered intranasally once daily (qd), vs. the active control, beclomethasone (Vancenase AQ) 168 µg administered twice daily (bid), and vs. placebo for a total of 12 weeks in the treatment of perennial allergic rhinitis. The study was also designed to examine HPA-axis suppression in mometasone treated subjects vs. placebo via roll-over of subjects into Study C93-014 (1 year follow-up of Study C92-280).

8.11.3. PROTOCOL

8.11.3.1.a POPULATION: Male or female subjects, ≥ 12 y.
with PAR documented by a positive response to allergen skin prick tests [218:14, 220:848].

(I) Inclusion Criteria [218:14, 220:848-849]:

1. History of perennial allergic rhinitis of at least 2 years duration.
2. If not performed within 2 years of study entry, demonstration of a positive response to skin (via the prick method or intradermal) testing to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander). The wheal size must have been 3 millimeters (mm) greater than or equal to the diluent control with prick

testing or 7 millimeters (mm) greater than or equal to the diluent control with intradermal testing. Subjects sensitive to animal dander must have had that animal as a constant (i.e. daily exposure) household pet [218:14, 220:848].

3. Clinical evidence of active symptoms at both screening and baseline. Nasal rhinorrhea and/or congestion symptom scores of at least moderate severity at screening and baseline. The combined score of nasal symptoms must total at least 5 at both the screening and baseline visit [218:26, 220:846]. The nasal rhinorrhea and/or congestion diary scores must be ≥ 2 during 4 of the 7 days (as assessed via a.m. or p.m. scores or via the rescue medication diary) just prior to the baseline visit.
4. Other than PAR, subjects must in good health and free of clinically significant disease that would interfere with the study schedule or evaluation of PAR.
5. Ability to adhere to dose and visit schedules and record symptom scores accurately and consistently twice daily in a diary.
6. Nonpregnant women of childbearing potential must have been using a medically acceptable form of birth control for at least 3 months prior to screening and were to continue its use for the duration of the study.

Reviewer's Note: The diluent control used for skin testing to allergen (saline vs. sterile water) was not specified in either the study protocol or report for this study.

(II) Exclusion Criteria [218:15, 220:849].

1. History of asthma which required therapy with inhaled or systemic corticosteroids.
2. Clinical evidence of large nasal polyps, marked septal deviation, or any other nasal structural abnormality that may significantly interfere with nasal airflow, as determined by the principal investigator.
3. History of an upper respiratory or sinus infection that required antibiotic therapy within 2 weeks prior to study enrollment.
4. History of significant renal, hematologic, neurologic, cardiovascular, hematologic, metabolic, cerebrovascular, respiratory, gastrointestinal, or other significant medical illness, which in the judgement of the principal investigator could interfere with the study or require medical treatment that would interfere with the study.

5. History or evidence of posterior subcapsular cataracts.
6. History of allergy to corticosteroids, or a history of multiple drug allergies.
7. Subject dependency on nasal, oral, or ocular decongestants; as determined by the principal investigator, or diagnosis of rhinitis medicamentosa.
8. Subject use of any chronic medication which could affect the course of PAR.
9. Use of any investigational drug within the previous 90 days unless the investigational drug was a nasal corticosteroid or has a short (≤ 12 hours) duration of action, in which case the washout period was to be 30 days.
10. Presence of any clinically relevant abnormal vital signs, laboratory test results outside the normal range, or clinically significant abnormal ECG.
11. Subjects on immunotherapy, unless on maintenance therapy.
12. Pregnant or nursing women, pre-menarchal females or women of child-bearing potential not using a medically acceptable form of birth control.
13. Subjects with recurrent clinically significant sinusitis by history and/or chronic purulent postnasal drip, or subjects with an abnormal Water's view X-ray (opacification, mucosal thickening ≥ 6 mm, and/or air-fluid levels).
14. Subjects allergic to a seasonal aeroallergen (e.g. trees, grass, or weeds) with seasonal exacerbation anticipated to occur or occurring during the study.

(II) Concurrent Medication Restrictions [218:19, 220:851-8.]

(A) General Considerations:

1. No subject was permitted to concurrently receive any medication linked with a clinically significant incidence of hepatotoxicity (e.g. methotrexate, 17α-alkylsteroids) or which may cause significant liver enzyme induction (e.g. barbiturates).
2. All previous and concomitant medications taken for the month prior to study entry (exception: astemizole or intramuscular/intra-articular corticosteroids, 3 months) including any over-the-counter drugs, must be recorded in the case report form. The daily dose, route of administration, duration of treatment and reason for use, was to be recorded on the case report form. No significant dose change in chronic medication was allowed during the study.

3. Subjects who developed an upper respiratory tract infection, including infectious rhinitis, sinusitis or otitis, could be treated with one course (up to 21 days) of antibiotics during the study.

(B) Medications restricted before screening (Visit 1) [218:20, 220:851-852]:

	Medication	Time Discontinued Prior to Visit 1
1.	Cromolyn sodium, all forms	2 weeks
2.	Corticosteroids, nasal or ocular	2 weeks
3.	Corticosteroids, inhaled, oral or intravenous	1 month
4.	Corticosteroids, intra-muscular or intra-articular	3 months
5.	High potency topical corticoids-Class 3 or higher in potency, For dermatological use [Stoughten/Cornell Scale]	1 month
6.	Antihistamines, short acting (e.g. chlorpheniramine)	12 hours
7.	Antihistamines, long acting (e.g. cetirizine, loratadine, atarax)	96 hours
8.	Terfenadine, clemastine, long-acting forms of chlorpheniramine	48 hours
	Astemizole	3 months
	Topical nasal and ocular decongestants	24 hours
11.	Oral decongestants	24 hours
12.	Systemic antibiotics	2 weeks
13.	Immunotherapy	24 hours

(C) Concurrent medications restricted after screening and for the duration of the study [218:20-21, 220:852]:

1. Systemic, inhaled, topical nasal, and topical ocular corticosteroids.
2. High potency topical corticosteroids (≥ class 3).
3. Cromolyn sodium.
4. Antihistamines (except the short-acting antihistamine chlorpheniramine, given as the sole antihistamine allowed between screening and baseline as long as washout was 12

hours before baseline.

5. Topical (nasal and ocular decongestants).
6. Oral decongestants.
7. Immunotherapy 24 hours prior to any visit.
8. Systemic antibiotics (unless on a stable dose 1 month prior to the study with the dose remaining unchanged for the duration of the study).
9. Aspirin or nonsteroidal anti-inflammatory agents, except for chronic low dose (≤ 325 mg/day) aspirin for atherosclerosis prophylaxis.

(D) Medications allowed during the study duration [218:21, 220:852-853]:

1. Acetaminophen (for appropriate indications).
2. Inhaled or oral beta-agonists on an as needed basis, for asthma.
3. Theophylline, if on a stable dose before and during the study.
4. Topical antimicrobials.
5. Medium potency (≤ class 4) topical corticosteroids for dermatological use only if the patient had been on a stable dose for at least 2 weeks prior to the study.
6. Thyroid replacement therapy, if on a stable dosage before and during the study.
7. Saline eye drops, as needed.
8. Hormone replacement therapy for postmenopausal women, if on a stable dosage before and during the study.
9. Systemic antibiotics, if on a stable dose for the duration of the study.
10. Occasional use of ASA or NSAIDs (e.g. for menstrual cramps) was permitted.
11. Rescue medication consisting of chlorpheniramine 4 mg po q 4-6 hours not to exceed 6 tablets per 24 hours, for the relief of intolerable PAR symptoms.

8.11.3.1.b. PROCEDURE:

(I) Screening Visit (Visit 1) [218:22-23, 220:856-858]:

A complete medical history (including allergy history), physical examination (including a nasal exam and an ophthalmic exam with tonometry and slit lamp exam to assess glaucoma and cataracts), laboratory evaluation, 12-lead ECG, Water's view sinus film to rule out sinusitis and significant sinus mucosal thickening, and confirmation of the subject's perennial allergen hypersensitivity with skin prick testing (if not performed within the last 2 years) was performed at

the screening visit. Documentation of any seasonal allergy (trees, grasses, weeds relevant to the geographical vicinity of the study site) was to be performed at the screening visit. Subjects were to be symptomatic at both the screening and baseline visits with physical findings compatible with perennial allergic rhinitis. Subjects demonstrating a significant skin test response, by prick or intradermal [illegible] with a history of symptomatic exacerbations would not be enrolled during the relevant season.

Symptoms and overall condition of the PAR were rated using the following set of (A) nasal and non-nasal symptoms and according to the following (B) symptom severity scale:

(A) **Perennial Allergic Rhinitis Symptom Categorization** [218:25, 220:864]:

Nasal Symptoms:	Non-nasal Symptoms:
Rhinorrhea (nasal discharge/ runny nose)	Itching/burning eyes
Stuffiness/congestion	Tearing/watering eyes
Nasal itching	Redness of eyes
Sneezing	Itching of ears or palate

(B) **Perennial Allergic Rhinitis Symptom Severity Scale** [218:25, 220:864-865]:

Symptom Severity Score:	Severity Definition:
0= None	No sign/symptom evident.
1= Mild	Sign/Symptom clearly present but minimal awareness; easily tolerated.
2= Moderate	Definite awareness of sign/symptom which is bothersome but tolerable.
3= Severe	Sign/symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping.

Reviewer's Note:

According to this symptom rating scale, any given study subject could achieve a: minimum score=0 or maximum score=12; for either nasal symptoms or non-nasal symptoms, respectively; and a minimum score =0, maximum score 24 for combined nasal and non-nasal symptoms.

Using this scale, study subjects were to have at least moderate rhinorrhea and/or nasal congestion (symptom score ≤ 2) at both screening and baseline and at least moderate rhinorrhea and/or nasal congestion (symptom score ≤ 2) on diary entries for 4 of the last 7 days of the run-in period to continue to qualify for study randomization. The combined score of total nasal symptoms was to be at least 5 [219:25-56, 220:865].

Subjects were given diary cards and rescue medication cards and were to be trained in the accurate recording of symptoms in the diary reflectively over the previous 12 hours (to be recorded twice daily at the same time of the day), and trained in the documentation of symptom scores for investigator review. From the screening visit onward, the amount and time of use of rescue medication (only chlorpheniramine allowed) was recorded in the rescue medication diary, in addition to the severity of symptoms prior to the dose. All concomitant medications, including any over-the-counter drugs, were recorded. The daily dose, route of administration, duration of treatment and reason for use were also recorded. The subject or parent/guardian (if subject < 18 years of age) was instructed to return to the office within 7-14 days for the baseline visit (Visit 2).

(II) Baseline Visit (Visit 2= Day 1) [218:23-24, 220:858-861]:

Again, during the baseline visit, subjects were re-evaluated in terms of their perennial allergic rhinitis symptoms, physical exam (including nasal exam), vital signs, adverse events, concomitant medications taken, laboratory tests, and ECGs. Subjects were to continue to meet all inclusion and exclusion criteria at this visit in order to qualify to enroll in the study. For any laboratory abnormality, the subject could be included in the study if the abnormal result was expected in the disease setting and was considered unlikely to create an increased risk or the abnormal laboratory value was considered clinically insignificant and would not interfere with the conduct of the study or interpretation of results [218:23, 220:858]. Using the scoring scale described in Section 8.12.3.1.b., the subject's rhinorrhea and/or nasal congestion score (as per subject diary) must each have been at least moderate (score ≥ 2) in severity for 4 of the last 7 days of the run-in period in order to allow the subject to qualify for study enrollment. Subject rescue medication cards were examined for evidence of [illegible] rescue medication.

Following the performance of all medical and laboratory procedures, subjects who met entry criteria had a treatment number assigned and were randomized in a 1:1:1 ratio (using a SAS random number generator) to one of the following 3 treatment groups:

STUDY GROUP	a.m. dosing	p.m. dosing	µg/day
(A) Mometasone (SCH 32088)	mometasone	placebo	200
(B) Beclomethasone (Vancenase AQ)	beclomethasone	beclomethasone	336
(C) Placebo	placebo	placebo	0

Subjects received 8 sprays per day (2 sprays in each nostril from the a.m. bottle

each morning and 2 sprays in each nostril from the p.m. bottle each evening).

Reviewer's Note: While the protocol and general study document state that study medication packages were identical in appearance for all 3 treatments, thus insuring blinding of both the subject and investigator to the treatment identity [218:16-17, 220:859, 866-868], the documents do not state how these bottles were 'made identical' to ensure double-blinding. It appears from the protocol and general study document in the NDA submission that each active drug did not have a placebo control, i.e. a double-dummy design. Nonetheless, in speaking with Ms. Paula Rinaldi, Regulatory Affairs, of Schering Plough, Inc. [Telecon, Ms. Paula Rinaldi, Regulatory Affairs, Schering Plough, Inc. 08/28/97], all study medications were administered in Vancenase AQ bottles (including placebo), thus ensuring blinding.

Subjects were instructed about dosing and received the first dose at the study center. Rescue medication (chlorpheniramine) was dispensed for the relief of intolerable symptoms of PAR during the study, not to exceed 6, 4 mg tablets of chlorpheniramine per 24 hour period. Additionally, subjects received new diary cards on which to record symptoms, rescue medication use, and other concomitant medications.

In summary, the study was designed to recruit at least 20 subjects with documented PAR in each of the 19 centers to ensure a total of at least 375 evaluable subjects. Subjects completing the initial 3 month double-blind phase (study C92-280) were given the option of entering the one year, open-label mometasone safety study (C93-014).

(III) Evaluation Visits [218:24-25, 220:861-864]

[illegible]ts were defined as follows:
Visit 3=Day 8 ± 2 days,
Visit 4=Day 15 ± 2 days,
Visit 5=Day 29 ± 4 days,
Visit 6=Week 8 ± 4 days,
Visit 7=Week 12 ± 4 days.

Treatment days were numbered relative to the start of treatment which was designated as Day 1. During the follow-up visits, subjects had their diary cards checked for completeness and accuracy of recording and diary cards were reviewed to evaluate perennial allergic rhinitis symptoms. Of note, the evaluation included the entire time period since the last visit, up to and including the most current observation. Based on this data (diary review and symptom scoring), the overall condition of rhinitis was assessed by the principal investigator. Response to therapy was evaluated by the investigator at each visit, based upon the subject's clinical status over time since the baseline visit using the symptom scale (0-3

rating) defined in Section 8.12.3.1.b. and using the following (C) therapeutic response scale:

(C) Therapeutic Response Scale [218:26, 220:866]:

[illegible]	[illegible] no symptoms present.
2= Marked Relief	**Symptoms are greatly improved and although present, are scarcely troublesome.**
3= Moderate Relief	Symptoms are present and may be troublesome but are noticeably improved.
4= Slight Relief	Symptoms are present and only minimal improvement has been obtained.
5= Treatment Failure	No relief, symptoms unchanged or worse than pretreatment baseline.

New diary cards were issued and medication bottles were collected from the subjects at the last visit. Safety evaluations were made at these evaluation visits and are discussed in Section 8.12.4.3. Subjects underwent repeat clinical laboratory tests, 12 lead ECG, and nasal and ophthalmic examinations on Visit 7 (Week 12 of the study).

Reviewer's Note: Given that response to perennial allergen(s) were assessed in Study C92-280, seasonal allergen pollen counts were not evaluated or maintained for this study.

The basic study procedure is outlined in Table I. below.

Table 1.

Table 1 Schedule of Study Procedures and Evaluations (Study No C92-280)

	(Visit 1)	(Visit 2)	(Visit 3)	(Visit 4)	(Visit 5)	(Visit 6)	(Visit 7)
Informed Consent, Medical and Allergy History	X						
Check Inclusion/ Exclusion Criteria	X	X					
Review Concomitant Medications	X	X	X	X	X	X	X
Physical and Ophthalmic Examination	X						X
Vital Signs	X	X	X	X	X	X	X
Body Weight	X						X
Height	X						
Sion Testing[a] and Water's View X-ray	X						
12 lead ECG	X						X
Nasal Examination	X	X					X
Laboratory Tests and Pregnancy Test[b]	X						X
Physician Assessment of Rhinitis Symptoms	X	X	X	X	X	X	X
Physician and Patient Assessment of Overall Condition	X	X	X	X	X	X	X
Physician and Patient Assessment of Response to Treatment			X	X	X	X	X
Dispense Study Medication		X			X	X	
Retrieve Study Medication					X	X	X
Study Drug Administered in Office		X			X	X	
Dispense Symptoms and Rescue Medication Diary	X	X	X	X	X	X	
Dispense Rescue Medication[c]	X	X	#	#	#	#	
Retrieve Rescue Medication[c]		X	X	X	X	X	X
Symptoms and Rescue Medication Diary Retrieval and Review		X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X

a. If not done in past 2 years
b. All women
#. As needed
c. Chlorpheniramine

8.11.3.2. CLINICAL ENDPOINTS

(1) Primary Efficacy Variable [218:33-35, 38-39, 220:871-872]:
The mean change from baseline in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject [illegible]):

(1) Mean Change in Total nasal symptom score=

15 Day Interval Score[(Nasal a.m. average $_{\text{Day 1-15}}$) + (Nasal p.m. average$_{\text{Day 1-15}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 3 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 3 Consecutive Days Prior to Baseline Visit}}$)]/2

where the **total nasal symptom score=[discharge+ stuffiness+ sneezing+** [illegible] previously defined in Section 8.12.1.1.b.

Reviewer's Note: The sponsor, in determining this variable when one of the two averages (a.m. or p.m. average) in the above function was missing for a subject, calculated the overall average based on the non-missing average. If both the a.m. and p.m. averages were missing, then the overall average was also missing. For subjects missing either the baseline or the post-baseline visit score for a given variable and visit, no change from baseline calculation was possible and these subjects were not included in any of the efficacy analyses or summaries of that variable at that visit. For this reason, the number of subjects included in the analysis and corresponding summary table may vary from variable to variable and across time points. For each 15-day time interval, the daily composite score described above was averaged over all non-missing days in the interval, separately for the a.m. and p.m. observations, resulting in 2 different averages for that interval. These 2 (a.m. + p.m.) averages were then averaged to obtain an overall average for the interval.

For subjects who used rescue medication between study visits, the last set of symptom scores recorded in the rescue medication diary prior to using rescue medication were considered the appropriate evaluation of symptoms for the next 12-hour period [218:34]. In other words, the subject symptom scores from the rescue medication diary replaced the corresponding scores in the [illegible] for the appropriate 12-hour period in all analyses if rescue medication was used.

Additional analysis of the primary efficacy variable consisted of sub-analysis by week 1 (Day 1-7) and week 2 (Day 8-15) of total nasal symptom scores in order to assess onset of action of mometasone.

(II) Secondary Efficacy Variables:

(1) The mean change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30 (a.m. and p.m. combined), Days 31-45, Days 46-60, Days 61-75, and Days 76-90:

Mean Change in Total nasal symptom score$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$ =

Day 16-30 (or Day 31-45, Day 46-60, Day 61-75, Day 76-90) Interval Score[(Nasal a.m. average $_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$) + (Nasal p.m. average$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$)]/2 - **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 3 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 3 Consecutive Days Prior to Baseline Visit}}$)]/2

where the **total nasal symptom score=[discharge+ stuffiness+ sneezing+ itching]**

(2) Endpoint total nasal symptom score (a.m. and p.m. combined): Endpoint score defined as the last available post-baseline value for each study subject, pooled across the 19 participating centers. The total nasal symptom score was determined as per the 0-3 point PAR symptom severity score [218:25, 220:864-865].

(3) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit). Again, nasal and non-nasal symptom scores were determined as per the 0-3 point PAR severity score [218:25, 220:

(4) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit). Total non-nasal scores were determined as per (2) and (3) above.

(5) Physician's evaluation of total nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8 , Week 12, and the endpoint visit). The total nasal symptom score was determined as per (2)-(4) above.

(6) Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit). The total symptom score was determined as per (2)-(5) above.

Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit). Total non-nasal symptoms were determined as per (2)-(6) above.

(7) Subject's self-evaluation of overall disease condition using the PAR 0-3 [illegible] scale (Day 8, 15, 29, Week 8, Week 12, and the endpoint visit [218:26, 220:865].

(9) Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study day 8, 15, 29, Week 8, Week 12, and the endpoint visit [218:26, 220:865]. Again, the baseline score for physician-rated responses was based exclusively on the baseline visit (visit 2).

(10) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study day 8, 15, 29, Week 8, Week 12, and the endpoint visit [218:26, 220:866].

(11) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study day 8, 15, 29, Week 8, Week 12, and the endpoint visit [218:26, 220:866].

Reviewer's Note: For all physician rated responses, the baseline score was based on the baseline visit only (visit 2), whereas for all subject rated responses (including subject's evaluation of overall disease condition and therapeutic response), the baseline score was based on an average of the baseline visit and the 3 previous visits. Of note, secondary efficacy variables **(1) and (2)-(11) were listed in the general study document [218:39] but discussed in a superficial manner in the study protocol itself [220:872]. Therefore, listed as secondary efficacy variables (2)-(6) above are additional clinical parameters assessed by the sponsor and relevant to determination of treatment efficacy.**

8.11.3.3. STATISTICAL ANALYSIS [218:36-39, 220:870, 873]

A sample size of 125 valid subjects per treatment group or 375 valid subjects total was calculated to detect a treatment difference of approximately 1.43 units or more with respect to the primary efficacy variable--the mean change from baseline in the total nasal symptom score (diary scores averaged over the first 15 days of treatment) based on an estimated pooled standard deviation of 3.5 units with a power of 90% at an α=0.05 (2-tailed). A total of 491 subjects were randomized and 476 were considered evaluable by the sponsor.

Efficacy and safety analyses for this study were based on the following two subject populations:

(1) Efficacy evaluable subjects- randomized subjects who met eligibility criteria and completed at least 1 valid post-baseline visit. The sponsor's primary efficacy analysis was based on this population.

(2) Intent-to-Treat (ITT) Population- all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline evaluation. The sponsor's confirmatory efficacy analyses and all summaries of safety data were based on this population.

The primary efficacy variable was analyzed for all efficacy evaluable and

intent-to-treat subjects (pooled across all centers) using a two-way analysis of variance (ANOVA) which extracted sources of variation due to treatment, center, and treatment by center interaction. The primary efficacy comparison of mometasone vs. placebo was then based on the least squares (LS) means from the ANOVA using a 5% two-sided significance level. The beclomethasone group was [illegible] marketed nasal corticosteroid. No adjustment for multiple comparisons was made using this primary efficacy comparison.

Analysis of secondary efficacy variables was performed using the same two-way ANOVA described above for the primary efficacy variable.

For both the efficacy population and the intent-to-treat population, comparability of treatment groups at baseline was assessed by comparing the three treatment groups with respect to demographic and disease characteristics (gender, age, race, weight, asthma, seasonal allergic rhinitis and disease condition). Continuous variables (age, weight, duration of disease condition) were analyzed by [illegible] which extracted sources of variation due to treatment and center (SAS GLM). Discrete variables (gender, history of asthma, and presence or absence of seasonal allergic rhinitis) were analyzed by categorical linear models (SAS CATMOD), race was analyzed by Fischer's exact test for Caucasians vs. non-Caucasians. Rescue medication use among the 3 treatment groups was not analyzed in any statistical manner, however a tabulation of the frequency of rescue medication use among the 3 treatment groups for each study interval (e.g. Day 1-15, 16-30, etc.) for both ITT and efficacy evaluable subjects was provided by the sponsor [218:250-253].

Reviewer's Note: For the purposes of efficacy and safety review of this and all studies in this submission, the intent-to-treat population was utilized rather than the sponsor's efficacy evaluable population, except where otherwise noted. Also of note, the sponsor lists perennial rhinitis rather than seasonal allergic rhinitis [illegible] represents a typographical error [218:36, 37].

8.11.4. RESULTS

8.11.4.1. SUBJECT DEMOGRAPHICS

(A) Distribution of Subject Populations

A total of 491 subjects were randomized into the study, with 13 subjects excluded from the efficacy analysis because of protocol violations; thus resulting in [illegible] comprising the intent-to-treat population. One subject in the placebo group (subject C92-280-04, #021) was excluded from all [illegible] efficacy evaluations as she received the first dose of medication at the study center and was an

immediate dropout from the study [218:42]. The distribution of subject populations is summarized in Table II. below:

Table II: Distribution of Subject Populations [171:40-41]

	Mometasone (SCH 32088)	Beclomethasone (BDP)	Placebo	Total
Efficacy Population	160 (1 subject did not meet entry criteria, 2 subjects had insufficient efficacy data, and 1 subject had an unacceptable baseline)	157 (1 subject did not meet entry criteria, 1 subject had unsufficient efficacy data, and 4 subjects had an unacceptable baseline)	160 (1 subject had insufficient efficacy data, 1 subject had insufficient efficacy data and insufficient medication, and 1 subject had an unacceptable baseline)	477
Safety Population (ITT)	164	163	163	490
Total # Randomized	164	163	164	[illegible]

(B) Pooled demographic data with regard to subject characteristics in the safety population (ITT) is summarized in Table III. below [218:44].

Table III: Subject Demographics (Protocol C92-280): Intent-to-Treat Population

Table 7 Summary of Demographic Data (Safety [Intent-to-Treat] Population) (Study No. C92-280)

	SCH 32088 (n = 164)	BDP (n = 163)	Placebo (n = 163)	Overall Treatment P-Value
Age (years)				
Mean	35	34	33	0.57
Median	34	33	33	
Range (Min-Max)	12.68	12.74	12.66	
Sex				
Female	82	92	77	
Male	82	71	86	0.10
Race				
White	151	144	139	0.15
Black	4	7	14	
Other	9	12	10	
[illegible]				
[illegible]	167	165	165	0.99
Median	163	157	162	
Range (Min-Max)	73-289	71-350	73-260	
Duration of Perennial Rhinitis (yrs)				
Mean	19	16	16	0.05
Median	17	13	14	
Range (Min-Max)	2-65	2-50	2-58	
Seasonal Allergic Rhinitis				
No	52	47	44	
Yes	112	116	119	0.07
History of Asthma				
No	136	136	137	
Yes	28	27	26	0.98

Sch 32088 = Mometasone furoate

Reviewer's Note: With the exception of the duration of perennial allergic rhinitis (which was greatest in the mometasone treatment group, [illegible] years, median=17 years), all 3 treatment groups had comparable demographic and disease characteristics. The majority of subjects were Caucasian in all 3 treatment groups, as previously noted for the other 2 pivotal studies (SAR and prophylaxis of SAR) in the mometasone NDA submission. However, in contrast to these other studies, in study C92-280, approximately equal numbers of male and female subjects were enrolled in each treatment group. Finally, the majority (approximately 2/3 or greater than 2/3 (beclomethasone and placebo group, respectively)) of all subjects enrolled in this trial had a history or documentation via skin testing of seasonal allergic rhinitis. The majority of subjects in all 3 treatment groups (approximately 75%) did not have a history of asthma.

(C) Subject Distribution by Disease Severity at Baseline in Efficacy Evaluable Subjects [218:49]:

Table 10 Distribution of Patients by Disease Severity at

Treatment Group	% Moderate	% Severe
SCH 32088	75%	23%
BDP	80%	18%
Placebo	81%	19%

Reviewer's Note: The mometasone treatment group was noted to be comprised of a greater % of subjects with severe perennial allergic rhinitis at baseline, as compared with the active control, beclomethasone and the placebo group.

(D) Subject Discontinuation

A total of 64 subjects (20 treated with Mometasone, 19 treated with Beclomethasone, 25 treated with placebo) discontinued the study prior to scheduled completion. This data is summarized in Table IV. [218:44-45].

Table IV: Number and Percentage of Randomized Subjects Who Completed Treatment and Number/(%) Who Discontinued the Study with Reasons for Discontinuation

	TREATMENT GROUP			
	Mometasone (n=164)[1]	Beclomethasone (n=163)	Placebo (n=164)	Total (n=491)
Number (%) Completed	144 (88%)	144 (88%)	139 (85%)	427 (87%)
Reason for Discontinuation				
--Adverse event	5 (3%)	9 (6%)	8 (5%)	22 (4%)
--Treatment Failure	5 (3%)	3 (2%)	5 (3%)	13 (3%)
--Did not meet entry requirements	1 (1%)	2 (1%)	1 (1%)	4 (1%)
--Administrative reasons	2 (1%)	0	2 (1%)	4 (1%)
--Noncompliance with Protocol	1 (1%)	0	1 (1%)	2 (<1%)
--Noncompliance with dosing regimen[2]	0	0	1 (1%)	1 (<1%)
--Subject did not Return	6 (4%)	5 (3%)	7 (4%)	18 (4%)
TOTAL # (%) DISCONTINUED	20 (12%)	19 (12%)	25 (15%)	64 (13%)

[1] n=number of randomized subjects at the time of study initiation.
[2] Patient C92-280-05-0018.

Reviewer's Note: In all 3 treatment arms, the total % of subject discontinuations is greater than 10% of the total enrolled--a relatively high discontinuation rate.

(E) Subject Validity

146 subjects (44 treated with mometasone, 46 treated with beclomethasone, and 56 treated with placebo) valid for efficacy had data invalidated for some visits. These subjects and the reasons for invalidation are summarized in Attachment 6 [218:213-248] and Table 9 [218:45-46] of the NDA. The most common reason for visit invalidation at most study visits was improper visit spacing, followed by concurrent illness [218:46-47].

Reviewer's Note: While the reason(s) for invalidation are reasonable, a relatively large number of subjects had data invalidated for some visits that could potentially influence results for the efficacy evaluable subjects. Interestingly, comparison of the ITT and efficacy evaluable subjects for the

primary efficacy variable (see below, Section 8.12.4.2) did not show a significant difference in results between these two subject populations in terms of total nasal symptom scores.

[illegible] EFFICACY ENDPOINT [illegible]

(1) Primary Efficacy Variable (Mean change in the total nasal symptom score for days 1-15 post-initiation of treatment)

All efficacy analyses in this review were based on the intent-to-treat population (n=164 for mometasone, n=163 for beclomethasone, n=163 for placebo) for the primary efficacy variable--the average change from baseline in the total nasal symptom scores from patient diaries over the first 15 days of treatment. For the average change from baseline in total nasal symptom scores over the day 1-15 interval, both active treatment groups--mometasone and beclomethasone, respectively; were significantly more effective than placebo ($p=0.02$ for [illegible] vs. placebo comparison of the mean change in the total nasal symptom score and $p<0.01$ for beclomethasone vs. placebo comparison of the mean change in the total nasal symptom score). Furthermore, the mometasone and beclomethasone treatment groups were not statistically significantly different from one another ($p=0.43$), although the beclomethasone group showed a numerical advantage with regard to response (mean change in the total nasal symptom score: a -1.5 point change for the mometasone group and a -1.7 point change for the beclomethasone group), compared with the mometasone group. Because of study design and underpowering to detect a difference between these 2 groups, no conclusion can be made regarding the true meaning of a p-value of 0.43 in this context. The mean % decrease in total nasal symptom scores (and raw total nasal symptom score) for subjects receiving mometasone (200 µg qd) was 20% (raw score=5.1), in comparison with a 23% (raw score=5.0) decrease in subjects receiving beclomethasone (168 µg bid) and a 13% (raw score=5.9) decr[illegible] in the [illegible]bo treatme[illegible] group [218:318]

Reviewer's Note: Of note, the findings for the efficacy evaluable group were the same as that for the above intent-to-treat group with the exception of a 21% (rather than the ITT group's 20%) decrease in total nasal symptom scores for the mometasone group [218:255].

Regarding any potential difference of mometasone drug effect over the course of the day (i.e. a.m. vs. p.m.) and detection of waning of drug effect as demonstrated by a change in the primary efficacy variable, subset analysis comparing the combined a.m. and p.m. total nasal scores vs. the a.m. total nasal and vs. the p.m. total nasal symptom score for days 1-15 was performed. No significant numerical difference in symptom scores was found between any of these [illegible] group with the [illegible] p.m. total nasal score$_{DAY\ 1-15}$=5.1, a.m. total nasal score$_{DAY\ 1-15}$= 5.2, p.m. total nasal score$_{DAY\ 1-15}$= 4.9), nor

was any significant a.m. vs. p.m. difference noted in the beclomethasone and placebo treatment groups [218:318-320], however statistical comparisons of the a.m. vs. the p.m. total nasal symptom scores against one another was not performed. Statistical comparison of the change in a.m. and p.m. scores were compared to the change in the combined a.m. and p.m. total nasal score, and for [illegible] be statistically significantly lower during the day 1-15 interval than placebo [218:320].

Reviewer's Note: The a.m. and the p.m. scoring system represents an integration of the subject's symptoms over the previous 12 hours and does not represent a 'snap-shot' of the subject's clinical status at the particular time of symptom recording.

A summary of all of these findings for the primary efficacy variable is provided in Table V. below

A sub-analysis of the primary efficacy variable on a per week basis was performed using the SAS data files provided by the Sponsor (and generated by Dr. Jim Gebert, Biostatistics, Division of Pulmonary Drug Products, FDA, Attachment 1 for Study C92-280). A summary of the efficacy findings for week 1 and week 2 are summarized in Tables V.a. and V.b. Overall, a greater response in total nasal symptoms was noted for the 2 active treatment groups, mometasone and beclomethasone, during week 2 of treatment, however a statistically significant response in total nasal symptom scores for both active treatment groups was evident by week 1 of treatment (mometasone group vs. placebo: raw total nasal symptom score comparison, $p<.01$; mean change in total nasal symptom score, $p<.02$; beclomethasone group vs. placebo: raw total nasal symptom score comparison, $p<.01$; mean change in total nasal symptom score, $p<.01$) [Table

A separate analysis of a.m. vs. p.m. differences in drug efficacy for week 1 of the study (Table V.a., Table V.b. and Attach. 2) showed that for the first week of treatment (days 1-7, Table V.a.) the treatment group [illegible] beclomethasone had slightly greater nasal symptoms during the a.m. recording as compared with the p.m. recording (0.4 point difference between a.m. and p.m. scores). A post-hoc analysis of significance was not performed comparing the differences between these two symptom recording times. Both the a.m. and combined a.m. and p.m. (but not p.m. alone) scores for week 1 and week 2 of treatment demonstrated that mometasone had a clinically and statistically significant effect in reducing total nasal symptoms of PAR compared with placebo, but that this effect was greater by the second week of treatment. Based on this weekly analysis, one may conclude that clinical efficacy of mometasone (also beclomethasone) in reducing total nasal symptom scores was evident after 1 week [illegible] The [illegible] mometasone, as discussed in study C93-184.

An analysis of the impact of rescue medication (chlorpheniramine) use in the ITT population during the day 1-15 interval was performed by the Sponsor and 37% (60/164) of subjects in the mometasone group, 33% (53/163) of subjects in the beclomethasone group, and 47% (76/163) of subjects in the placebo group were found to have used rescue medication during this study interval [218:251]. [illegible] between 1-5 times during the 15 day interval. Findings for the day 1-15 interval in terms of rescue medication use are in contrast to findings for all 3 treatment groups during the screening to baseline period were each treatment group showed approximately equal frequency (50-56%) of rescue medication use [218:251].

Table V.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of PAR:
Primary Efficacy Variable--Intent-to-Treat (ITT) POPULATION, [218:318-3..].

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			AIRWISE COMPARISONS B	A-C	B-C
DAYS	**N**	Mean	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**SD**	**TRT**	**INV**	**T X I**	B	A-C	B-C
BASELINE																
--am & pm nasal	**163**	6.6	2.2	163	6.7	2.0	162	6.9	2.0	2.0	0.34	0.01	0.06	0.69	0.16	0.31
--am nasal	163	6.8	2.2	163	6.8	2.1	162	7.0	2.1	2.1	0.4	0.03	0.07	0.73	0.34	0.19
--pm nasal	162	6.3	2.3	163	6.6	2.1	162	5.7	2.2	2.1	0.2	0.01	0.09	0.26	0.08	0.5
DAYS 1-15																
--am & pm nasal																
RAW	**163**	**5.1**	**2.2**	163	5.0	**2.3**	**162**	**5.9**	**2.1**	[illegible]	**<.01**	**<.01**	**0.57**	**0.75**	**<.01**	**<.01**
CHG	**163**	**-1.5**	**2.0**	163	-1.7	**2.0**	**162**	**-1.0**	**1.6**	**1.9**	**0.01**	**0.07**	**0.6**	**0.43**	[illegible]	**<.01**
%CHG	**163**	**-20**	**32.2**	163	-23	**32.9**	**162**	**-13**	**26.1**	[illegible]						
--am nasal																
RAW	163	5.2	2.3	163	5.0	2.3	162	6.0	2.2	2.2	<.01	<.01	0.56	0.46	<.01	<.01
CHG	163	[illegible]	2.0	163	-1.7	2.1	162	-1.0	1.6	1.9	<.01	0.11	0.58	0.64	0.01	<.01
%CHG	163	[illegible]	32.7	163	-23	33.0	162	-13	25.0							
--pm nasal																
RAW	162	4.9	2.2	163	5.0	2.3	162	5.7	2.2	[illegible]	<.01	<.01	0.59	0.89	<.01	<.01
CHG	162	-1.4	2.2	163	-1.7	2.0	162	-1.0	1.9	[illegible]	0.02	0.08	0.54	0.31	0.08	0.01
%CHG	162	-16	41.4	163	-20	57.6	162	-11	34.9							

SD= Standard Deviation CHG=Change T X I = Treatment by investigator interaction
# P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table V.a.
Efficacy of Mometa[illegible]ne vs. Beclomethasone [illegible]s. Placebo in the Treatment [illegible]
Weekly Analysis of [illegible]e Primary Efficacy Vari[illegible]le: WEEK 1 (Intent-to-Treat [illegible] [illegible]LATION), [SAS Datafiles]

	(A) Mo[illegible]etasone			(B) Beclome[illegible]asone			(C) Placebo			A[illegible]-Values		PAIRWISE COMPARISONS A-B	A-C	B-C
DAYS	N	[illegible]an	SD	N	Mean	SD	N	Mean	SD	INV	TXI	A-B	A-C	B-C
BASELINE														
--am & pm nasal	163	5.6	2.2	163	6.7	2.0	162	6.9	2.0	0.01	0.05	0.69	0.16	0.31
--am nasal	163	6.8	2.2	163	6.6	2.1	162	7.0	2.1	0.03	0.07	0.62	<.01	<.01
--pm nasal	162	6.3	2.3	163	6.6	2.1	162	6.8	2.1	0.01	0.09	0.26	0.08	0.5
DAYS 1-7														
--am & pm nasal														
RAW	162	5.4	2.3	163	5.4	2.3	162	6.2	2.1	<.01	0.5	0.06	<.01	<.01
CHG	162	-1.2	1.8	163	-1.3	1.9	162	-0.7	1.6	0.07	0.35	0.71	0.02	0.01
%CHG	162	-15	30.9	163	-17	32.1	162	-7.4	31.2					
--am nasal														
RAW	162	5.6	2.4	163	5.5	2.4	162	6.4	2.2	0.02	0.44	0.62	<.01	<.01
CHG	162	-1.2	1.9	163	-1.5	2.4	162	-0.4	2.2	0.02	0.44	0.62	<.01	<.01
%CHG	162	-19	34.1	163	-17	33.4	162	-6.6	33.2					
--pm nasal														
RAW	161	5.2	2.3	163	5.4	2.4	162	6.0	2.2	<.01	0.43	0.55	<.01	0.01
CHG	161	-1.1	2.0	163	-1.4	2.4	162	-0.8	1.9	0.07	0.17	0.6	0.08	0.02
%CHG	161	-13	36.3	163	-15	41.9	162	-6.3	38.2					

SD= Standard Deviation C[illegible]=Change T X I = Trea[illegible]ent by investigator interaction
# P-Values are from 2-way anal[illegible] of variance and LSMeans pairwise co[illegible]arisons (no adjustment for overall α level)

Table V.b.
Efficacy of Mometa... ne vs. Beclomethasone ... Placebo in the Treatme... PARI:
Weekly Analysis of ... e Primary Efficacy Vari... WEEK 2 (Intent-to-Treat (I...) P...OPULATION), [SAS ... ...s]

	(A) Mo...etasone		(B) Beclomet...asone		(C) Placebo			Po...	ANOVA P-Values			...RWISE C... A	...PARISONS B-C
DAYS	N	...an	SD	N	Mean	SD	N	Mean	SD	SD	...XT	INV	T X I	...	A ...	B C
BASELINE																
--am & pm nasal	16...	6.6	2.2	163	6.7	2.0	162	6.9	2.0	2.0	0.34	0.01	0.06	...9		0.3
--am nasal	163	6.8	2.2	163	6.8	2.1	162	7.0	2.1	2.1	0.4	0.03	0.07	62		< 0
--pm nasal	162	6.3	2.3	163	6.6	2.1	162	6.8	2.1	2.1	0.2	0.01	0.09	...6		0.5
DAYS 8-15																
--am & pm nasal																
RAW	162	4.8	...4	161	4.6	2.4	162	5.8	2.3	2.3	<.01	<.01	0.51	...3		<.0
CHG	162	1.8	2.3	161	-2.1	2.3	162	-1.3	1.9	2.2	0.01	0.02	0.54	43		<.01
%CHG	162	...4	35.5	161	-28	38.1	162	-17	28.3							
--am nasal																
RAW	162	4.9	2.4	161	4.7	2.5	162	5.7	2.4	2.3	< 01	< 01	0.47	45		< 01
CHG	162	1.9	2.3	161	-2.1	2.4	162	-1.3	1.9	2.2	< 01	0.03	0.5	...9		< 01
%CHG	162	...2	34.8	161	-27	37.5	162	-17	27.4							
--pm nasal																
RAW	159	4.6	2.3	160	4.6	2.5	161	5.5	2.4	2.3	< 01	< 01	0.63	...9		< 01
CHG	159	1.8	2.4	160	-2.0	2.4	161	-1.3	2.2	2.3	0.02	0.03	0.7	36		0.0
%CHG	159	...1	48.8	160	-23	77.0	161	-15	37.0							

SD= Standard Deviation ... Change ... T X I = Treat... t by investigator interaction
* P-Values are from 2-way analy... of variance and LSMeans pairwise co... risons (no adjustment for overall α level)

Analysis of the impact of each individual nasal symptom (a.m. and p.m. combined, a.m. alone, p.m. alone): rhinorrhea, nasal congestion, nasal itching, sneezing on the determination of the final total nasal symptom score (a.m. and p.m. combined, a.m. alone, p.m. alone) for the day 1-15 interval in each of the 3 treatment groups was performed to rule out excessive contribution and therefore, skewing of the total nasal symptom score by one or more of the 4 individual symptoms [221:1095-1097]. Similar to findings noted in SAR study C93-013, the nasal congestion score [221:1095-1097], closely followed by the nasal discharge score [221:1092-1094], was found to contribute a slightly greater numerical weight in the determination of the final nasal symptom score than the other 3 parameters for all 3 treatment groups but this difference was consistent across all 3 groups. Regarding clinical response in terms of the each nasal symptom, statistical significance was achieved in the mometasone treatment group for days 1-15 of treatment for the nasal symptoms of nasal discharge [221:1092], sneezing [221:1098] and a numerically significant but marginally statistically significant response in nasal itching [221:1101], compared with placebo. In contrast to the pivotal SAR trial C93-013, a statistically significant response of nasal congestion scores in the mometasone treatment group was not demonstrated in this pivotal perennial rhinitis trial, C92-280.

In terms of categorizing treatment response by age and sex using the efficacy evaluable population (ITT population data not available), pooled data from all 19 centers for the primary efficacy variable revealed that female subjects overall had a similar response to mometasone as to beclomethasone [218:326-327] for the day 1-15 interval. Both active treatments demonstrated a greater response in both sexes than did placebo, as expected [218:326-327]. For male and female subjects combined, subjects < 34 years of age (n=78 for the mometasone group, n=81 for the beclomethasone group and n=81 for the placebo group) had a numerically (but not statistically significantly) greater response than the older age group (subjects ≥ 34 years of age) to mometasone in terms of total nasal symptom scores [218:323-324]. The older age subject group (n=82 for the mometasone group, n=75 for the beclomethasone group, and n=77 for the placebo group) conversely demonstrated a numerically greater response to beclomethasone treatment in terms of total nasal symptom scores, compared with the < 34 year age group [218:324]. While noted, the clinical significance of this small difference in age in this small number of subjects is unlikely to be relevant to the pathophysiology of PAR and furthermore, was not noted in other PAR studies in this NDA submission. Regarding racial differences, Caucasian subjects, who of note, comprised the majority of all study subjects (n=147 for the mometasone group, n=138 for the beclomethasone group, and n=135 for the placebo group) had a statistically significantly and numerically greater response in total nasal symptoms to mometasone than did non-Caucasian subjects (n=13 for the mometasone group, n=18 for the beclomethasone group, and n=23 for the placebo group) for the day 1-15 interval (-22% change in total nasal symptoms for Caucasian subjects treated with mometasone vs. -4.2% change in total nasal

symptoms for non-Caucasian subjects treated with mometasone) [218:329-330]. Because of severe underpowering of non-Caucasian subjects due to small subject numbers, no conclusions regarding racial differences in clinical response of perennial rhinitis can be made on the basis of this observation.

An analysis to assess the impact of treatment imbalance at baseline with [illegible] addition [illegible] efficacy variable was performed by the sponsor by incorporating the variable of duration of perennial rhinitis as an additional factor in the analysis of variance model used for the primary efficacy analysis. The duration of perennial rhinitis was not found to be significantly related to outcome (p=0.97), hence the potential treatment imbalance with respect to duration of perennial rhinitis did not bias the treatment comparisons. Thus, no adjustment on this score was made in the primary efficacy variable analysis or in any of the other analyses included in the NDA submission for study C92-280 [221:1976].

An assessment of data consistency across the 19 centers participating in protocol C92-280 showed that although the treatment by [illegible] interaction was not significant (p=0.10) [218:38] and mometasone was numerically favored over placebo at 16 of the 19 centers for the day 1-15 interval [218:255-274], mometasone treatment nonetheless demonstrated a statistically significant reduction in the total nasal symptom score at only one center (study center C92-280-01) [218:255]. Ten centers showed that numerically, beclomethasone reduced the mean nasal symptom score the most, followed in turn by mometasone, and then placebo. Four centers showed numerically, that mometasone reduced the mean nasal symptom score the most, followed by beclomethasone, and then placebo. With the exception of study center C92-280-16 [218:271], where significantly lower total nasal symptom scores were recorded for all 3 treatment groups for the day 1-15 interval, the 19 centers participating in the study did not show significant variability of efficacy results. Based on the overall findings of this study, [illegible] including the 3 centers which showed decreased efficacy of mometasone compared with placebo, the pooled [illegible] primary efficacy variable appear adequate to be [illegible] results.

(II Secondary Efficacy Variables (Intent-to-Treat population):

The change from baseline in the total nasal symptom scores averaged over day 16-30, day 31-45, day 46-60, day 61-75, day 76-90, and the endpoint interval were considered secondary efficacy variables. These time points were analyzed using the same model described for the primary efficacy variable. All other composite (total) and individual diary symptom scores and physician evaluated composite and individual symptom scores, as well as the subject's and physician's evaluation of overall disease condition and therapeutic response, were also considered secondary efficacy variables. All of these secondary variables were analyzed using the same two-way ANOVA as used for analysis of the primary efficacy variable. Summary tables of the secondary efficacy variables from the NDA submission are presented in Attachments 1 and 2.

(1) **Mean change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30, Days 31-45, Days 46-60, Days 61-75, and Days 76-90 (a.m. and p.m. combined) [218:318-320]:**

A review of the combined (a.m. and p.m.) mean change in the total nasal [illegible] days 16-30, as summarized in Table VI, showed a further decrease in the total nasal symptom score from a mean of 5.1 (for days 1-15) to a mean of 4.4 (days 16-30) for the mometasone treatment group (10% difference). This symptom score decrease by day 16-30 of treatment was comparable to that of the beclomethasone treatment group which showed a decrease to a mean score of 4.2 (or 10 % difference) for the day 16-30 interval from a mean score of 5.0 (days 1-15). Similar to findings in the pivotal SAR study C93-013, most of the response in total nasal symptom scores for both mometasone and beclomethasone was found to occur within the first 2 weeks of treatment (Tables V. and VI.). No significant difference in a.m. and p.m. scores were noted for either of the active treatments during any of the 15 day study intervals thus supporting evidence that [illegible] appears to be effective over 24 hour dosing (mometasone group: day 16-30: 4.5=a.m. score vs. 4.3=p.m. score; day 31-45: 4.3=a.m. score vs. 4.0=p.m. score, day 46-60: 3.9=a.m. score vs. 3.7=p.m. score;; day 61-75: 3.8=a.m. score vs. 3.6=p.m. score; day 76-90: 3.8=a.m. score vs. 3.6=p.m. score) [218:319-320].

In summary, an overall greater numerical response to treatment by days 16-30 was seen in the beclomethasone group (33%) than in the mometasone group (30%), although both active treatments were found to have greater efficacy than placebo (18%). A similar trend for the beclomethasone treatment group to have numerically lower raw total nasal symptom scores and greater mean change in the total nasal symptom score than the mometasone treatment group (with greater efficacy of both active treatments compared with placebo) was likewise noted for [illegible] day study intervals [illegible] al were the [illegible] numerical differences between [illegible] active [illegible] roups statistically [illegible]ificant. A summary of total [illegible] l symptom scores for all 3 treatment groups is provided in Tables VI. and VII.

(2) **Endpoint total nasal symptom score (a.m. and p.m.) [218:318-320]:**

Analysis of the endpoint total nasal symptom scores demonstrated a greater response of the mometasone treatment group than placebo. Using the last available post-baseline value for each study subject as the endpoint determination, endpoint nasal symptom score values were not found to be significantly different from nasal symptom scores for the day 46-60 interval. A gain, distinction between the a.m. and p.m. scores revealed a small but clinically and statistically insignificant difference between a.m. and p.m. dosing with a slight decrease in total nasal symptom [illegible] the p.m. [illegible] a trend [illegible] ted in both the pivotal SAR study and pivotal prophylaxis of SAR [illegible]ly (4.0=a.m. score vs. 3.7=p.m. score). These results are summarized in Table VII.

Table Vi.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of PAR:
Subject Evaluated Total Nasal Symptom Scores
Secondary Efficacy Variables--Intent-to-Treat (ITT) POPULATION [218:318-320]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARISONS A-B		B-C
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE																
--am & pm total	163	6.6	2.2	163	6.7	2.0	162	6.9	2.0	2.0	0.34	0.01	0.06	0.69	0.16	0.31
DAYS 16-30	am & pm total nasal symptom scores															
RAW	159	4.4	2.3	157	4.2	2.4	157	5.3	2.2	2.2	< 01	< 01	0.54	0.51		< 0
CHG	159	-2.2	2.3	157	-2.4	2.5	157	-1.6	2.1	2.2	< 01	< 01	0.37	0.37		< 0
%CHG	159	-30	34.9	157	-33	40.5	157	-18	59.4							
DAYS 31-45	am & pm total nasal symptom scores															
RAW	152	4.2	2.5	157	4.0	2.5	153	5.1	2.4	2.4	< 01	< 01	0.34	0.58		< 0
CHG	152	-2.5	2.7	157	-2.7	2.6	153	-1.8	2.3	2.5	< 01	0.01	0.22	0.52		< 0
%CHG	152	-3	41.6	157	-37	41.1	153	-19	85.9							
DAYS 46-60	& pm total nasal symptom scores															
RAW	147	-3.8	2.4	157	-3.8	2.5	148	-4.9	2.4	2.4	< 01	< 01	0.47			< 0
CHG	147	-2.8	2.7	157	-2.9	2.6	148	-2.0	2.4	2.5	0.01	0.02	0.52	0.86		< 0
%CHG	147	-3	40.5	157	-40	38.5	148	-22	86.9							

SD= Standard Deviation C =Change T X I = Treatment by Investigator interaction
# P-Values are from 2-way analysis of variance and LSMeans pairwise comparisons (no adjustment for overall α level)

Table VII.
Efficacy of Mometa e vs. Beclomethasone vs. Placebo in the Treatmen PA
Subject Evaluated al Nasal Symptom Scores
Secondary Efficacy ariables--Intent-to-Treat (ITT) POPULATION, [218.18-3

	(A) Mometasone			(B) Beclomet one			(C) Placebo			ed	OVA P-Values			PAIRWISE A-B		MPARISONS B-C
DAYS	N	an	SD	N	Mean	SD	N	Mean	SD			INV	TXI	A-B	A C	B-C
BASELINE																
–am & pm total	163	.8	2.2	163	6.7	2.0	162	6.9	2	.0	34	0.01	0.0	0.69	16	0.31
DAYS 61-75		& pm total nasal symptom scores														
RAW	144	.7	2.3	150	3.7	2.4	142	4.5	2.4	3	01	< 01	0.9	0.76	01	<.01
CHG	144	2.9	2.5	150	-3.0	2.5	142	-2.3	2.5	4	06	< 01	0.0	0.87	05	0.0
%CHG	144		35.3	150	-43	35.1	142	-26	90.4							
DAYS 76-90		& pm total nasal symptom scores														
RAW	142	3.7	2.3	145	3.6	2.4	139	4.6	2.5	3	01	< 01	0.8	0.74	01	< 01
CHG	142	-2.9	2.5	145	-3.0	2.5	139	-2.3	2.7	5	04	< 01	0.3	0.75	05	0.0
%CHG	142	-42	36.0	145	-43	35.1	139	-25	95.1							
ENDPOINT VISIT		am & pm total nasal symptom scores														
RAW	163		2.5	163	3.9	2.6	162	4.8	2.7	5	01	<.01	0.90	0.92	01	< 01
CHG	163	.7	2.7	163	-2.8	2.5	162	-2.1	2.7	6	0.03	0.01	0.61	0.83		0.02
%CHG	163		40.5	163	-41	35.6	162	-24	89.3							

SD= Standard Deviation nange TXI = Treatment by li gator interaction
# P-Values are from 2-way ana ariance and LSMeans pairwise co parisons (no adjustment for overall α level)

(3) **Subject's self-evaluation of total symptom scores (nasal + non-nasal) for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit), [221:1086-1088]:**

Total symptom scores were not found to be statistically significantly [illegible] compared to placebo for any of the 15 day study intervals, although they were numerically lower at all time points compared to placebo treated subjects. This is in contrast to the beclomethasone treatment group which showed a significant response in total symptom scores compared to placebo for the day 1-15, day 16-30, day 31-45, and day 46-60 study intervals. As noted for the total nasal symptom scores, the greatest decrease in total symptom scores for all 3 treatment groups occurred during the first two weeks of study drug administration (day 1-15) [221:1086]. Separation of the day 1-15 interval into weekly intervals of day 1-7 and day 8-15, respectively, (Refer to Attachment 2) revealed a statistically significant decrease in total symptom scores ([illegible] and p.m. combined) in the mometasone treated sub[illegible] week 1, as compared with placebo (p=0.04) but not during week 2 of treatment (p=0.14). Separation of the day 1-15 interval revealed that the greatest change in the total symptom score occurred during week 1 of treatment with mometasone, a finding consistent with mometasone's onset of action. Analysis of the duration of effect of mometasone in terms of total symptom scores revealed a slight difference in the a.m. and p.m. total symptom scores for all 15 day intervals (range 0.3-0.4 difference) with higher total symptom scores recorded in the a.m. This insignificant difference is consistent with prior observations (Refer to discussion of the primary efficacy variable in Section 8.12.4.2. (1) Change in total nasal symptom scores) and supports once a day dosing of mometasone for the treatment of symptoms of PAR.

(4) **Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90 and [illegible]), [221:1088-1089]:**

[illegible]

not found to be significantly decreased in either the mometasone treatment group or the active comparator, beclomethasone treatment, as compared to placebo, for any of the 15-day intervals (p-value range for the mean change of total non-nasal symptom scores for the mometasone group compared to placebo: 0.45-0.91) [221:1089]. In terms of each individual non-nasal symptom, a review of the [illegible] show a statistically significant symptom score response. Furthermore, mometasone treated subjects failed to have numerically lower individual non-nasal symptom scores, as compared to placebo for all 4 non-nasal symptoms. A similar failure of beclomethasone treated subjects to demonstrate a statistically significant [illegible]

each respective individual non-nasal symptom score [221:1104-1115]. Analysis of drug effect by evaluation of a.m. and p.m. scores for total non-nasal symptoms and each individual non-nasal symptom for mometasone treated subjects, did not reveal a significant difference between a.m. and p.m. scores, again supporting once daily dosing of mometasone [221:1090-1091, 1105-1106, 1108-1109, 1111-1112, 1114-1115]. The results of [illegible] symptoms are summarized in Table VIII. A summary of total symptoms, total nasal and total non-nasal responses for mometasone treated subjects at all study interval time points is presented in Table IX. below.

APPEARS THIS WAY

APPEARS THIS WAY

APPEARS THIS WAY

Table VIII. Change in Individual PAR Symptoms with Mometasone Treatment [221:1104-1115]

PAR SYMPTOM	Clinical Response$_{DAY\ 1-15}$ (Yes=Y/No=N)	Clinical Response$_{DAY\ 16-30}$ (Y/N)	Clinical Response$_{DAY\ 31-45}$ (Y/N)	Clinical Response$_{DAY\ 46-60}$ (Y/N)	Clinical Response$_{DAY\ 61-75}$ (Y/N)	Clinical Response$_{DAY\ 76-90}$ (Y/N)	Clinical Response$_{L.}$ (Y/N)
NASAL							
--Rhinorrhea	Yes	Yes	Yes	Yes	Yes	No (p^2=0.08)	Yes
--Congestion	No (p=0.33)	No (p=0.06)	Yes	Yes	No (p=0.07)	No (p=0.19)	No (p=0
--Itching	No (p=0.17)	No (p=0.39)	No (p=0.12)	No (p=0.18)	No (p=0.24)	No (p=0.12)	No (p=0
--Sneezing	Yes	Yes	Yes	Yes	No (p=0.11)	Yes	Yes
NON-NASAL							
--Eye Itching	No (p=0.67)	No (p=0.89)	No (p=0.6)	No (p=0.5)	No (p=0.71)	No (p=0.99)	No (p=0
--Eye Tearing	No (p=0.2)	No (p=0.49)	No (p=0.4)	No (p=0.27)	No (p=0.37)	No (p=0.75)	No (p=0
--Eye Redness	No (p=0.94)	No (p=0.96)	No (p=0.[illegible])	No (p=0.79)	No (p=0.39)	No (p=0.25)	No (p=0
--Ear/palate itching	No (p=0.6)	No (p=0.9)	No (p=0.88)	No (p=0.7)	No (p=0.71)	No (p=0.61)	No (p=0

* Clinical Response= Clinical response of mometasone treatment group, as compared with placebo (for am and pm scores combined)

† p values were calculated based on the change in symptom score(s) from baseline.

Table IX. Summary of Change in PAR Symptoms (a.m. and p.m. combined) with Mometasone Treatment, [218:318, 221:1086, 1089]

PAR SYMPTOM	*Statistical Response$_{DAY\ 1-15}$ (Yes=Y/No=N)	Statistical Response$_{DAY\ 16-30}$ (Y/N)	Statistical Response$_{DAY\ 31-45}$ (Y/N)	Statistical Response$_{DAY\ 46-60}$ (Y/N)	Statistical Response$_{DAY\ 61-75}$ (Y/N)	Statistical Response$_{DAY\ 76-90}$ (Y/N)	Stati Resp (Y/N
Total symptoms	No (p^2=0.08)	No (p=0.12)	No (p=0.09)	No (p=0.06)	No (p=0.23)	No (p=0.32)	N
Total nasal symptoms	Yes	Yes	Yes	Yes	Yes	Yes	
Total non-nasal symptoms	No (p=0.45)	No (p=0.69)	No (p=0.59)	No (p=0.48)	No (p=0.89)	No (p=0.79)	N

* Statistical Response= Statistical response of the mometasone treatment group, as compared with placebo
* p values were calculated based on the change in symptom score(s) from baseline.

(5) **Physician's evaluation of total nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8 , Week 12, and the endpoint visit)** [221:1116].

Physician evaluations of subjects' total nasal symptoms demonstrated that at all study visits after initiation of drug treatment (i.e. Day 8, 15, 29, Week 8, Week 12, and the endpoint visit), subjects in the mometasone treatment group were found to have a statistically significant decrease in total nasal symptoms, as compared with placebo (p= 0.01-0.03 range for all visits except baseline). Again, beclomethasone was found to have a statistically significant and greater response than mometasone in decreasing total nasal symptoms at all study visits after the baseline visit.

(6) **Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit)** [221:1117].

With the exception of Day 15 and Week 12, subjects in the mometasone treatment group were not found to have a statistically significant decrease in total symptoms compared with placebo, although numerically a decrease in symptom scores was noted with mometasone treatment (marginally statistically significant differences between mean change in total symptoms for the mometasone group vs. placebo, p=0.06-0.07) were noted for the Day 29, Week 8, and the endpoint visit) [221:1117]. The beclomethasone treatment group demonstrated a numerically greater response in total symptom scores at all study visits than the mometasone group. With beclomethasone treatment, a statistically significant decrease in total symptoms was noted on study Day 8, 15, and 29 with a marginally statistically significant decrease (p=0.06 for beclomethasone vs. placebo comparison) at Week 8 of the study.

(7) **Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit)** [221:1118]:

Subjects in the mometasone treatment group were not found to have a clinically and statistically significant decrease in total non-nasal symptoms compared with placebo, and again, no numerical decrease in symptom scores was noted with mometasone treatment as compared with placebo. Likewise, subjects in the beclomethasone treatment group were not noted to have a statistically significant improvement in total non-nasal symptoms at any visits, compared with placebo, although a greater numerical response in non-nasal symptom scores was demonstrable with beclomethasone treatment than with mometasone treatment [221:1118].

(8) **Subject's self-evaluation of overall disease condition using the PAR 0-3 point severity scale for study Day 8, 15, 29, Week 8, Week 12, and the endpoint visit** [221:1128]:

With the exception of Day 8 and Week 12, and the marginal exception of the endpoint visit (p=0.07), subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall condition compared with placebo. This clinical improvement in mometasone treated subjects was comparable numerically to the beclomethasone treatment group beginning Day 15 of the study till Week 12 of the study.

(9) **Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study Day 8, 15, 29, Week 8, Week 12, and the endpoint visit [221:1127]:**

Subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall condition compared with placebo at Day 29, Week 8, and the endpoint study visit ($p \leq 0.05$). Furthermore, responses for the mometasone and beclomethasone treatment groups were comparable at most study visits (Day 29, Week 12, endpoint visit) [221:1127].

(10) **Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study Day 8, 15, 29, Week 8, Week 12, and the endpoint visit [221:1130]:**

Subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall response to treatment, as compared to the placebo group only at Day 15 of the study (p=0.01), although mometasone treated subjects demonstrated a numerically greater overall response to treatment than placebo subjects. The beclomethasone treatment group demonstrated a statistically significant and numerically greater overall response to treatment than did the mometasone group per subject self-evaluation, as had been previously noted in several of the other secondary efficacy variables ($p \leq 0.02$ at all study visits) [221:1130].

(11) **Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study Day 8, 15, 29, Week 8, Week 12, and the endpoint visit [221:1129]:**

Subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall response to treatment, as compared with placebo at all study visits ($p \leq 0.04$) with the exception of Day 8 (p=0.14). The beclomethasone treatment group demonstrated a statistically significant and a slightly greater response to treatment than did the mometasone

group ($p \leq 0.03$ at all study visits), again consistent with previous analyses of the primary efficacy variable and several secondary efficacy variables.

A summary of the secondary efficacy variable findings for mometasone is summarized in Table X. below and presented as primary data in Attachment 1 (for variables (3)-(11)):

Table X. Secondary Efficacy Variables of PAR and Treatment with Mometasone [218:318, 221:1086, 1089, 1116-1118, 1127-1130]

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1	Subject evaluated mean Δ in Total Nasal Sx Score DAY 16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90	Yes:	All study intervals.	
2	Subject evaluated mean Δ in Endpoint Total Nasal Sx Score	Yes:	Endpoint visit.	
3	Subject evaluated mean Δ in Total Sx Score DAY 1-15, DAY 16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90, Endpoint visit	No:	All study intervals	
4	Subject evaluated Total non-nasal Sx Score DAY 1-15, DAY 16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90, Endpoint visit	No:	All study intervals.	
5	Physician Evaluated Total Nasal Sx Score	Yes	All study visits:	Day 8, 15, 29, Week 8, Week 12, Endpoint visit
6	Physician Evaluated Total Sx Score	Yes:	Study visits:	Day 15, Week 12
		No:	Study visits:	DAY 8, 29, Week 8, Endpoint visit
7	Physician Evaluated Total non-nasal Sx Score	No:	All study visits	
8	Subject overall condition evaluation	Yes:	Study visits:	Day 15, 29, Week 8
		No:	Study visits:	Day 8, Week 12, Endpoint visit
9	Physician overall condition evaluation	Yes:	Study visits:	Day 29, Week 8, Endpoint visit
		No:	Study visits:	Day 8, 15, Week 12
10	Subject overall Rx Response evaluation	Yes:	Study visit:	Day 15
		No:	Study visits:	Day 8, 29, Week 8, Week 12, Endpoint visit
11	Physician overall Rx Response evaluation	Yes:	Study visits:	Day 15, 29, Week 8, Week 12, Endpoint visit
		No:	Study visit:	Day 8

Δ=Change, Sx=Symptom, Rx=Treatment

Reviewer's Note: Summary of Efficacy Findings

Overall, mometasone was found to be effective in reducing total nasal symptoms at a dose of 200 µg po qd, as related to perennial allergic rhinitis symptoms over the course of all study visits. Because of a lack of a clinically significant effect on non-nasal symptoms, mometasone did not demonstrate a significant effect on decreasing total symptoms of PAR, the total non-nasal symptoms or any of the individual non-nasal symptoms of PAR.

Rescue medication overall was used less frequently during the study by mometasone treated subjects, as compared to placebo or beclomethasone treated subjects. 59% of mometasone treated subjects (ITT population [218:250]) used the rescue antihistamine, chlorpheniramine, at some point during study C92-280, in contrast to 72% of placebo subjects and 67% of beclomethasone subjects.

Mometasone did not demonstrate a significant waning of clinical efficacy based on separate a.m. and p.m. scoring of symptoms in subject diaries, a finding which supports once a day (qd) dosing of mometasone.

In terms of the primary efficacy variable, mometasone treatment demonstrated a numerically greater but not statistically greater effect in individuals < 34 years of age . No commentary can be made regarding efficacy and racial differences as the majority of enrolled subjects were caucasian, however non-caucasian subjects were noted to have a statistically significantly and numerically smaller response to mometasone treatment for the day 1-15 interval than did caucasian subjects.

In summary, given a reasonable study design to assess a therapeutic response in the treatment of seasonal allergic rhinitis and reasonable clinical efficacy results, mometasone was found to be effective in decreasing the symptoms of PAR as compared with placebo.

ATTACHMENT 2:

Secondary Efficacy Variables of PAR and Response to Mometasone Treatment

(3) Subject's evaluation of total symptom scores:

(A) Subject a.m. and p.m. combined scores [221:1086]:

AM & PM AVERAGED DIARY TOTAL SYMPTOM SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

DAYS	(A) FLUTICASONE N	MEAN	SD	(B) MOMETASONE AQ N	MEAN	SD	(C) PLACEBO N	MEAN	SD	POOLED SD	ANOVA P-VALUES # TRT	INV	T X I	PAIRWISE COMPARISONS # A-B	A-C	B-C
BASELINE	163	10.8	4.6	161	10.5	4.1	162	11.3	4.3	4.3	0.36	0.01	0.04	0.3*	0.61	0.36
1-15 RAW	163	8.5	4.4	161	7.9	4.2	162	9.4	4.2	4.3	0.01	<.01	0.39	0.18	0.04	<.01
CHG	163	-2.3	3.6	161	-2.6	3.8	162	-1.7	3.0	3.3	0.06	0.0*	0.3	0.58	0.08	0.02
%CHG	163	-17	39.0	161	-21	37.4	162	-12	35.9							
16-30 RAW	159	7.5	4.5	157	6.7	4.4	157	8.3	4.3	4.2	<.01	<.01	0.43	0.09	0.1	<.01
CHG	159	-3.4	4.1	157	-3.8	4.3	157	-2.7	3.9	3.8	0.05	<.01	0.28	0.41	0.12	0.02
%CHG	159	-27	40.8	157	-32	47.0	157	-20	69.2							
31-45 RAW	152	7.1	4.8	157	6..	4.5	153	7.9	4.6	4.4	<.01	<.01	0.38	0.15	0.06	<.01
CHG	152	-3.9	4.7	157	-4.2	4.4	153	-3.1	4.2	4.3	0.07	0.01	0.2	0.62	0.09	0.03
%CHG	152	-31	48.0	157	-36	47.2	153	-22	83.8							
46-60 RAW	147	6.6	4.6	157	6.3	4.5	148	7.5	4.6	4.4	<.01	<.01	0.19	0.32	0.03	<.01
CHG	147	-4.4	4.8	157	-4.5	4.4	148	-3.5	4.2	4.4	0.06	0.04	0.44	0.93	0.06	0.06
%CHG	147	-36	44.8	157	-40	42.0	148	-26	85.6							
61-75 RAW	144	6.3	4.3	150	5.8	4.6	142	6.8	4.4	4.2	0.07	<.01	0.58	0.31	0.21	0.02
CHG	144	-4.7	4.4	150	-4.6	4.2	142	-4.0	4.4	4.2	0.61	<.01	0.5	0.9	0.23	0.27
%CHG	144	-40	39.0	150	-43	36.5	142	-30	71.2							
76-90 RAW	142	6.6	4.6	145	5.8	4.6	139	7.0	4.6	4.3	0.05	<.01	0.76	0.25	0.2	0.02
CHG	142	-4.6	4.5	145	-4.7	4.3	139	-4.0	4.7	4.4	0.65	<.01	0.2	0.86	0.32	0.24
%CHG	142	-39	40.7	145	-43	37.0	139	-28	72.8							
CHOPT RAW	163	6.6	4.6	163	6.1	4.5	162	7.6	5.0	4.6	0.03	<.01	0.76	0.39	0.06	0.01
CHG	163	-4.3	4.8	163	-4.4	4.3	162	-3.7	4.7	4.6	0.32	0.02	0.54	0.97	0.2	0.10
%CHG	163	-35	44.4	163	-40	38.9	162	-28	69.5							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 8 SYMPTOMS FROM AVERAGED AM AND PM DIARIES
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM AND PM BASELINE VALUES
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
CHOPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT
SYMPTOMS ADJUSTED FOR RESCUE MEDICATION

ATTACHMENT 2--*continued*

(B) Subject a.m. scores [221:1087]

AM DIARY TOTAL SYMPTOM SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

DAYS	(A) FENOTEROL			(B) VANCOMARC AQ			(C) PLACEBO			POOLED SD	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD		TRT	INV	T X I	A-B	A-C	B-C
BASELINE	163	11.3	4.6	163	10.6	4.3	162	11.2	4.2	4.3	0.26	0.01	0.03	0.10	0.91	0.34
1-15 RAW	163	0.8	4.4	163	0.0	4.3	16.	0.6	4.3	4.2	<.01	<.01	0.35	0.04	0.1	<.01
CHG	163	-2.3	3.6	163	-2.6	3.5	162	-1.6	3.0	3.3	0.03	0.09	0.34	0.54	0.05	0.01
%CHG	163	-17	39.9	163	-21	36.6	162	-12	31.1							
16-30 RAW	159	7.7	4.5	157	6.8	4.4	157	8.5	4.3	4.2	<.01	<.01	0.51	0.06	0.1	<.01
CHG	159	-3.5	4.1	157	-3.8	4.3	157	-2.6	3.9	4.0	0.03	<.01	0.23	0.59	0.05	0.01
%CHG	159	-28	39.1	157	-31	42.9	157	-19	43.3							
31-45 RAW	151	7.2	4.8	157	6.6	4.5	153	8.1	4.6	4.4	<.01	<.01	0.23	0.12	0.06	<.01
CHG	152	-4.0	4.7	157	-4.1	4.5	153	-3.0	4.2	4.4	0.04	<.01	0.31	0.84	0.04	0.02
%CHG	152	-32	45.9	157	-35	48.5	153	-22	57.4							
46-60 RAW	147	8.7	4.6	157	8.2	4.6	148	7.7	4.6	4.4	<.01	<.01	0.15	0.31	0.02	<.01
CHG	147	-4.8	4.7	157	-4.6	4.5	148	-3.6	4.3	4.4	0.05	0.03	0.36	0.93	0.02	0.05
%CHG	147	-37	42.2	157	-38	45.1	148	-25	64.5							
61-75 RAW	144	6.4	4.3	150	5.9	4.5	142	7.1	4.3	4.2	0.05	<.01	0.58	0.23	0.21	0.01
CHG	144	-4.8	4.4	150	-4.8	4.3	142	-4.0	4.5	4.3	0.27	<.01	0.52	0.69	0.32	0.24
%CHG	144	-40	39.6	150	-41	40.4	142	-29	66.8							
76-90 RAW	142	6.5	4.4	145	5.8	4.4	139	7.2	4.6	4.3	0.03	<.01	0.8	0.2	0.10	0.01
CHG	142	-4.7	4.4	145	-4.7	4.4	139	-4.0	4.8	4.4	0.34	<.01	0.3	0.88	0.10	0.23
%CHG	142	-39	40.6	145	-41	43.0	139	-30	62.4							
ENDPT RAW	163	6.7	4.6	163	6.2	4.5	162	7.5	5.0	4.6	0.07	<.01	0.77	0.33	0.04	0.01
CHG	163	-4.6	4.8	163	-4.6	4.4	162	-3.7	4.7	4.4	0.22	0.01	0.57	0.9	0.1	0.17
%CHG	163	-36	45.7	163	-39	43.4	162	-29	60.4							

(C) Subject p.m. scores [221:1088]:

PM DIARY TOTAL SYMPTOM SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

DAYS	(A) FENOTEROL			(B) VANCOMARC AQ			(C) PLACEBO			POOLED SD	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD		TRT	INV	T X I	A-B	A-C	B-C
BASELINE	162	10.6	4.7	163	10.4	4.2	162	11.0	4.3	4.3	0.42	<.01	0.09	0.60	0.30	0.19
1-15 RAW	162	0.3	4.4	163	7.0	4.2	162	0.2	4.2	4.1	0.01	<.01	0.43	0.41	0.04	<.01
CHG	162	-2.3	3.7	163	-2.5	3.5	162	-1.8	3.4	3.5	0.13	0.00	0.31	0.03	0.15	0.05
%CHG	162	-14	40.9	163	-16	37.7	162	-9.0	47.5							
16-30 RAW	156	7.1	4.5	157	6.6	4.4	157	8.0	4.3	4.2	0.01	<.01	0.4	0.15	0.1	<.01
CHG	156	-3.3	4.2	157	-3.8	4.4	157	-2.0	4.1	4.1	0.1	<.01	0.43	0.32	0.36	0.03
%CHG	156	-26	33.3	157	-30	103	157	-13	80.4							
31-45 RAW	150	6.0	4.8	157	6.2	4.6	153	7.7	4.6	4.4	4.01	<.01	0.10	0.26	0.05	<.01
CHG	150	-3.9	4.7	157	-4.2	4.5	153	-3.2	4.3	4.4	0.1	0.01	0.13	0.54	0.13	0.04
%CHG	150	-28	61.1	157	-27	138	153	-22	70.3							
46-60 RAW	144	6.4	4.8	157	5.9	4.8	144	7.4	4.6	4.4	0.01	<.01	0.26	0.34	0.03	<.01
CHG	144	-4.2	5.0	157	-4.5	4.4	144	-3.5	4.3	4.5	0.12	0.00	0.35	0.62	0.14	0.00
%CHG	144	-32	39.0	157	-38	80.0	144	-25	66.2							
61-75 RAW	143	6.1	4.6	149	5.8	4.5	142	6.8	4.5	4.3	0.11	<.01	0.56	0.62	0.21	0.04
CHG	143	-4.6	4.8	149	-4.7	4.3	142	-4.1	4.5	4.3	0.35	<.01	0.51	0.88	0.38	0.33
%CHG	143	-38	43.6	149	-40	86.0	142	-30	70.5							
76-90 RAW	141	6.2	4.6	145	5.8	4.5	139	8.0	4.7	4.3	0.08	<.01	0.7	0.34	0.22	0.03
CHG	141	-4.4	4.8	145	-4.7	4.4	139	-4.0	4.8	4.5	0.53	0.02	0.30	0.68	0.31	0.27
%CHG	141	-36	46.3	145	-43	48.2	139	-27	88.2							
ENDPT RAW	162	6.6	4.5	163	6.1	4.5	162	7.3	5.1	4.6	0.04	<.01	0.76	0.56	0.07	0.01
CHG	162	-4.2	4.8	163	-4.6	4.3	162	-3.7	4.9	4.7	0.43	0.04	0.5	0.64	0.31	0.22
%CHG	162	-33	51.0	163	-38	47.6	162	-28	84.5							

ATTACHMENT 2--continued

(4) Subject's evaluation of total non-nasal symptom scores

(A) Subject a.m. and p.m. combined scores [221:1089]

AM & PM AVERAGED DIARY NON-NASAL SYMPTOM SCORE @ - POOLED DIARY DATA 15-001 AVERAGE

DAYS	(A) FEXOFENADINE			(B) PHENYLPROPANOLAMINE AD			(C) PLACEBO			POOLED SD	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD		TRT	INV	T X I	A-B	A-C	B-C
BASELINE	163	4.3	2.8	165	3.8	2.5	162	4.2	2.8	2.5	0.16	0.01	0.04	0.09	0.77	0.35
1-15 RAW	163	3.5	2.7	163	3.0	2.3	162	3.5	2.6	2.3	0.01	<.01	0.16	0.04	0.81	0.02
CHG	163	-0.8	1.9	163	-0.9	1.7	162	-0.7	1.7	1.7	0.6	0.03	0.06	0.04	0.45	0.34
%CHG	158	28.2	324	158	-31.8	105	161	1.8	95.6							
16-30 RAW	159	3.1	2.5	157	2.5	2.3	157	3.0	2.6	2.3	0.03	<.01	0.3	0.01	0.68	0.04
CHG	159	-1.2	2.2	157	-1.6	2.1	157	-1.1	2.3	2.1	0.83	<.01	0.22	0.55	0.69	0.32
%CHG	154	-15	106	152	-38	151	156	-17	78.6							
31-45 RAW	152	2.9	2.5	157	2.6	2.3	153	3.0	2.5	2.3	0.05	<.01	0.13	0.03	0.88	0.04
CHG	152	-1.4	2.3	157	-1.5	2.3	153	-1.3	2.3	2.2	0.72	0.03	0.36	0.8	0.59	0.43
%CHG	147	-24	107	152	-39	136	152	-17	125							
46-60 RAW	147	2.7	2.6	157	2.2	2.6	160	2.7	2.5	2.3	0.1	<.01	0.09	0.07	0.94	0.06
CHG	147	-1.6	2.6	157	-1.8	2.2	160	-1.5	2.2	2.3	0.73	0.09	0.38	0.9	0.68	0.5
%CHG	142	-29	92.9	152	-35	89.6	147	-27	132							
61-75 RAW	144	2.6	2.3	150	2.2	2.3	142	2.6	2.3	2.2	0.27	<.01	0.21	0.11	0.96	0.33
CHG	144	-1.8	2.1	150	-1.8	2.2	142	-1.7	2.4	2.2	0.91	0.02	0.61	0.68	0.89	0.78
%CHG	139	-34	81.4	145	-34	115	141	-32	86.8							
76-90 RAW	142	2.7	2.6	145	2.2	2.3	139	2.6	2.5	2.3	0.19	<.01	0.61	0.07	0.65	0.3
CHG	142	-2.7	2.4	145	-1.7	2.2	139	-1.7	2.6	2.5	0.95	0.06	0.17	0.84	0.79	0.77
%CHG	137	-30	77.6	140	-29	166	138	-31	93.7							
ENDPT RAW	163	2.7	2.6	163	2.3	2.3	162	2.7	2.6	2.4	0.17	<.01	0.62	0.09	0.85	0.32
CHG	163	-1.6	2.5	163	-1.8	2.2	162	-1.8	2.5	2.4	0.99	0.05	0.39	0.07	0.91	0.96
%CHG	158	-5.2	319	158	-27	144	161	-28	91.8							

ATTACHMENT 2--continued

(B) Subject a.m. non-nasal scores [221:1090]:

AM DIARY NON-NASAL STEPTON SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

DAYS	(A) FLUTICASONE N	MEAN	SD	(B) VANCERIL 4Q N	MEAN	SD	(C) PLACEBO N	MEAN	SD	POOLED SD	ANOVA P-VALUES @ TRT	INV	T X I	PAIRWISE COMPARISONS @ A-B	A-C	B-C
BASELINE	161	4.3	2.8	163	3.8	2.7	162	4.2	2.6	2.6	0.16	0.01	0.02	0.06	0.56	0.18
1-15 RAW	163	3.6	2.5	163	3.0	2.3	162	3.6	2.6	2.3	0.02	<.01	0.16	0.01	0.9.	0.02
CHG	163	-0.8	1.9	163	-0.9	1.7	162	-0.6	1.9	1.8	0.65	0.04	0.1	0.5.	0.68	0.21
%CHG	155	-5.6	96.6	156	-12	73.2	159	-1.8	68.9							
16-30 RAW	159	3.1	2.5	157	2.5	2.3	157	3.0	2.4	2.3	0.02	<.01	0.32	0.01	0.61	0.04
CHG	158	-1.2	2.2	157	-1.6	2.2	157	-1.1	2.2	2.1	0.53	<.01	0.10	0.65	0.5	0.25
%CHG	153	-32	109	150	-26	96.5	154	-10	64.1							
31-45 RAW	15.	3.0	2.5	157	2.4	2.4	153	2.9	2.5	2.3	0.05	<.01	0.16	0.03	0.88	0.04
CHG	152	-1.5	2.4	157	-1.5	2.3	153	-1.2	2.4	2.3	0.57	0.01	0.2	0.93	0.39	0.34
%CHG	146	-23	107	150	-21	138	150	-22	70.6							
46-60 RAW	147	2.9	2.4	157	2.3	2.4	148	2.7	2.5	2.3	0.33	<.01	0.07	0.09	0.91	0.07
CHG	147	-1.7	2.5	157	-1.6	2.3	148	-1.6	2.3	2.3	0.56	0.68	0.36	0.72	0.28	0.45
%CHG	141	-28	98.7	150	-31	114	145	-32	58.1							
61-75 RAW	144	2.6	2.3	150	2.2	2.4	142	2.4	2.3	2.2	0.22	<.01	0.18	0.08	0.66	0.32
CHG	144	-1.8	2.4	150	-1.7	2.2	142	-1.7	2.4	2.3	0.88	0.01	0.43	0.82	0.7	0.82
%CHG	138	-36	66.9	143	-38	107	139	-38	61.6							
76-90 RAW	142	2.7	2.4	145	2.2	2.3	139	2.5	2.5	2.3	0.2	<.01	0.65	0.07	0.66	0.31
CHG	142	-1.7	2.6	145	2.7	2.2	139	-1.7	2.5	2.3	0.97	0.02	0.24	0.81	0.95	0.86
%CHG	136	-31	74.4	138	-35	109	136	-36	61.0							
ENDPT RAW	163	2.7	2.5	163	2.3	2.3	162	2.7	2.7	2.4	0.19	<.01	0.43	0.09	0.79	0.15
CHG	163	-1.6	2.5	163	-1.5	2.3	162	-1.5	2.5	2.4	0.92	0.03	0.76	0.72	0.72	0.99
%CHG	155	-31	74.0	156	-33	106	159	-33	63.1							

(C) Subject p.m. non-nasal scores [221:1091]:

PM DIARY NON-NASAL STEPTON SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

DAYS	(A) FLUTICASONE N	MEAN	SD	(B) VANCERIL 4Q N	MEAN	SD	(C) PLACEBO N	MEAN	SD	POOLED SD	ANOVA P-VALUES @ TRT	INV	T X I	PAIRWISE COMPARISONS @ A-B	A-C	B-C
BASELINE	162	4.2	2.8	163	3.8	2.5	162	4.2	2.7	2.6	0.18	<.01	0.08	0.11	0.99	0.11
1-15 RAW	162	3.3	2.4	163	2.9	2.3	162	3.5	2.6	2.3	0.06	<.01	0.2	0.1	0.56	0.02
CHG	162	-0.9	1.8	163	-0.9	1.8	162	-0.7	1.9	1.8	0.71	0.05	0.12	0.83	0.62	0.56
%CHG	152	0.4	161	155	2.5	182	161	9.5	132							
16-30 RAW	158	3.0	2.5	157	2.4	2.3	157	2.9	2.4	2.3	0.06	<.01	0.32	0.02	0.81	0.04
CHG	158	-1.2	2.2	157	-1.6	2.2	157	-1.2	2.2	2.1	0.72	<.01	0.3	0.54	0.84	0.63
%CHG	148	-15	107	149	-37	106	156	-16	62.5							
31-45 RAW	150	2.8	2.5	157	2.3	2.3	153	2.8	2.5	2.3	0.07	<.01	0.35	0.05	0.99	0.05
CHG	150	-1.3	2.3	157	-1.5	2.3	153	-1.4	2.4	2.3	0.83	0.02	0.33	0.07	0.67	0.55
%CHG	140	-24	130	149	-24	107	152	-22	66.5							
46-60 RAW	146	2.7	2.5	157	2.2	2.4	148	2.6	2.5	2.3	0.08	<.01	0.36	0.06	0.97	0.06
CHG	146	-1.6	2.6	157	-1.6	2.3	148	-1.5	2.3	2.3	0.85	0.32	0.62	0.8	0.75	0.57
%CHG	137	-28	91.8	149	-30	74.0	147	-32	70.8							
61-75 RAW	143	2.5	2.3	149	2.2	2.3	142	2.6	2.6	2.2	0.27	<.01	0.28	0.17	0.87	0.35
CHG	143	-1.8	2.3	148	-1.6	2.3	142	-1.7	2.6	2.3	0.88	0.02	0.67	0.66	0.97	0.66
%CHG	134	-37	63.6	141	-42	62.8	141	-32	77.6							
76-90 RAW	141	2.6	2.4	145	2.3	2.3	139	2.6	2.5	2.3	0.22	<.01	0.58	0.08	0.69	0.3
CHG	141	-1.8	2.6	145	-1.7	2.2	139	-1.7	2.5	2.3	0.87	0.34	0.36	0.09	0.61	0.7
%CHG	132	-31	85.2	137	-37	73.5	138	-38	83.9							
ENDPT RAW	162	2.7	2.6	163	2.2	2.3	162	2.7	2.7	2.6	0.13	<.01	0.68	0.11	0.98	0.11
CHG	162	-1.6	2.6	163	-1.6	2.3	162	-1.6	2.6	2.6	0.99	0.09	0.65	0.93	0.99	0.92
%CHG	152	-30	167	155	-30	109	161	-36	83.8							

ATTACHMENT 2--continued

(5) Physician's evaluation of total nasal symptoms [221:1116]:

VISIT NASAL SYMPTOM SCORE @ - POOLED VISIT DATA

	(A) FLUTICASONE			(B) VANCENASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	164	7.3	1.9	163	7.6	1.8	163	7.6	1.9	1.8	0.51	0.06	0.11	0.86	0.28	0.36
DAY 8 RAW	164	5.4	2.3	161	5.3	2.5	163	6.2	2.5	2.4	<.01	<.01	0.95	0.68	<.01	<.01
CHG	164	-1.9	2.5	161	-2.1	2.5	163	-1.4	2.5	2.5	0.02	0.02	0.95	0.59	0.03	0.03
%CHG	164	-24	32.2	161	-28	32.8	163	-17	32.6							
DAY15 RAW	160	5.0	2.4	159	4.6	2.7	159	5.9	2.4	2.4	<.01	0.01	0.27	0.3	<.01	<.01
CHG	160	-2.4	2.7	159	-2.7	2.8	159	-1.7	2.6	2.7	<.01	<.01	0.77	0.41	0.02	<.01
%CHG	160	-30	33.7	159	-35	35.9	159	-19	36.0							
DAY29 RAW	158	4.5	2.3	157	4.3	2.7	157	5.3	2.3	2.4	<.01	0.01	0.58	0.63	<.01	<.01
CHG	158	-2.8	2.6	157	-3.0	2.9	157	-2.2	2.7	2.7	0.03	0.01	0.65	0.65	0.03	0.02
%CHG	158	-37	31.5	157	-40	36.0	157	-26	34.0							
WK 8 RAW	151	4.2	2.7	157	4.1	2.6	151	5.1	2.7	2.6	<.01	<.01	0.9	0.99	<.01	<.01
CHG	151	-3.2	3.0	157	-3.3	2.8	151	-2.4	2.7	2.8	0.02	<.01	0.94	0.81	0.01	0.02
%CHG	151	-41	37.0	157	-43	36.8	151	-31	33.7							
WK 12 RAW	147	3.8	2.3	148	3.8	2.5	143	4.7	2.4	2.4	<.01	0.01	0.89	0.96	<.01	<.01
CHG	147	-3.6	2.8	148	-3.5	2.8	143	-2.9	2.5	2.7	0.07	0.01	0.85	0.55	0.03	0.1
%CHG	147	-46	33.6	148	-46	36.1	143	-37	32.3							
ENDPT RAW	164	4.0	2.4	163	4.1	2.7	163	4.8	2.7	2.6	<.01	<.01	0.85	0.61	<.01	<.01
CHG	164	-3.4	2.9	163	-3.3	2.9	163	-2.7	2.7	2.8	0.03	0.01	0.83	0.72	0.01	0.03
%CHG	164	-43	35.3	163	-43	38.0	163	-34	35.5							

(6) Physician's evaluation of total symptoms [221:1117]:

VISIT TOTAL SYMPTOM SCORE @ - POOLED VISIT DATA

	(A) FLUTICASONE			(B) VANCENASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	164	11.9	4.1	163	11.6	3.8	163	11.8	3.9	3.8	0.67	0.01	0.02	0.38	0.76	0.57
DAY 8 RAW	164	8.0	4.4	161	8.4	4.4	163	9.6	4.5	4.3	0.03	<.01	0.53	0.19	0.2	0.01
CHG	164	-3.8	4.3	161	-3.2	4.1	163	-2.2	3.9	4.1	0.07	0.00	0.86	0.54	0.1	0.02
%CHG	16.	-20	62.4	161	-25	35.8	163	-17	34.3							
DAY15 RAW	160	8.5	4.8	159	7.6	4.7	159	9.3	4.5	4.5	0.01	<.01	0.35	0.1	0.13	<.01
CHG	160	-3.5	4.4	159	-3.9	4.5	159	-2.4	4.6	4.4	0.01	<.01	0.05	0.44	0.04	<.01
%CHG	160	-26	36.9	159	-32	41.0	159	-17	39.5							
DAY29 RAW	159	7.7	4.3	157	7.0	4.7	157	8.4	4.1	4.3	0.02	<.01	0.44	0.13	0.18	<.01
CHG	159	-4.3	4.5	157	-4.6	4.8	157	-3.3	4.4	4.5	0.06	0.02	0.83	0.67	0.07	0.03
%CHG	159	-33	35.3	157	-38	39.4	157	-25	35.4							
WK 8 RAW	151	7.1	4.8	157	6.5	4.5	151	7.7	4.7	4.5	0.06	<.01	0.01	0.3	0.2	0.02
CHG	151	-4.9	5.0	157	-5.0	4.8	151	-3.9	4.9	4.8	0.09	<.01	0.03	0.86	0.06	0.06
%CHG	151	-39	40.0	157	-41	40.6	151	-31	39.4							
WK 12 RAW	147	6.4	4.8	148	6.2	4.2	143	7.1	4.1	4.0	0.16	<.01	0.07	0.52	0.2	0.05
CHG	147	-5.7	4.7	148	-5.3	4.5	143	-4.6	4.8	4.5	0.15	0.01	0.59	0.5	0.05	0.23
%CHG	147	-44	36.6	148	-44	37.6	143	-37	35.6							
ENDPT RAW	164	6.8	4.2	163	6.7	4.6	163	7.6	4.7	4.4	0.09	<.01	0.47	0.75	0.09	0.04
CHG	164	-5.1	5.0	163	-4.8	4.7	163	-4.2	4.8	4.8	0.17	0.04	0.39	0.69	0.07	0.16
%CHG	164	-38	44.8	163	-40	40.6	163	-34	38.9							

ATTACHMENT 2--continued

(7) Physician's evaluation of total non-nasal symptoms [221:1118]:

VISIT NON-NASAL SYMPTOM SCORE @ - POOLED VISIT DATA

DAYS	(A) FOPCTASONE N	MEAN	SD	(B) VANCENASE AQ N	MEAN	SD	(C) PLACEBO N	MEAN	SD	POOLED SD	ANOVA P-VALUES @ TRT	INV	T X I	PAIRWISE COMPARISONS @ A-B	A-C	B-C
BASELINE	164	4.6	2.9	163	4.2	2.5	163	4.2	2.6	2.6	0.31	<.01	0.07	0.16	0.22	0.85
DAY 8 RAW	164	3.6	2.6	161	3.2	2.3	163	3.6	2.6	2.4	0.15	<.01	0.09	0.05	0.5	0.21
CHG	164	-1.0	2.5	161	-1.1	2.2	163	-0.6	2.3	2.5	0.52	0.93	0.48	0.62	0.52	0.25
%CHG	153	-18	62.8	150	-18	66.0	155	-12	66.3							
DAY15 RAW	160	3.5	2.7	159	3.0	2.5	153	3.4	2.7	2.6	0.36	<.01	0.68	0.06	0.64	0.15
CHG	160	-1.1	2.6	159	-1.3	2.5	159	-0.7	2.7	2.5	0.28	0.02	0.87	0.02	0.3	0.11
%CHG	150	-19	65.1	148	-27	67.6	151	-4.3	80.5							
DAY29 RAW	159	3.2	2.5	157	2.8	2.6	157	3.0	2.6	2.6	0.08	<.01	0.66	0.03	0.5	0.53
CHG	159	-1.4	2.7	157	-1.6	2.6	157	-1.3	2.6	2.6	0.34	0.06	0.78	0.59	0.37	0.15
%CHG	149	-26	61.0	146	-37	66.3	149	-35	78.0							
WK 8 RAW	151	3.0	2.6	157	2.5	2.4	151	2.6	2.6	2.5	0.57	<.01	0.79	0.06	0.27	0.64
CHG	151	-1.7	2.7	157	-1.8	2.6	153	-1.5	2.8	2.7	0.66	0.01	0.69	0.66	0.49	0.59
%CHG	143	-34	59.5	148	-37	82.8	143	-26	85.5							
WK 12 RAW	147	2.8	2.2	148	2.6	2.2	143	2.6	2.3	2.2	0.64	<.01	0.3	0.21	0.36	0.75
CHG	147	-2.1	2.7	148	-1.9	2.6	143	-1.7	2.8	2.6	0.58	0.12	0.58	0.57	0.5	0.82
%CHG	139	-41	54.0	137	42	57.9	135	-34	66.0							
ENDPT RAW	164	2.8	2.6	163	2.6	2.6	163	2.7	2.6	2.3	0.31	<.01	0.32	0.25	0.54	0.59
CHG	164	-1.8	2.8	163	-1.6	2.5	163	-1.8	2.9	2.6	0.83	0.28	0.33	0.74	0.56	0.78
%CHG	153	-36	56.0	152	-31	82.4	155	-29	78.5							

(8) Subject's self-evaluation of overall condition [221:1128]:

SUBJECT'S EVALUATION OF SUBJECT'S OVERALL CONDITION (POOLED)

DAYS	(A) FOPCTASONE N	MEAN	SD	(B) VANCENASE AQ N	MEAN	SD	(C) PLACEBO N	MEAN	SD	POOLED SD	ANOVA P-VALUES @ TRT	INV	T X I	PAIRWISE COMPARISONS @ A-B	A-C	B-C
BASELINE	164	2.3	0.5	162	2.2	0.5	163	2.3	0.4	0.5	0.35	0.34	0.5	0.2	0.06	0.22
DAY 8 RAW	164	1.8	0.8	160	1.7	0.7	163	1.8	0.8	0.7	<.01	0.43	0.8	0.02	0.26	<.01
CHG	164	-0.4	0.7	160	-0.6	0.7	163	-0.4	0.8	0.7	0.06	0.28	0.84	0.2	0.28	0.02
DAY15 RAW	159	1.6	0.7	158	1.6	0.7	159	1.8	0.8	0.7	<.01	0.28	0.97	0.77	0.01	<.01
CHG	159	-0.6	0.8	158	-0.6	0.8	159	-0.4	0.7	0.7	0.03	0.19	0.95	0.38	0.02	0.05
DAY29 RAW	159	1.6	0.7	157	1.6	0.7	157	1.8	0.7	0.7	0.01	0.46	0.81	0.02	<.01	0.01
CHG	159	-0.7	0.8	157	-0.7	0.8	157	-0.5	0.7	0.8	0.03	0.45	0.79	0.33	0.01	0.3
WK 8 RAW	151	1.6	0.7	157	1.6	0.7	151	1.7	0.8	0.7	<.01	<.01	0.97	0.88	<.01	<.01
CHG	151	-0.8	0.8	157	-0.8	0.8	151	-0.6	0.8	0.8	0.02	0.84	0.81	0.54	0.01	0.04
WK 12 RAW	147	1.6	0.7	148	1.6	0.7	143	1.5	0.7	0.7	0.15	<.01	0.79	0.88	0.11	0.08
CHG	147	-0.6	0.8	148	-0.8	0.8	143	-0.7	0.7	0.8	0.36	<.01	0.63	0.43	0.14	0.5
ENDPT RAW	164	1.5	0.7	162	1.5	0.7	163	1.6	0.7	0.7	0.06	0.01	0.76	0.05	0.05	0.06
CHG	164	-0.8	0.8	162	-0.8	0.8	163	-0.7	0.8	0.8	0.2	0.05	0.48	0.42	0.07	0.32

ATTACHMENT 2--continued

(9) Physician's evaluation of subject's overall condition [221:1127]:

PHYSICIAN'S EVALUATION OF SUBJECT'S OVERALL CONDITION (POOLED)

	(A) FLUTICASONE			(B) VANCERIL AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	164	2.2	0.6	163	2.2	0.6	163	2.2	0.6	0.6	0.62	<.01	0.57	0.36	0.88	0.44
DAY 8 RAW	164	1.8	0.6	161	1.7	0.6	163	1.9	0.6	0.6	0.01	0.15	0.57	0.16	0.08	<.01
CHG	164	-0.4	0.7	161	-0.5	0.7	163	-0.3	0.6	0.7	0.05	0.68	0.96	0.47	0.1	0.02
DAY15 RAW	160	1.7	0.6	159	1.5	0.6	159	1.8	0.6	0.6	<.01	0.08	0.15	0.01	0.18	<.01
CHG	160	-0.5	0.7	159	-0.7	0.7	159	-0.4	0.7	0.7	0.02	0.07	0.56	0.14	0.19	0.01
DAY29 RAW	159	1.5	0.6	157	1.5	0.7	157	1.7	0.6	0.6	0.01	0.2	0.22	0.75	0.01	<.01
CHG	159	-0.7	0.7	157	-0.7	0.8	157	-0.5	0.7	0.7	0.03	0.03	0.5	0.68	0.01	0.04
WK 8 RAW	151	1.5	0.7	157	1.6	0.7	151	1.8	0.7	0.7	0.06	0.03	0.96	0.82	0.04	0.04
CHG	151	-0.8	0.8	157	-0.7	0.8	151	-0.6	0.7	0.8	0.13	<.01	0.89	0.47	0.05	0.19
WK 12 RAW	147	1.6	0.7	148	1.6	0.7	143	1.5	0.7	0.7	0.15	<.01	0.91	0.77	0.13	0.07
CHG	147	-0.8	0.8	148	-0.8	0.8	143	-0.7	0.7	0.7	0.36	0.01	0.8	0.51	0.16	0.44
ENDPT RAW	164	1.6	0.7	163	1.6	0.7	163	1.6	0.7	0.7	0.05	<.01	0.8	0.71	0.02	0.05
CHG	164	-0.8	0.8	163	-0.7	0.8	163	-0.6	0.7	0.8	0.09	0.03	0.88	0.4	0.03	0.18

(10) Subject's self-evaluation of overall response to treatment [221:1130]:

SUBJECT'S EVALUATION OF SUBJECT'S OVERALL RESPONSE TO TREATMENT (POOLED)

	(A) FLUTICASONE			(B) VANCERIL AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
DAY 8 RAW	164	3.4	1.0	161	3.2	1.1	163	3.5	0.9	1.0	<.01	0.21	0.99	0.1	0.06	<.01
DAY15 RAW	159	3.2	1.0	159	3.0	1.1	159	3.5	1.0	1.0	<.01	0.04	0.88	0.09	0.01	<.01
DAY29 RAW	159	3.1	1.1	157	2.9	1.0	157	3.3	1.1	1.1	0.01	0.01	0.65	0.16	0.08	<.01
WK 8 RAW	151	3.0	1.2	157	2.8	1.1	151	3.2	1.1	1.1	0.03	0.03	0.93	0.29	0.12	0.01
WK 12 RAW	147	2.9	1.1	148	2.8	1.1	143	3.1	1.1	1.1	0.05	0.01	0.82	0.47	0.09	0.02
ENDPT RAW	164	3.0	1.2	163	2.8	1.2	163	3.2	1.2	1.1	0.03	0.00	0.57	0.47	0.06	0.01

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS ~ ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
RESPONSE IS SCORED AS: 1=EXCELLENT 2=GOOD 3=FAIR 4=POOR 5=TREATMENT FAILURE
MODEL: SCORE = TREATMENT (TRT) INVESTIGATOR (INV) TREATMENT X INVESTIGATOR (T X I)

(11) Physician's evaluation of subject's overall response to treatment [221:1129]:

PHYSICIAN'S EVALUATION OF SUBJECT'S OVERALL RESPONSE TO TREATMENT (POOLED)

	(A) FLUTICASONE			(B) VANCERIL AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
DAY 8 RAW	164	3.5	0.9	161	3.4	1.0	163	3.7	0.9	1.0	0.09	0.11	0.99	0.5	0.14	0.03
DAY15 RAW	160	3.3	1.0	159	3.1	1.0	159	3.5	1.0	1.0	<.01	0.1	0.92	0.08	0.04	<.01
DAY29 RAW	159	3.1	1.1	157	2.9	1.1	157	3.4	1.0	1.1	<.01	0.01	0.97	0.43	<.01	<.01
WK 8 RAW	151	3.0	1.1	157	2.8	1.1	151	3.3	1.1	1.1	<.01	0.04	0.99	0.29	<.01	<.01
WK 12 RAW	147	2.8	1.1	148	2.6	1.2	143	3.2	1.1	1.1	0.02	<.01	0.71	0.08	0.02	0.01
ENDPT RAW	164	2.9	1.1	163	2.9	1.2	163	3.3	1.2	1.1	<.01	0.01	0.55	0.79	0.01	<.01

8.11.4.3. SAFETY ANALYSIS

A review of safety data was performed on the safety (intent-to-treat) population which consisted of all randomized subjects who received at least one post-baseline evaluation. For the safety population, 164 subjects were treated with mometasone and 163 subjects each were treated with beclomethasone or placebo.

Safety data consisted of clinical adverse events (further characterized as treatment emergent [218:71-74, 219:415-424] and treatment related (severe and non-severe) [218:78-80, 76-77], laboratory test values, ECGs, vital signs, and pertinent physical exam findings such as: the presence of nasal septal perforation, nasal ulceration(s) or nasal candidiasis, and/or presence of abnormally elevated (i.e. >22 mm Hg, as defined by the Sponsor) intraocular pressure measurements or cataract formation. A review of all safety parameters submitted by the sponsor by line listings was performed and those laboratory results, vital sign abnormalities, physical exam findings, and adverse events deemed by the medical reviewer to be clinically significant or pertinent negative results, are discussed in the sections below.

Overall, analysis of the safety data for protocol C92-280 indicates that mometasone was safe and well tolerated by subjects. Adverse events were similar to those observed with beclomethasone and in general, similar to those seen with nasal corticosteroid use. The incidence of adverse events was found, as expected, to be highest in the placebo treatment group. No significant difference in adverse event rates was found based on age, gender, or race.

Adverse events were reported by 81% of subjects treated with mometasone, compared to 81% of subjects treated with beclomethasone, and 77% of subjects treated with placebo. The most frequently reported adverse events are summarized in Table 20 of the NDA submission (see below) [218:71]. For a complete listing of adverse events, please refer to [NDA 20-762: Volumes 225, 226, 227, and 228].

Table 20 Incidence of Patients Reporting Frequent Treatment Emergent Adverse Events[a] Safety (Intent-to-Treat) Population (Study No. C92-290)

	Number[c] (%) of Patients		
	SCH 32088 (n = 164)	BDP (n = 167)	Placebo (n = 163)
Any Adverse Event	133 (81)	132 (81)	126 (77)
Body As A Whole - General Disorders			
fever	3 (2)	0	8 (5)
headache	55 (34)	66 (34)	51 (31)
influenza-like symptoms	17 (10)	19 (12)	20 (12)
Central and Peripheral Nervous System Disorders			
dizziness	1 (1)	8 (5)	4 (2)
Gastrointestinal System Disorders			
abdominal pain	0	7 (4)	3 (2)
nausea	7 (4)	4 (2)	2 (1)
vomiting	1 (1)	5 (3)	1 (1)
Hearing and Vestibular Disorders			
earache	9 (5)	9 (5)	9 (6)
Musculoskeletal System Disorders			
musculoskeletal pain	14 (9)	12 (7)	5 (3)
myalgia	6 (4)	6 (4)	10 (6)
Reproductive Disorders, Female[d]			
dysmenorrhea	2 (2)	1 (1)	7 (9)
Resistance Mechanism Disorders			
infection viral	35 (21)	30 (18)	27 (17)
Respiratory System Disorders			
cough, nonproductive	5 (3)	0	2 (1)
coughing	13 (8)	17 (10)	18 (11)
epistaxis	31 (19)	37 (22)	10 (6)
nasal burning	5 (3)	7 (4)	11 (7)
nasal irritation	4 (2)	6 (4)	3 (2)
pharyngitis	28 (17)	23 (14)	31 (19)
rhinitis	6 (4)	11 (7)	2 (1)
sinusitis	10 (6)	12 (7)	21 (13)
sneezing	1 (1)	8 (5)	6 (4)
upper respiratory infection	11 (7)	9 (5)	12 (7)
Vision Disorders			
conjunctivitis	7 (4)	7 (4)	0

a= occurring in ≥ 3% of any treatment group.

b= without regard to relationship.

c= # of subjects reporting adverse events at least once during the study. Some subjects reported > 1 adverse event.

d= % calculated based on total female population.

Headache was reported as the most frequent adverse event and was found to be present in 34% of subjects treated with mometasone, 34% of subjects treated with beclomethasone, and 31% of subjects treated with placebo [226:5465-5523, 227:5717-5762]. The second most frequent adverse event was epistaxis (present in 19% of mometasone subjects, 23% of beclomethasone subjects, and 6% of placebo subjects), followed by pharyngitis (present in 17% of mometasone subjects, 14% of beclomethasone subjects, and 19% of placebo subjects). In general, epistaxis was mild or moderate in severity, intermittent, and of short duration in all treatment groups. In summary, the most frequent adverse events cited were symptoms known to be associated with perennial allergic rhinitis itself, and not necessarily related to drug use, per se.

Nasal examinations performed at each visit generally revealed nasal

mucosal findings consistent with allergic rhinitis such as boggy or erythematous mucosa indicative of nasal turbinate swelling. No cases of nasal septal perforation were reported in any of the three treatment groups, although one case each of nasal ulceration in the both the mometasone (study subject C92-280-015, #013 [228:6791]) and placebo group (study subject C92-29-80-009, #014, [228:6746]) and 4 cases of nasal ulceration in the beclomethasone group (study subjects C92-280-009, #028 [228:6744], -010, #019 [228:6752], -015, #017 [228:6794], and -017, #013 [228:6808]) were noted after initiation of study drug. Only one case of cataract formation was noted in a placebo group subject--subject C92-280-009, #003 during week 12 of treatment [227:5915] (none noted in either active treatment group). One additional placebo treated subject (C92-280-05, #008 [218:85] had a trace posterior subcapsular cataract in the left eye at both screening and week 12 of the study. In terms of study subject intraocular pressure monitoring to rule out glaucoma, mean and median intraocular pressures the right and left eyes for all 3 treatment groups at screening and week 12 of the study failed to show any significant difference in measurements with all 3 treatments [220:839]. Evaluation of individual study subject intraocular pressures revealed only 1 subject in the mometasone treatment group who at week 12 had a 3 mm Hg increase in intraocular pressure (to a total pressure of 24 mm Hg) in the right eye [228:6597]. This difference was not felt to represent a significant change from baseline (daily fluctuations of 4 mm Hg felt to be acceptable) per the ophthalmology consultant for study center C92-280-006. Another mometasone treated subject, while not detected to have increased intraocular pressures by week 12 of treatment, was noted to have developed several scattered punctate cortical opacities in the right eye > left eye [228:6609]. The clinical significance of these opacities were deemed unknown by the principal investigator. One beclomethasone treated subject (C92-280-008, #027 [228:6604]) likewise developed a borderline increased intraocular pressure to 22 mm Hg in the right eye after 12 weeks of treatment with beclomethasone. The other several beclomethasone and placebo subjects who had borderline elevated intraocular pressures had these values at screening (with no significant increase post-initiation of study drug), hence these results could not be attributed to administration of the study drug.

In terms of infections, overall 11/164 or 7% of mometasone treated subjects reported upper respiratory infections, compared with 9/163 or 6% of beclomethasone treated subjects and 1/163 or 1% of placebo treated subjects. 10/164 or 6% of mometasone treated subjects reported sinusitis, compared with 12/164 or 7% of beclomethasone treated subjects and 21/163 or 13% of placebo treated subjects. Interestingly, 2 cases of pneumonia (incidence 1%) were reported solely in mometasone treated subjects on weeks 8 and 12 (subject C92-280-004, #002 and subject C92-280-013, #008) [226:5406]-a 39 year old male and 33 year old female subject, respectively. In neither case was the pneumonia felt related to mometasone treatment by the principal investigator. Two cases of cystitis were reported in mometasone treated subjects (1% incidence) [226:5436],

compared to 1 case of cystitis reported in a beclomethasone treated subject (1% incidence) and no cases in placebo treated subjects (0% incidence) [218:74]. No cases of herpes simplex or candidiasis were reported in any mometasone treated subjects during any study visit [218:79].

Regarding laboratory test results, one serious[2] adverse event consisting of elevated liver enzymes (SGOT (AST)=1144, SGPT (ALT)=1119, LDH=522, and alkaline phosphatase=291) at the last study visit was reported for one subject (34 year old female) treated with beclomethasone who was later confirmed to have active hepatitis B. The subject was treated conservatively by her personal physician and recovered without clinical sequelae. Aside from this finding, no other clinically relevant abnormal laboratory test results were reported in this study. Although there were scattered laboratory test values outside the normal ranges for several subjects, as assessed by shift tables, none were remarkable.

No clinically relevant changes in mean values from pretreatment were in noted in any of the subjects' vital signs or body weight. Shift tables were similar among all 3 treatment groups. ECGs performed pretreatment and at endpoint failed to reveal any relevant abnormal findings.

Gender, race and age subgroup analyses of vital signs, body weight, laboratory data, ECGs, and adverse events failed to reveal any significant differences between any of these subgroups and the overall subject population, with the exception of the following minor observations. In non-Caucasian subjects (n=53 total), mometasone treatment group subjects (n=12) were noted to have a greater mean weight (n=12, mean weight=177.4 lbs.) than the beclomethasone treated non-Caucasian subjects (n=18, mean weight=154.7 lbs.) and placebo group non-Caucasian subjects (n=23, mean weight=166.6 lbs.) [220:776]. Adverse event profiles for all subgroups based on age, gender and race were similar with the exception of the following instances: (1) a slightly higher incidence of epistaxis in mometasone treated subjects < 18 years of age (2 cases, 18% incidence based on n=11 subjects) compared with beclomethasone treated subjects < 18 years of age (n=16, 1 case (6% incidence)) and placebo treated subjects < 18 years of age (n=17, 0 cases (0% incidence)) [219:364], (2) a significantly higher incidence of headache in mometasone treated subjects ≥ 65 years of age (n=2, 1 case (50% incidence), compared with beclomethasone treated subjects ≥ 65 years of age (n=1, 0 cases (0% incidence)) and placebo treated subjects ≥ 65 years of age (n=1, 0 cases (0% incidence)) [219:375], (3) a higher incidence of headache in Black subjects treated with mometasone (n=4, 2 cases (50% incidence)), compared with beclomethasone treated Black subjects (n=7, 2 cases (29% incidence)) and placebo treated Black subjects (n=14, 0 cases (0% incidence)) [219:405], and (4) a higher incidence of viral infections in Hispanic subjects treated with mometasone (n=8, 3 cases (38% incidence)), compared with beclomethasone treated Hispanic subjects

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[2]Serious is defined as any adverse event which resulted in death, hospitalization, or prolongation of an existing hospitalization, a permanent or significant disability, or was considered life-threatening. Reports of malignancy, overdose, congenital anomaly, and end-organ toxicity are likewise categorized as 'serious' events

(n=10, 1 case (10% incidence)) and placebo treated Hispanic subjects (n=8, 0 cases (0% incidence)) [219:411]. Because of the small number of subjects analyzed in these subgroups of study subjects no meaningful conclusions can be made based on these observations.

Regarding subject drop-outs due to adverse events, a total of 22 subjects (5 treated with mometasone, 9 treated with beclomethasone, and 8 treated with placebo) discontinued treatment because of adverse events. Only 6/22 of these subjects had discontinued treatment 'possibly' due to adverse events incurred by the treatment given (all other cases were unrelated to treatment with the exception of the cataract present in a placebo group subject which was classified as 'probably' related to treatment) and 3 of these 6 drop-outs had 'mild' symptoms (subject C92-280-13, #015: hyperesthesia, subject C92-280-10, #009: epistaxis, and subject C92-280-12, #029: nausea [218:81]). No subject deaths were reported in any of the 3 treatment arms for Protocol C92-280.

8.11.5. Reviewer's Conclusion of Study Results:

In this PAR trial 164 subjects received mometasone treatment, 163 subjects received the active comparator beclomethasone, and 163 subjects received placebo treatment.

With the exception of a greater percentage of subjects in the mometasone group consisting of subjects with a 'severe' rating of PAR (subject self-rated 0-3 score) and longer duration of disease, all 3 treatment arms were otherwise similar in demographic and clinical characteristics.

Results that Support Approval:

Mometasone administered at a dose of 200 µg qd was statistically better than placebo in decreasing the average change from baseline in the subject self-rated total nasal symptom score (rhinorrhea, nasal congestion, nasal itching, and sneezing) for days 1-15 of treatment--the primary efficacy variable ($p=0.02$). Mometasone provided an approximately 20% decrease in the total nasal symptom score as compared to a 13% decrease achieved with placebo treatment [Table V.]. Separation of the subject self-rated total nasal symptom score by week 1 and week 2 of treatment indicates that mometasone was effective in decreasing total nasal symptoms during both weeks, with a clinically and statistically significant improvement in symptoms achieved by week 1 of treatment ($p=0.02$). Of the 4 nasal symptoms, mometasone appeared to exert its greatest effect on decreasing the severity of rhinorrhea (nasal discharge), closely followed by sneezing.

Mometasone was likewise statistically better than placebo in decreasing the average change from baseline in the subject self-rated total nasal symptom score for days 16-30, days 31-45, days 46-60, days 61-75, and days 76-90 of treatment ($p \leq 0.05$), and the subject self-rated total nasal symptom score at the endpoint visit ($p=0.03$). In terms of study sub-analysis, mometasone was statistically better than

placebo in decreasing the average change from baseline in the subject self-rated total symptom score for week 1 of treatment. Physician-rated subject total nasal symptom scores taken during all study visits were likewise significantly reduced with mometasone treatment, as compared with placebo [Attachment 1 (5)]. Additional treatment response was gained during the third to twelfth weeks of treatment with mometasone, in addition to efficacy achieved by the second week of mometasone treatment.

Finally, physician rated total PAR subject symptom scores, along with both subject and physician overall PAR evaluation, and both subject and physician treatment response evaluations [Attachment 1 (8)-(11)] support greater efficacy of mometasone in reducing the symptoms of PAR for at least some study visits, as compared with placebo.

8.12. Trial C93-014 Long-term Safety of Mometasone Furoate Nasal Spray in the Treatment of Perennial Allergic Rhinitis (PAR)

Principal Investigator: Robert A. Berkowitz, M.D.

Participating Centers: 19 U.S. centers.

8.12.1. OBJECTIVES:

1. To characterize the long-term safety profile (including assessment of glaucoma/cataract formation) of a fixed dose of mometasone furoate nasal spray (200 µg qd) and a variable dose of mometasone furoate nasal spray (200 µg qd initially, titrated between 100-400 µg qd depending on the subject's therapeutic response), compared with beclomethasone (Vancenase) 168 µg bid.
2. To evaluate long-term efficacy of mometasone aqueous nasal spray in the treatment of symptoms of PAR (efficacy assessment was not the primary objective of this study).

8.12.2. STUDY DESIGN:

This was a randomized, multi-center, open-label, active-controlled, parallel group trial in adult subjects with perennial allergic rhinitis which was an extension of the 3 month double-blind PAR study C92-280. Study enrollable subjects consisted of those who successfully completed the double-blind study C92-280 or who were dropped from C92-280 due to treatment failure or intercurrent illness. A variable mometasone dose group was included in this study in order to obtain additional efficacy and safety information on doses of mometasone which were above or below the 200 µg qd dose and also to gain information regarding the individualization of mometasone dosing for PAR. Study medications were given to PAR subjects for a total duration of 52 weeks (1 year).

8.12.3. PROTOCOL:

8.12.3.1.a. POPULATION:

Entry criteria for this study after completion of a washout period (up to 7 days) were essentially the same as those for study C92-280, namely: (1) age ≥ 12 years [253:10], (2) presence of IgE-mediated hypersensitivity to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 1 year of study entry via the prick testing method, and (3) successful completion of study C92-280, or discontinuation secondary to treatment failure or intercurrent illness [253:12, 256:1010, 1014].

8.12.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the sponsor in Table 1.

study design of PAR study C92-280. Subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Week 4 (Visit 3), 8 (Visit 4), 12 (Visit 5), 24 (Visit 6), 36 (Visit 7), and 52 (Visit 8) of therapy. Subjects entered a washout phase (up to 7 days) between the screening and baseline visit, during which they took no medications except for rescue medication (note: no restrictions outlined in the protocol with regard to the type of rescue medication that could be used by a subject with the exception of corticosteroid use), as prescribed by the principal investigator for relief of intolerable PAR symptoms prior to initiation of the open-label treatment [253:15, 256:1019]. Of note, for C92-280 roll-over subjects, the final visit determination (Visit 7 of study C92-280) served as the screening (Visit 1) determination for study C93-014. Following the washout period, subjects who met all inclusion criteria were randomly assigned to one of the following 3 treatment groups, received diary cards to record symptoms and began therapy with mometasone (fixed and variable doses) administered in the a.m. and beclomethasone administered in the a.m. and p.m. (bid):

(A)	**Mometasone aqueous nasal spray 200 µg qd** (FIXED DOSE)
(B)	**Mometasone aqueous nasal spray 100, 200 or 400 µg qd** (VARIABLE DOSE)
(C)	**Beclomethasone 168 µg bid (336 µg qd total)**

Subjects underwent clinical efficacy and safety evaluation (including nasal exam on Visits 3-8) during each study visit [256:1016-1020, 1023-1030]. Eye examinations to assess glaucoma and cataract formation were performed during the screening and final (Visit 8) study visit [253:20-21, 256:1009]. Efficacy evaluation was again based on a 0-3 severity scale [253:21-22, 256:1026] and a 1-5 scale of therapeutic response [253:22, 256:1027].

In concordance with the supervising physician, subjects randomized to the mometasone 'variable dose' group were allowed to lower the medication dose to 100 µg qd if nasal symptoms (specifically rhinorrhea and nasal congestion) were well controlled or to increase the dose to 400 µg qd in order to improve control of nasal symptoms [256:1015, 1021, 1023]. Rescue medication use was allowed throughout the study duration for all 3 treatment groups, excluding steroid formulations (nasal, inhaled, etc.)

A primary efficacy variable was not defined in this study. Supplementary efficacy variables consisted of: (1) physician and (2) subject evaluations of overall condition and (3) physician and (4) subject evaluations of therapeutic response [253:29] in the ITT population [253:29, 256:1031]. Pollen counts were not collected in this study. Rescue medication use between the 3 treatment groups was not analyzed in any systematic manner in this study, thus making it difficult to reach any solid conclusions about clinical efficacy of the different treatments evaluated in this study.

8.12.4. RESULTS

A total of 296 subjects with PAR were randomized into study C93-014, with 3 immediate drop-outs (subjects did not receive any study drug)[253:81-83], leaving 293 subjects for the ITT population [253:32]. One hundred (100) subjects in the ITT population received mometasone 200 µg qd, 95 subjects received variable dose (100-400 µg qd) mometasone, and 98 subjects received beclomethasone [253:32]. Of note, the attrition rates for study subjects by Week 52 of the study were quite high with 14.2% (14/98) of mometasone 200 µg qd subjects, 18.9% (18/95) of variable dose mometasone subjects, and 14.4% (14/97) of beclomethasone subjects discontinuing treatment by this study endpoint.

The treatment groups in this study were comparable with regard to demographic and disease characteristics with the exception of a marginally statistically significant difference among the treatment groups in age (mean age of the mometasone 200 µg group=37 years vs. mean age of the mometasone variable dose group=33 years vs. mean age of the beclomethasone group=35 years; p=0.06) [253:33, 86-87]. Again, for all 3 treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the treatment groups was approximately equal. The majority of subjects (64-77% range) had SAR in addition to PAR. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a statistically significant difference among the 3 treatment groups although the mometasone 200 µg group had a numerically greater % of subjects with 'severe' PAR (18%) in comparison with the other 2 groups (mometasone variable group; 'severe' subjects=11%, vs. beclomethasone group, 'severe' subjects=13%) [253:35-36]. Therefore, at baseline, the majority of subjects in all 3 treatment groups were assessed as having 'mild' or 'moderate' PAR.

Analysis of the efficacy variables for the ITT population showed that overall, subjects in all 3 active treatment groups demonstrated an improvement in symptoms which was maintained for the study duration. For the physician's evaluation of the overall condition of PAR, subjects in all 3 treatment groups demonstrated an improvement by Week 4 of the study (as supported by the majority of subjects having 'mild' PAR symptoms) and this improvement was maintained through the Week 52 visit [253:37, 247, 268-269]. Subject self-evaluation of the overall condition of PAR paralleled that of the physician evaluation; namely that improvement in symptoms was noted by Week 4 of the study (supported by the majority of subjects rating their overall PAR condition as 'mild') and was maintained throughout the study duration [253:39-40, 254:296, 317-318]. Both of these findings support maintenance of a therapeutic effect for mometasone (fixed and variable dose) and beclomethasone throughout the open-treatment period. Physician evaluation of subjects' therapeutic response to treatment (1-5 scale) indicated that all 3 treatment groups experienced moderate-marked relief in PAR symptoms starting at Week 4 of the study and continuing throughout the open-treatment period, again providing evidence of maintenance of a therapeutic effect throughout the study duration [253:42, 254:345-346, 367].

Subject evaluation of therapeutic response paralleled the physician evaluation of subjects' therapeutic response with the majority of study subjects reporting moderate-marked relief in PAR symptoms by Week 4 of treatment [253:44, 254:388-389, 410]. Again, this response was maintained for the study duration.

Regarding the 'variable dose' mometasone group, 10/95 (10.5%) of subjects received mometasone 100 µg qd, 57/95 (60.0%) of subjects received mometasone 200 µg qd, and 28/95 (29.5%) of subjects received mometasone 400 µg qd [253:45]. Within the variable mometasone group, the majority of subjects either maintained the 200 µg qd dose throughout the study (54%) or changed the dose level only once and maintained that dose level for the remainder of the study (28% of subjects titrated their dose to 400 µg qd and 10% of subjects in this subgroup titrated their mometasone dose downwards to 100 µg qd). The remaining 8% of subjects had their mometasone dose changed > 1 times during the study. In summary, these data for the 'variable dose' mometasone group suggest that the most effective dose of mometasone for the control of PAR symptoms was 200 µg qd. Gradual increase in dose of mometasone over the course of the study was not observed.

While this trial was not blinded and not designed to provide enough power to conduct inferences on efficacy, results of these supplementary analyses nonetheless provide supportive information that mometasone is effective in the treatment of symptoms of PAR. Results of the 4 efficacy variables for the 2 mometasone treatment groups are summarized in Table I. below.

Table I. Efficacy Variables of PAR and Treatment with Mometasone 200 µg qd and 'Variable Dose' Mometasone (100, 200, or 400 µg qd) (ITT Population), [253:36-45, 247, 268-269, 254:296, 317-318, 345-346, 367, 388-389, 410]

	EFFICACY VARIABLE	Improvement in PAR symptoms throughout study duration: Mometasone 200 µg qd: (Yes/No)	Improvement in PAR symptoms throughout study duration: 'Variable dose' Mometasone: (Yes/No)
1	Physician's evaluation of subject overall PAR condition compared to baseline	Yes	Yes
2	Subject self evaluation of overall PAR condition compared to baseline	Yes	Yes
3	Physician evaluated response to Rx compared to baseline	Yes	Yes
4	Subject self-evaluated response to Rx compared to baseline	Yes	Yes

sx=Symptom, Rx=Treatment, ITT=Intent-to-treat
Statistical analysis for between group differences performed using 2-way ANOVA

8.12.4.3. ADVERSE EVENTS:

The safety analysis was based on 293 subjects in the ITT population: 100 subjects were treated with mometasone 200 µg qd, 95 subjects were treated with variable dose mometasone (100, 200, or 400 µg qd), and 95 subjects were treated with beclomethasone [253:46, 254:431]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, nasal, and ophthalmologic examinations, and clinical laboratory tests relative to baseline [256:1023-1030].

Adverse events were similar for all three treatment groups, with headache being the most frequently reported treatment-related adverse event. Overall, adverse events were reported in 86% of subjects in the mometasone 200 µg qd treatment group, 81% of subjects in the variable dose mometasone treatment group, and 85% of subjects in the beclomethasone group [253:50, 254:431]. Headache was reported in 36% of subjects in the mometasone 200 µg qd group, 37% of subjects in the variable dose mometasone group, and 32% of subjects in the beclomethasone group [253:48, 254:432, 259:2258-2311, 2518-2554, 2740-2792]. Interestingly, for this long-term study headache was followed by sinusitis as the second most frequently reported adverse event; reported in 24% of mometasone 200 µg qd subjects compared to 16% of variable dose mometasone subjects and 16% of beclomethasone treated subjects [253:49, 254:438, 259:2446-2459, 2686-2693, 2920-2931]. Reported next in frequency was pharyngitis; with 15% of subjects in the mometasone 200 µg qd group, 18% of subjects in the variable dose mometasone group, and 21% of subjects in the beclomethasone group recording this adverse event [253:49, 254:438]. Other relatively frequent ADRs reported in this follow-up study included coughing (15% of mometasone 200 µg qd subjects, 9% of variable dose mometasone subjects, and 12% of beclomethasone subjects [253:49, 254:438]), viral infection (18% of mometasone 200 µg qd subjects, 16% of variable dose mometasone and beclomethasone subjects [253:48, 254:437]), upper respiratory tract infection (13% of mometasone 200 µg and variable dose mometasone subjects, and 15% of beclomethasone subjects [253:4, 254:438]), musculoskeletal pain (13% of mometasone 200 µg qd subjects, 7% of variable dose mometasone subjects, and 17% of beclomethasone subjects [253:51, 254:435]), and epistaxis (12% of mometasone 200 µg qd and variable dose mometasone subjects, and 9% of beclomethasone subjects [253:49, 254:438]). Furthermore, there was no apparent dose relationship in the overall incidence of ADRs in the mometasone variable dose group noted for the study duration (incidence of ADRs for mometasone 100 µg qd group=65%, incidence of ADRs for mometasone 200 µg qd group=71%, incidence of ADRs for mometasone 400 µg qd group=62% [253:69]) or for specific ADRs with the exception of a small proportional increase in the incidence of headache [254:502], earache [254:505], and pharyngitis [254:509] with increasing doses of mometasone [254:501-514].

There were no reports of nasal septal perforation in either the of the 2 mometasone treatment groups or the beclomethasone active comparator [illegible]

Nasal ulcers were however reported in all 3 treatment groups as follows:

(1) mometasone 200 µg qd group: reports in 4 subjects (1 at Visit 3, 1 at Visit 4, 1 at Visit 5, and 1 at Visit 6) [261:4098, 4111, 4176, 4178].

(2) mometasone variable (100-400 µg qd) group: reports in 3 subjects (1 at Visit 3, 1 at Visit 5, and 1 at Visit 6) [261:4114, 4161, 4171], and

(3) beclomethasone group 168 µg bid group: reports in 8 subjects (1 at Visit 3, 1 at Visit 4, 2 at Visit 5, 1 at Visit 6, 2 at Visit 7, and 1 at Visit 8 [2260:2906, 2907, 2932, 61:4079, 4106, 4107, 4142, 4154, 4182, 4191, 4201]. In 2 of these 8 beclomethasone subjects, the nasal ulcers were noted to be nasal septal ulcerations [253:53, 260:2907].

Evaluation for glaucoma by tonometry indicated that the mean (right and left) intraocular pressures for the screening and Week 52 visits were similar for the 3 treatment groups and ranged from 14.8 mm Hg-15.7 mm Hg with no significant mean increase in intraocular pressure noted for any of the 3 groups between screening and the Week 52 visit [254:533]. For individual study subjects, 1 subject in the variable mometasone dose group and 1 subject in the beclomethasone group demonstrated a significant elevation in intraocular pressures in both eyes post-screening [260: 2728, 261:3968, 3985]. One subject in the beclomethasone group also developed a mild anterior subcapsular cataract of the right lens by day 397 of the study [261:3965]. No subjects in either mometasone treatment group were noted have cataract formation as determined via slit lamp eye examination. Again, no assessments of HPA-axis were performed in this follow-up study. No deaths were reported in any of the three treatment groups.

In terms of infection, 18% of subjects in the mometasone 200 µg qd group reported viral infections, while 16% of subjects in both the variable dose mometasone and the beclomethasone group, respectively, reported viral infections [253:52]. One subject in the mometasone 200 µg qd treatment group and one subject in the beclomethasone group reported herpes simplex labialis [253:52]. One subject in the in the mometasone 200 µg qd group (subject C93-014-09, #005) and one subject in the variable dose mometasone treatment group (subject C93-014-16, #011, patient was receiving 200 µg qd of mometasone) were noted by the examining physician to have moniliasis (i.e. oral candidiasis) on study Visit 7 and Visit 6, respectively [254:507, 259:2403, 2634]. One subject in the variable dose mometasone group (subject C93-014-19, #002, patient was receiving mometasone 200 µg qd) also reported pneumonia which was felt by the principal investigator to be unrelated to study medication [254:509, 259:2678]. No subjects in either of the three treatment groups were reported to have nasal candidiasis on any clinic visits.

A total of 15 subjects discontinued treatment because of adverse events (7 subjects in the mometasone 200 µg qd group, 4 subjects in the variable dose mometasone group, and 4 subjects in the beclomethasone group) [253:62, 228-238]. The most common reason for discontinuation that was considered 'possibly related' to study medication involved nasal irritation. One subject in the [illegible]

dose mometasone group (subject C93-014-06, #003: the subject was receiving mometasone 200 µg qd at the time of the adverse event) discontinued treatment on the day of hospitalization for meningitis which was considered not to be related to study drug administration but rather secondary to a local outbreak of meningitis in the community [254:601, 259:2564]. One subject in the beclomethasone group (C93-014-09, #001) discontinued treatment because of 'moderate' nasal septum ulceration that was considered to be related to study medication. Otherwise, most subject discontinuations due to ADRs were considered unrelated to treatment by the principal investigator.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the three treatment groups. Three subjects in the variable dose mometasone group were reported to have minor or transient decreases in their white blood cell count (WBC) [255:606]. Of note, in all 3 cases, the pre-baseline WBC for each subject was already below or at the lower limit of normal (WBC lower limit of normal = 4.36 x 10^3/mL) [255:606]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change. Adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects between 12-17 years and > 64 years of age was too small to draw meaningful conclusions.

8.12.5. CONCLUSIONS:

1. The results of this study support the safety of mometasone 100 µg, 200 µg and 400 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 52 weeks (1 year) in subjects with PAR.
2. While not specifically designed to evaluate efficacy, assessment of subject overall condition and response to treatment with mometasone over 52 weeks (by study subjects and their respective physicians), supports the efficacy of mometasone in doses of 100-400 µg qd for the treatment and maintenance treatment of symptoms of PAR. For the majority of study subjects, 'moderate-marked' relief of PAR symptoms and an overall rating of PAR symptoms as 'mild' in severity was demonstrable by week 4 of mometasone treatment and was maintained though week 52 of the study.

Results that did not Support Approval:

Overall, mometasone did not demonstrate a statistically significant effect in decreasing any of the subject self-rated or physician rated non-nasal symptoms of PAR (eye itching, eye tearing, eye redness, ear or palatal itching), at any of the study intervals (day 1-15, day 16-30, day 31-45, day 46-60, day 61-75, day 76-90, or the endpoint visit), as compared with placebo. Because of this lack of significant effect on the non-nasal symptoms of PAR, mometasone likewise did not

score in treated subjects, as compared with placebo. As the non-nasal symptoms of PAR represent a group of secondary efficacy measurements which clinically are less important symptoms of PAR, lack of significant efficacy of mometasone on these parameters does not change the overall conclusion about efficacy of mometasone in the treatment of PAR. Furthermore, non-nasal symptoms are generally less likely to be affected by medications administered intranasally, therefore a lack of significant response with intranasal corticosteroid administration (also seen with beclomethasone) is not unexpected.

Mometasone treatment likewise did not demonstrate a statistically significant effect in decreasing total subject self-rated PAR symptom scores at any of the study intervals. As mentioned previously, mometasone treatment did not uniformly decrease the subject or physician rated overall condition or overall treatment response evaluation for all study visits, as compared with placebo.

Other Results:

Mometasone (200 µg qd) appeared to exert its effect at decreasing the nasal symptoms of PAR throughout the day, with similar subject self-rated total and individual nasal symptom scores achieved during the a.m. and p.m. measurements. Hence, mometasone administered as a 200 µg dose once a day demonstrated a reasonable 24 hour duration of effect in this study.

Safety:

Overall, mometasone was safe and well-tolerated administered as a once a day, 200 µg dose. No serious adverse events occurred in subjects treated with mometasone, nor were any deaths reported. Similar to placebo, headache was the most common adverse event associated with mometasone use, followed by epistaxis and then, pharyngitis. No nasal septal perforations or cases of nasal candidiasis were reported. While no cases of cataracts were reported with mometasone treatment this study did not evaluate (because of study duration) hypothalamic-pituitary-adrenal (HPA) axis suppression. A 1 year follow-up study of C92-280, study C93-014, evaluated the potential long term effects of steroid use and specifically addressed glaucoma and cataract formation in mometasone treated subjects (Refer to Section 8.13: Study C93-014).

Summary:

Based on the results of this perennial allergic rhinitis (PAR) trial, mometasone demonstrated adequate evidence of efficacy and safety compared with placebo in the treatment of the symptoms of PAR.

8.13. Trial I92-293. Efficacy and Safety of Mometasone Furoate Nasal Spray vs. Beconase and vs. Placebo in the Treatment of Perennial Allergic Rhinitis (PAR).

Principal Investigator: Peter Clement, M.D.

Participating Centers: 24 centers in Europe (Belgium, Finland, Germany, The Netherlands, Norway, Sweden, Switzerland, and the U.K.) and Canada.

8.13.1. OBJECTIVES:

1. To investigate the safety and efficacy of mometasone furoate aqueous nasal spray 200 µg qd in the treatment of symptoms of perennial allergic rhinitis (PAR).

8.13.2. STUDY DESIGN:

The study was a phase III, randomized, multi center, double-blind, double-dummy, active- and placebo-controlled parallel group study to determine the safety and efficacy of mometasone furoate 200 µg administered intranasally once daily (qd), vs. the active control, beclomethasone (Beconase AQ) 200 µg administered twice daily (bid), and vs. placebo for a total of 12 weeks in the treatment of perennial allergic rhinitis. The study was also designed to examine long-term safety in mometasone treated subjects vs. placebo via roll-over of subjects into Study I93-018 (1 year follow-up of Study I92-293).

8.13.3. PROTOCOL:

8.13.3.1.a. POPULATION:

Entry criteria for this study were very similar to those for all other PAR studies, namely: (1) age ≥ 12 years [235:16, 238:997, 999], (2) presence of IgE-mediated hypersensitivity to a relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 1 year of study entry via the prick testing or intradermal method [235:16, 238:999], and (3) presence of PAR symptoms of sufficient severity (nasal rhinorrhea and/or congestion scores at least moderate in severity (≥ 2), a total symptom score ≥ 5 at both screening and baseline, and rhinorrhea and/or congestion scores ≥ 2 during 4 of the last 7 days prior to the baseline visit), in order to begin study drug treatment [235:16, 29, 238:997, 999, 1015-1016].

8.13.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1 of Trial I92-293 in the NDA submission [235:15, 238:1028] and is similar to the study design of PAR study C92-280. Subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Day 8 (Visit 3), 15 (Visit 4), 29 (Visit 5), and Weeks 8 (=Day 57, Visit 6), and 12 (=Day 85, Visit 7) of therapy [235:35-36]. Day 1 was designated as the start of treatment date [235:35]. Medication restrictions consisted of those previously discussed for mometasone SAR and PAR studies [235:22-24, 238:1001-1003], although subjects were allowed to use a rescue medication (loratadine, up to 10 mg po qd maximum dose) for intolerable PAR symptoms starting with the screening visit (the 'run-in' phase) and continuing for the duration of the study [235:20, 238:998, 1018]. Subjects who met all inclusion criteria were randomized to one of the following 3 treatment groups, received diary cards to record symptoms reflectively over the previous 12 hours and began therapy with study drug every a.m. and p.m. (4 bottles utilized for this double dummy design--each active drug had a matching placebo) [235:18, 25-27, 238:9981017-1018]:

(A) Mometasone aqueous nasal spray 200 µg qd		
a.m. dosing	Bottle 1: Mometasone 200 µg	Bottle 2: Beconase Placebo
p.m. dosing	Bottle 3: Mometasone Placebo	Bottle 4: Beconase Placebo
(B) Beclomethasone nasal spray (Beconase) 200 µg bid		
a.m. dosing:	Bottle 1: Mometasone Placebo	Bottle 2: Beconase 200 µg
p.m. dosing:	Bottle 3: Mometasone Placebo	Bottle 4: Beconase 200 µg
(C) Placebo (0 µg qd)		
a.m. dosing	Bottle 1: Mometasone placebo	Bottle 2: Beconase Placebo
p.m. dosing:	Bottle 3: Mometasone placebo	Bottle 4: Beconase Placebo

Subjects underwent clinical efficacy and safety evaluation (including nasal exam on Visits 2 (baseline) and 7 (Week 12)) during each study visit [235:15, 27-33, 238:998, 1006-1016]. Efficacy evaluation was again based on a 0-3 severity scale [235:29, 238:1015], a 0-3 scale of the overall condition of PAR [235:29, 238:1015], and a 1-5 scale of therapeutic response [235:30, 238:1016].

The primary efficacy variable [358:42-43, 238:998] was defined as: the mean change from baseline (the mean of the a.m. and p.m. baseline scores and the a.m. and p.m. scores from the 7 prior consecutive days) in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject diaries) where the:

Mean Change in Total nasal symptom score= 15 Day Interval Score[(Nasal a.m. average $_{\text{Day 1-15}}$) + (Nasal p.m. average$_{\text{Day 1-15}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

and the **total nasal symptom score=[discharge+ stuffiness+ sneezing+ itching].**

Secondary efficacy variables consisted of the following [235:43-44, 238:1023]:

(1) The mean change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30 (a.m. and p.m. combined), Days 31-45, Days 46-60, Days 61-75, and Days 76-90 [235:43]:

Mean Change in Total nasal symptom score$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$**=Day 16-30 (or Day 31-45, Day 46-60, Day 61-75, Day 76-90) Interval Score**[(Nasal a.m. average $_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$) + (Nasal p.m. average$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

(2) Endpoint total nasal symptom score (a.m. and p.m. combined)[235:44]: Endpoint score defined as the last available post-baseline value for each study subject, pooled across the 24 participating centers.

(3) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit) [235:44].

(4) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit) [235:44].

(5) Physician's evaluation of total nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8 , Week 12, and the endpoint visit) [235:44].

(6) Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit) [235:44].

(7) Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit) [235:44].

(8) Subject's self-evaluation of overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, and the endpoint visit.

(9) Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study day 8, 15, 29, Week 8, Week 12, and the endpoint visit.

(10) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study day 8, 15, 29, Week 8, Week 12, and

(11) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study day 8, 15, 29, Week 8, Week 12, and the endpoint visit [235:44].

Pollen counts were not collected in this study. Rescue medication use between the 3 treatment groups was not analyzed statistically but a frequency of rescue medication for all 3 treatment groups was tabulated, thus providing a general overview of differences in rescue medication use.

8.13.4. RESULTS

A total of 430 subjects with PAR were randomized into study 192-293, with 3 immediate drop-outs from the placebo group (subjects did not receive any double-blind medication and were excluded from all analyses) [235:46], leaving 427 subjects evaluable in the ITT population [235:46]. One hundred and forty three (143) subjects in the ITT population received mometasone treatment, 146 subjects received beclomethasone, and 138 subjects received placebo [235:46]. An additional 40 subjects were excluded from efficacy analyses because of various protocol violations, leaving 387 subjects in the efficacy evaluable population [235:46].

The treatment groups in this study were comparable with regard to demographic and disease characteristics. Again, for all 3 treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the treatment groups was approximately equal. Approximately half of the subjects had SAR in addition to PAR and the majority did not have asthma (68-77%) [235:48]. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a statistically significant difference among the 3 treatment groups with the majority of subjects in all 3 groups having 'moderate' PAR symptoms [235:53].

Analysis of the primary efficacy variable for the ITT population demonstrated greater efficacy of both active treatment groups in decreasing total nasal symptoms for the day 1-15 interval, compared with placebo. The raw total nasal symptom score for the mometasone treatment group was 4.5 (with a -1.7 unit decrease in total nasal symptoms from baseline or a -26% change), compared with a raw total nasal symptom score of 5.0 (-1.0 unit decrease in total nasal symptoms or -13% change) for the placebo group ($p<.01$) [235:350], and a raw total nasal symptom score of 4.1 (-1.9 unit decrease in total nasal symptoms or -29% change) for the beclomethasone treatment group ($p<.01$ for beclomethasone vs. placebo). No statistically significant difference was noted between the mometasone and beclomethasone treatment groups. Furthermore, no significant difference was noted between the a.m. and p.m. total nasal symptom scores in the mometasone treatment group for the day 1-15 interval, once again supporting once daily dosing of mometasone [235:352-353]. Additionally, no significant difference

population [235:284, 350]. A summary of results for the primary and secondary efficacy variables is summarized in Table I. and Table II. below and overall support the efficacy of mometasone in decreasing the symptoms of PAR. No significant difference in clinical efficacy was noted based on age, sex, or racial group however some sub-groups were too small in number (i.e. age 12-17, age >64 or non-Caucasian subjects) to make any generalized conclusions.

Sub-analysis of subject and physician-rated individual nasal and non-nasal symptoms are summarized in Table III. below. Based on these data and in support of previous findings of mometasone administration for the control of SAR or PAR symptoms, mometasone treatment was noted to have a greater effect on decreasing the symptoms of rhinorrhea and sneezing, with a statistically insignificant effect on nasal congestion and nasal itch, and little effect on the non-nasal symptoms of PAR (Table III.), as compared with placebo.

Analysis of rescue medication use (efficacy evaluable population) in the 3 treatment groups revealed similar overall rates of rescue medication use with slightly lower rates in the two active drug groups (48% of mometasone subjects, 46% of beclomethasone subjects, and 55% of placebo subjects used rescue medication > 1 time during the study) [236:584-585].

Table I. Primary Efficacy Variable of PAR and Treatment with Mometasone (ITT Population) [235:350]

1° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1	Subject evaluated mean Δ in Total Nasal Sx Score$_{DAY\ 1-15}$	*Yes

sx=Symptom

* Note Statistically significant response for 1° efficacy variable in the efficacy evaluable population (ITT data not provided) carried by 2 of the 20 distinct study centers (i.e. 18/20 centers had a statistically non-significant response) [235:284-304]

Table II. Secondary Efficacy Variables of PAR and Treatment with Mometasone (Efficacy Evaluable Population, except where *otherwise noted). [235-349, 350, 236-357-376, 378-380, 382-385, 387, 424, 451, 478, 499]

	2° EFFICACY VARIABLE	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1	*Subject evaluated mean Δ in Total Nasal Sx Score DAY 16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90	Yes:	All study intervals.	
2	Subject evaluated mean Δ in Endpoint Total Nasal Sx Score	Yes:	Endpoint visit.	
3	Subject evaluated mean Δ in Total Sx Score DAY 1-15, DAY 16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90, Endpoint visit	Yes:	Day 31-45, 61-75, 76-90, Endpoint visit.	
		No:	Day 1-15, 16-30, 46-60.	
4	Subject evaluated Total non-nasal Sx Score DAY 1-15, DAY 16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90, Endpoint visit	No:	All study intervals	
5	Physician Evaluated Total Nasal Sx Score	Yes	Study visits:	Day 8, 15, 29, Week 12, Endpoint visit.
		No:	Week 8	
6	*Physician Evaluated Total Sx Score	Yes:	Study visit:	Day 8.
		No:	Study visits:	Day 15, 29, Week 8, Week 12, Endpoint visit
7	Physician Evaluated Total non-nasal Sx Score	No:	All study visits	
8	Subject overall condition evaluation	Yes:	Study visits:	Day 8
		No:	Study visits:	Day 15, Day 29, Week 8, Week 12, Endpoint visit.
9	Physician overall condition evaluation	Yes:	Study visits:	Day 8.
		No:	Study visits:	Day 15, 29, Week 8, Week 12, Endpoint visit
10	Subject overall Rx Response evaluation	Yes:	Study visit:	Day 8, 15, 29, Endpoint visit.
		No:	Study visits:	Week 8, Week 12.
11	Physician overall Rx Response evaluation	Yes:	Study visits:	Day 8, 15, Week 12, Endpoint visit.
		No:	Study visit:	Day 29, Week 8.

Δ=Change, Sx=Symptom, Rx=Treatment
*ITT=Intent-to-Treat Population.

Note: Analyses are for a.m. and p.m. combined symptom scores

Table III. Change in Individual PAR Symptoms (Subject and Physician Evaluated, a.m. and p.m. combined) with Mometasone Treatment (Efficacy Evaluable Population), [236.390-397, 399-422]

PAR SYMPTOM	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
Subject Evaluated Individual Nasal Sx Score	Yes:	Rhinorrhea:	All study visits.
		Sneezing:	Day 16-30, 31-45, 46-60, 61-75, 76-90, Endpoint visit.
		Nasal Itch:	Day 61-75.
	No:	Congestion:	All study visits
		Sneezing:	Day 1-15.
		Nasal Itch:	Day 1-15, 16-30, 31-45, 46-60, 76-90, Endpoint visit.
Physician Evaluated Individual Nasal Sx Score	Yes:	Rhinorrhea:	Day 8, 15, Week 8, 12, Endpoint visit.
		Sneezing:	Endpoint visit.
		Nasal Itch:	Day 8, 15, Endpoint visit.
	No:	Rhinorrhea:	Day 29.
		Congestion:	All study visits.
		Sneezing:	Day 8, 15, 29, Week 8 and 12.
		Nasal Itch:	Day 29, Week 8 and 12.
Subject Evaluated Individual non-nasal Sx Score	Yes:	Eye redness:	Day 76-90.
	No:	Eye tear:	All study visits.
		Eye redness:	Day 1-15, 16-30, 31-45, 46-60, 61-75, Endpoint visit.
		Eye Itch:	All study visits.
		Ear/palate Itch:	All study visits.
Physician Evaluated Individual non-nasal Sx Score	No:	For each non-nasal sx: All study visits.	

Sx=Symptom

8.13.4.3. ADVERSE EVENTS.

The safety analysis was based on 427 subjects in the ITT population; 143 subjects were treated with mometasone 200 µg qd, 146 subjects were treated with with beclomethasone, and 138 subjects were treated with placebo [235:77, 236:520]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, and nasal examinations, and clinical laboratory tests relative to baseline [235:30-33, 77, 238:1006-1016].

Adverse events were again similar for all three treatment groups, with viral infection being the most frequently reported treatment-related adverse event. Overall, adverse events were reported in 71% of subjects in the mometasone and beclomethasone treatment groups, and 65% of subjects in the placebo group [235:78, 79, 236:520-527]. Viral infection was reported in 29% of subjects in the mometasone group, 25% of subjects in the beclomethasone group, and 26% of subjects in the placebo group [235:78, 82, 236:524, 240:2120-2137, 2274-2289, 241:2419-2435]. Headache was the second most common adverse event; reported in 22% of mometasone subjects compared to 16% of beclomethasone treated subjects, and 19% of placebo subjects [235:78,79, 236:520, 240:2060-2079, 2214-2229, 241:2373-2388]. Reported next in frequency was epistaxis; with 21% of subjects in the mometasone gr[illegible] 24% of subjects in the beclomethasone group, and 13% of placebo subjects reporting this ADR [235:78, 79, 236:525]. As in other rhinitis studies in this NDA submission, episodes of epistaxis were generally mild and self-limited (but not always) in duration. And finally, pharyngitis was reported by 12% of subjects in all 3 treatment groups [235:78, 79, 236:525].

There were no reports of nasal septal perforation in any of the 3 treatment groups but nasal ulcers were reported in the 3 subjects in the beclomethasone group (1 report on Day 29, 2 reports on Week 12) [242:5855, 5856, 5994] and 2 subjects in the placebo groups (1 report on Day 15, 1 report on Week 12) [242:5861, 5867]. There were no reports of nasal ulceration in mometasone treated subjects. No assessment of glaucoma/cataract formation or suppression of the HPA-axis were performed in this PAR study. No deaths were reported in any of the 3 treatment groups.

In terms of infection, viral infection (see above) was reported as the most frequent ADR in all 3 treatment groups in this study. One subject in the placebo treatment group reported herpes simplex labialis on Day 15 of the study (subject I92-293-19, #001)[235:82, 241:2417] and additionally one subject in the placebo group (subject I92-293-04, #008) reported bronchial pneumonia during Week 8 of the study which was felt by the principal investigator to be unrelated to study medication [241:2466]. No subjects in either of the three treatment groups were reported to have nasal or oral candidiasis on any clinic visits.

A total of 16 subjects discontinued treatment because of adverse events (8 subjects in the mometasone group, 6 subjects in the beclomethasone group, and 2 subjects in the placebo group) [235:90]. Common reasons for discontinuation of treatment that were considered 'possibly related' to study medication primarily

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 3 treatment groups. Flag shift distributions of laboratory values failed to reveal any significant patterns of change. Adverse events did not appear to differ significantly based on age, sex, or race, although again, the number of non Caucasian subjects and subjects between 12-17 years and > 64 years of age was too small to draw meaningful conclusions.

8.13.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 12 weeks in subjects with PAR.
2. In terms of individual PAR symptoms and as noted in previous studies in this NDA submission, mometasone treatment demonstrated a greater effect in decreasing the nasal PAR symptoms of rhinorrhea and sneezing, as compared with placebo. Mometasone did not show a statistically significant response in decreasing nasal congestion or any of the non-nasal symptoms and showed a mixed response on nasal itch symptom scores.
3. Mometasone treatment demonstrated adequate duration of effect in treating PAR symptoms over 24 hours, supportive of once a day dosing.

APPEARS THIS WAY
ON ORIGINAL

8.14 Trial I93-018. Efficacy and Safety of Mometasone Furoate Nasal Spray vs. Beconase and vs. Placebo in the Treatment of Perennial Allergic Rhinitis (PAR).

Principal Investigator: Peter Clement, M.D.

Participating Centers: 24 centers in Europe (Belgium, Finland, Germany, the Netherlands, Norway, Sweden, Switzerland, and the U.K.) and Canada.

8.14.1. OBJECTIVES:

1. To characterize the long-term safety profile of a fixed dose of mometasone furoate nasal spray (200 µg qd) and a variable dose of mometasone furoate nasal spray (200 µg qd initially, titrated between 100-400 µg qd depending on the subject's therapeutic response), compared with beclomethasone (Beconase AQ) 200 µg bid.
2. To evaluate long-term efficacy of mometasone aqueous nasal spray in the treatment of symptoms of PAR (efficacy assessment was not the primary objective of this study).

8.14.2. STUDY DESIGN:

This was a randomized, multi-center, open-label, active-controlled, parallel group trial in adult subjects with perennial allergic rhinitis which was an extension of the 3 month double-blind PAR study I92-293. Study enrollable subjects consisted of those who successfully completed the double-blind study I92-293 or who were dropped from I92-293 due to treatment failure or intercurrent illness (with exception of the Netherlands, where subjects who dropped out due to treatment failure were not enrolled in I93-018) [273:12, 277:983-984]. For study subjects at the U.K. centers, total exposure to mometasone, which included any exposure that subjects received in study I92-293, was limited to 12 months total; hence subjects who received a total of 3 months of mometasone treatment in study I92-293 could only receive mometasone for 9 months in study I93-018 [273:12, 277:971]. A variable mometasone dose group was included in this study in order to obtain additional efficacy and safety information on doses of mometasone which were above or below the 200 µg qd dose and also to gain information regarding the individualization of mometasone dosing for PAR. Study medications were given to PAR subjects for a total duration of 52 weeks (1 year) (with the above noted exception of U.K. subjects).

8.14.3. PROTOCOL:

8.14.3.1.a. POPULATION:

Entry criteria for this study after completion of a washout period (up to 7

years [273:15], (2) presence of IgE-mediated hypersensitivity to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 1 year of study entry via the prick testing or intradermal method [273:15, 277:965], and (3) successful completion of study 192-293, or discontinuation secondary to treatment failure or intercurrent illness (exception: the Netherlands) [273:15].

8.14.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1 of Trial I93-018 in the NDA submission [273:14, 277:1005] and is similar to the study design of PAR study C93-014. Subjects were assessed at pre-baseline (Visit 1), baseline (Visit 2), and at Week 4 (Visit 3), 8 (Visit 4), 12 (Visit 5), 24 (Visit 6), 36 (Visit 7), and 52 (Visit 8) of therapy [277:985]. Subjects enrolled at U.K. centers completed the study by Visit 7 (Week 36)[273:14,277:992-999]. For 'roll-over' subjects, the final visit in I92-293 (Visit 7) served as the pre-baseline visit for study I93-018 [273:14, 277:971].

Subjects entered a washout phase (up to 7 days) between the pre-baseline and baseline visit, during which they took no medications except for rescue medication (note: no restrictions outlined in the protocol with regard to the type of rescue medication that could be used by a subject with the exception of corticosteroid use), as prescribed by the principal investigator for relief of intolerable PAR symptoms prior to initiation of the open-label treatment [273:18, 277:984]. Following the washout period, subjects who met all inclusion criteria were randomly assigned to one of the following 3 treatment groups, received diary cards to record symptoms reflectively over the previous 12 hours and began therapy with mometasone (fixed and variable doses) administered in the a.m. and beclomethasone administered in the a.m. and p.m. (bid) [277:984-985]:

(A)	**Mometasone aqueous nasal spray 200 µg qd (FIXED DOSE)**
(B)	**Mometasone aqueous nasal spray 100, 200 or 400 µg qd (VARIABLE DOSE)-subjects started treatment with mometasone 200 µg qd**
(C)	**Beclomethasone 200 µg bid (400 µg qd total)**

Subjects underwent clinical efficacy and safety evaluation (including nasal exam) during each study visit [273:23-29, 277:992-1001]. Of note, eye examinations to assess glaucoma/cataract formation and assessments of HPA-axis suppression were not performed in this study. Efficacy evaluation was again based on a 0-3 severity scale [273:25, 277:998] and a 1-5 scale of therapeutic response [273:25-26, 277:998-999].

Subjects randomized to the mometasone 'variable dose' group started treatment at 200 µg qd but were allowed to lower the medication dose to 100 µg qd if nasal symptoms were well controlled or to increase the dose to 400 µg qd in

were not to be done more frequently that once every 2 weeks, and an intermediate dose of 300 µg qd was not allowed [273:17, 277:990]. Rescue medication use was allowed throughout the study duration for all 3 treatment groups, excluding steroid formulations (nasal, inhaled, etc.).

A primary efficacy variable was not defined in this study. Supplementary efficacy variables consisted of: (1) physician and (2) subject evaluations of overall condition and (3) physician and (4) subject evaluations of therapeutic response in the ITT population [273:33, 277:1002]. Centers 3, 7, 9, 12, 14, 28, 22, and 24 were combined for efficacy analysis since each of these sites had ≤ 7 subjects randomized [273:33]. Pollen counts were not collected in this study. Rescue medication use between the 3 treatment groups was not analyzed in any systematic manner in this study, thus making it difficult to reach any solid conclusions about clinical efficacy of the different treatments evaluated in this study.

8.14.4. RESULTS

A total of 229 subjects with PAR were randomized into study I93-018, with 1 immediate drop-out (the subject did not receive any study drug)[273:36], leaving 228 subjects for the ITT population [273:36]. Seventy-seven (77) subjects in the ITT population received mometasone 200 µg qd, 80 subjects received variable dose (100-400 µg qd) mometasone, and 72 subjects received beclomethasone [273:36]. Similar to study C93-014, the attrition rates for study subjects by Week 52 of study I93-018 were quite high with 30.3% (23/76) of mometasone 200 µg qd subjects, 23.4% (19/80) of variable dose mometasone subjects, and 29.6% (21/71) of beclomethasone subjects discontinuing treatment by this study endpoint [274:277].

The treatment groups in this study were comparable with regard to demographic and disease characteristics with the exception of a marginally statistically significant difference among the treatment groups with respect to weight (mean weight of the mometasone 200 µg group subjects=76 kg vs. mean weight of the mometasone variable dose group subjects=72 kg vs. mean weight of the beclomethasone group subjects=72 kg; p=0.15) [273:36]. Given the minimal-absent systemic bioavailability of intranasally administered mometasone and therefore, unlikely relevance of weight in determining dosing requirements for individual subjects, the small weight difference between treatment groups in this study was not likely to be clinically significant. Again, for all 3 treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the treatment groups was approximately equal. Approximately 50% study subjects in all 3 treatment groups had SAR in addition to PAR. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a statistically significant difference among the 3 treatment groups although the mometasone variable group had a numerically greater % of subjects with 'severe' PAR (11%) in comparison with the other 2 groups (mometasone variable group; 'severe' subjects=6%, vs. beclomethasone group; 'severe'

groups were assessed as having 'moderate' or 'severe' PAR, indicating little carry-over effect from treatment in I9_ -293 to I93-018.

Analysis of the efficacy variables for the ITT population showed that overall, subjects in all 3 active treatment groups demonstrated an improvement in symptoms which was maintained for the study duration. For the physician's evaluation of the overall condition of PAR, subjects in the 2 (fixed and variable) mometasone treatment groups demonstrated an improvement by Week 4 of the study (as supported by the majority of subjects having 'mild' PAR symptoms) and this improvement was maintained through the Week 52 visit [273:40-41, 225, 248-249]. While beclomethasone treated subjects also demonstrated an improvement in the overall condition of PAR, this improvement was numerically lower than that of the mometasone treated subjects. Subjects' self-evaluation of the overall condition of PAR paralleled that of the physician evaluation; namely that improvement in symptoms was noted by Week 4 of the study (supported by the majority of subjects rating their overall PAR condition as 'mild') and was maintained throughout the study duration [274:277, 300-301]. Both of these findings support maintenance of a therapeutic effect for mometasone (fixed and variable dose) and beclomethasone throughout the open-treatment period. Physician evaluation of subjects' therapeutic response to treatment (1-5 scale) indicated that all 3 treatment groups experienced moderate-marked relief in PAR symptoms starting at Week 4 of the study and continuing throughout the open-treatment period, again providing evidence of maintenance of a therapeutic effect throughout the study duration [273:44-45, 329-330]. Subjects' evaluation of therapeutic response paralleled the physician evaluation of subjects' therapeutic response with the majority of study subjects reporting moderate-marked relief in PAR symptoms by Week 4 of treatment [273:48, 274:375-376]. Again, this response was maintained for the study duration.

Regarding the 'variable dose' mometasone group, 8/80 (10%) of subjects received mometasone 100 µg qd, 48/80 (60.0%) of subjects received mometasone 200 µg qd, and 24/80 (30%) of subjects received mometasone 400 µg qd at the time of the final study visit [253:45, 275:506]. Within the variable mometasone group, 35/80 (44%) of subjects maintained the 200 µg qd dose throughout the study, 22/80 (28%) increased their dose to 400 µg qd, and 8/80(10%) decreased their dose to 100 µg qd. Fifteen subjects (19%) varied their mometasone dose more than once during the study [275:507]. Again, these 'variable dose' mometasone group data suggest that the most effective dose of mometasone for the control of PAR symptoms was 200 µg qd. As noted in study C93-014, gradual increase in dose of mometasone over the course of study I93-018 was not observed.

While this trial was not blinded and hence not designed to provide enough power to conduct inferences on efficacy, results of these supplementary analyses nonetheless provide supportive information that mometasone is effective in the treatment of symptoms of PAR. Results of the 4 efficacy variables for the 2

Table I. Efficacy Variables of PAR and Treatment with Mometasone 200 µg qd and 'Variable Dose' Mometasone (100, 200, or 400 µg qd) (ITT Population), [273:225, 248-249, 329-330, 274:277, 300-301, 375-376]

EFFICACY VARIABLE		Improvement in PAR symptoms throughout study duration: Mometasone 200 µg qd: (Yes/No)	Improvement in PAR symptoms throughout study duration: 'Variable dose' Mometasone: (Yes/No)
1	Physician's evaluation of subject overall PAR condition compared to baseline	Yes	Yes
2	Subject self evaluation of overall PAR condition compared to baseline	Yes	Yes
3	Physician evaluated response to Rx compared to baseline	Yes	Yes
4	Subject self-evaluated response to Rx compared to baseline	Yes	Yes

sx=Symptom, Rx=Treatment, ITT=Intent-to-treat
Statistical analysis for between group differences performed using 2-way ANOVA

8.14.4.3. ADVERSE EVENTS:

The safety analysis was based on 228 subjects in the ITT population; 77 subjects were treated with mometasone 200 µg qd, 80 subjects were treated with variable dose mometasone (100, 200, or 400 µg qd), and 71 subjects were treated with beclomethasone [273:50]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, nasal, and clinical laboratory tests relative to baseline [273:26-29].

Adverse events were similar for all 3 treatment groups, with viral infection being the most frequently reported adverse event. Overall, adverse events were reported in 68% of subjects in the mometasone 200 µg qd treatment group, 76% of subjects in the variable dose mometasone treatment group, and 77% of subjects in the beclomethasone group [273:50].

Viral infection was reported in 35% of subjects in the mometasone 200 µg qd group, 30% of subjects in the variable dose mometasone group, and 28% of subjects in the beclomethasone group [273:50,52, 279:1797-1808, 280:1942-1952, 2084-2094]. Viral infection was followed by headache as the second most frequently reported adverse event; reported in 19% of mometasone 200 µg qd subjects, compared to 30% of variable dose mometasone subjects and 25% of beclomethasone treated subjects [273:50, 52, 279:1738-1750, 1875-1896, 280:2015-2037]. Reported next in frequency was pharyngitis; with 17% of subjects in the mometasone 200 µg qd group, 13% of subjects in the variable dose mometasone group, and 11% of subjects in the beclomethasone group recording this adverse event [273:51, 53, 279:1839, 280:1975-1978, 2111-2114]. Other relatively frequent ADRs reported in this follow-up study included epistaxis (8% of

mometasone 200 µg qd subjects, 13% of variable dose mometasone subjects, and 14% of beclomethasone subjects [273:51, 53, 279:1818-1830, 280:1959-1969, 2099-2106]), coughing (8% of mometasone 200 µg qd subjects, 8% of variable dose mometasone subjects, and 14% of beclomethasone subjects [273:51, 53, 279:1814-1817, 280:1957-1958, 2096-2098]), and sinusitis (5% of mometasone 200 µg qd subjects, 9% of variable dose mometasone subjects and 10% of beclomethasone subjects [273:51, 53, 279:1852-1853, 280:1982-1985, 2117-2118]).

Unlike study C93-014, for study I93-018 there did appear to be a dose relationship in the overall incidence of ADRs in the mometasone variable dose group noted for the study duration (incidence of ADRs for mometasone 100 µg qd group=42%, incidence of ADRs for mometasone 200 µg qd group=59%, incidence of ADRs for mometasone 400 µg qd group=71% [273:71]). ADRs which primarily exhibited a dose response for the varying doses of mometasone were coughing (0%, 4%, and 9% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose, respectively), epistaxis (0%, 8%, and 11% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose, respectively), and sinusitis (0%, 5%, and 9% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose of, respectively) [273:51]. Nonetheless, the small number of study subjects in the variable dose mometasone groups, especially the 100 µg group, precludes any definitive conclusion regarding the mometasone dose-relationship of adverse events.

There was one report of a distal nasal septal perforation at screening and at the one year follow-up visit (Visit 8) in a subject in the variable dose mometasone group (subject I93-018-05, #017) [281:2927]. Nasal ulcers were reported in all 3 treatment groups as follows:

(1) mometasone 200 µg qd group: a report in 1 subject (at Visit 3 (Week 4), [281:3034]),

(2) mometasone variable (100-400 µg qd) group: reports in 6 subjects (1 at Visit 3, 1 at Visit 5, 1 at Visit 6, 2 at Visit 7, and 1 at Visit 8) [281:3045, 3047, 3049, 3051, 3090, 3124], and

(3) beclomethasone group 200 µg bid group: reports in 7 subjects (1 at Visit 3, 3 at Visit 4, 1 at Visit 6, 1 at Visit 7, and 1 at Visit 8 [281:3055, 3056, 3061, 3063, 282:3082, 3134, 3222].

Again, no assessments of HPA-axis suppression or glaucoma/cataract formation were performed in this follow-up study. No deaths were reported in any of the three treatment groups.

In terms of infection, viral infection was the most frequently reported ADR in the study for all 3 treatment groups with a reported incidence of 35% in mometasone 200 µg qd subjects, 30% in variable dose mometasone subjects, and 28% in beclomethasone treated subjects [273:50]. In this study there were no reports of herpes simplex labialis, nasal or oral candidiasis for any of the 3 treatment groups.

A total of 15 subjects discontinued treatment because of adverse events (5

mometasone group, and 4 subjects in the beclomethasone group) [273:63]. The most common reason for discontinuation that was considered 'possibly or probably related' to study medication involved headache, epistaxis, or nasal irritation. Otherwise, most subject discontinuations due to ADRs were considered unrelated to treatment by the principal investigator.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 3 treatment groups with the exception of several reports of elevated LFTs and several reports of a decrease in the WBC. Three subjects total developed elevated LFTs: in 1 case this was felt to be possibly related to study medication (subject I93-018-08, #14 who received mometasone 200 µg qd and developed an increase in the SGOT from 40 IU/L at screening to 114 IU/L at Visit 5 and an increase in the SGPT from 88 IU/L at screening to 277 IU/L at Visit 5) [273:66, 67, 279:1780]. One additional subject in the mometasone 200 µg qd group (subject I93-018-20, #12) developed an elevated SGOT on the final study visit (111 IU/L from 24 IU/L at screening)[273:64, 66, 275:504, 279:1780] which was considered 'unaccessible' in terms of relation to study medication although no other etiology for this elevation was determined and one subject in the variable dose mometasone group (subject I93-018-02, #08) developed an elevated bilirubin (4.0 mg/dL at Week 23 from 3.6 mg/dL at screening) which was reported to be secondary to hepatitis (although hepatitis serology was negative) and not considered related to study medication [273:65-66, 275:502, 280:1921]. Two subjects in the variable dose mometasone group were reported to have minor or transient decreases in their white blood cell count (WBC) [273:66]. Of note, in both cases, the pre-baseline WBC for each subject was already below or at the lower limit of normal ($3.26 \times 10^3/mm^3$ and $4.03 \times 10^3/mm^3$) [273:66]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change. Adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects <18 or > 65 years of age was too small to draw meaningful conclusions.

8.14.5. CONCLUSIONS:

1. The results of this study support the safety of mometasone 100 µg, 200 µg and 400 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 52 weeks (1 year) in subjects with PAR.

8.15. Trial I94-079. Efficacy and Safety of Mometasone Furoate Nasal Spray vs. Fluticasone Proprionate Nasal Spray and vs. Placebo in the Treatment of Perennial Allergic Rhinitis (PAR).

Principal Investigator: None (Multi-center study)

Participating Centers: 25 centers in Canada, Latin America (Argentina, Chile, Venezuela, Mexico, Columbia, Guatemala), and Europe (Austria, Portugal, and the U.K.).

8.15.1. OBJECTIVES:

1. To investigate the safety and efficacy of mometasone furoate aqueous nasal spray 200 µg qd in the treatment of symptoms of perennial allergic rhinitis (PAR).

8.15.2. STUDY DESIGN:

The study was a phase III, randomized, multi center, double-blind, double-dummy, active- and placebo-controlled, parallel group study to determine the safety and efficacy of mometasone furoate 200 µg administered intranasally once daily (qd), vs. the active control, fluticasone (Flonase) 200 µg administered once daily (qd), and vs. placebo for a total of 12 weeks for the treatment of perennial allergic rhinitis (plus 1 additional week of observation at the end of the double-blind treatment period (the 'offset' or Week 13 visit) [243:37]).

8.15.3. PROTOCOL:

8.15.3.1.a. POPULATION:

Entry criteria for this study were very similar to those for all other PAR studies, namely: (1) age ≥ 12 years [243:16, 246:1137, 1140], (2) presence of IgE-mediated hypersensitivity to a relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 2 years of study entry via the prick testing or intradermal method; or in the absence of a positive skin test, a diagnosed or suspected history of non-allergic rhinitis with eosinophilia syndrome (NARES) which had been corroborated by nasal cytology demonstrating eosinophilia [243:16, 26, 246:1138, 1140], and (3) presence of PAR symptoms of sufficient severity (nasal rhinorrhea and/or congestion scores at least moderate in severity (≥ 2), a total symptom score ≥ 5 at both screening and baseline, and rhinorrhea and/or congestion scores ≥ 2 during 4 of the last 7 days prior to the baseline visit), in order to begin study drug treatment [243:30, 36, 246:1138].

8.15.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1 of Trial 194-079 in the NDA submission [243:15, 246:1173] and is similar to the study design of PAR study 192-293. Subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Day 8 (Visit 3), 15 (Visit 4), 29 (Visit 5), and Weeks 8 (=Day 57, Visit 6), and 12 (=Day 85, Visit 7) of therapy [243:14-15, 25-29, 246:1146-1147, 1148-1159]. Subjects were also evaluated at Week 13 at the end of the 'off-set' period (Visit 8) when subjects were no longer receiving double-blind medication in order to assess duration of effect of each treatment in decreasing PAR symptoms [243:14, 246:1158]. Day 1 was designated as the start of treatment date [243:37]. Medication restrictions consisted of those previously discussed for the mometasone SAR and PAR studies [243:22-24, 246:1142-1145], although subjects were allowed to use a rescue medication (loratadine, up to 10 mg po qd maximum dose) for intolerable PAR symptoms starting with the screening visit (the 'run-in' phase) and continuing for the duration of the study, including the offset period [243:20, 21, 26-27, 246:1145, 1148, 1163].

Subjects who met all inclusion criteria were randomized to one of the following 3 treatment groups, received diary cards to record symptoms reflectively over the previous 12 hours (upon awakening, before the a.m. medication dose and before retiring (p.m. recording)) and began therapy with study drug every a.m. and p.m. (4 bottles utilized for this double dummy design--each active drug had a matching placebo) [243:18, 21, 27-28, 246:1138-1139, 1146-1147]:

(A) Mometasone aqueous nasal spray 200 µg qd		
a.m. dosing:	Bottle 1: Mometasone 200 µg	Bottle 2: Fluticasone Placebo
p.m. dosing	NONE	
(B) Fluticasone nasal spray (Beconase) 200 µg qd		
a.m. dosing:	Bottle 1: Mometasone Placebo	Bottle 2: Fluticasone 200 µg
p.m. dosing:	NONE	
(C) Placebo (0 µg qd)		
a.m. dosing:	Bottle 1: Mometasone placebo	Bottle 2: Fluticasone Placebo
p.m. dosing:	NONE	

Subjects underwent clinical efficacy and safety evaluation (including nasal exam on Visits 2 (baseline) and 7 (Week 12) during each study visit [243:28-34, 246:1148-1165]. Efficacy evaluation was again based on a 0-3 severity scale [243:30, 246:1159], a 0-3 scale of the overall condition of PAR [243:30, 246:1160], and a 1-5 scale of therapeutic response [243:31, 246:1160].

The primary efficacy variable [243:43-44, 246:1168-1169] was defined as: the mean change from baseline (the mean of the a.m. and p.m. baseline scores and

the a.m. and p.m. scores from the 7 prior consecutive days) in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject diaries) where the:

Mean Change in Total nasal symptom score= 15 Day Interval Score[(Nasal a.m. average $_{\text{Day 1-15}}$) + (Nasal p.m. average$_{\text{Day 1-15}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

and the **total nasal symptom score=[discharge+ stuffiness+ sneezing+ itching].**

Secondary efficacy variables consisted of the following [243:44, 246:1169]:

(1) The mean change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30 (a.m. and p.m. combined), Days 31-45, Days 46-60, Days 61-75, and Days 76-90 [243:44]:

Mean Change in Total nasal symptom score$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$**=Day 16-30 (or Day 31-45, Day 46-60, Day 61-75, Day 76-90) Interval Score**[(Nasal a.m. average $_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$) + (Nasal p.m. average$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

(2) Endpoint total nasal symptom score (a.m. and p.m. combined): Endpoint score defined as the last available post-baseline value for each study subject, pooled across the 24 participating centers [243:38].

(3) Mean change in the total nasal symptom score for the 'offset' (Week 13) visit [243:40].

(4) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, endpoint visit, and the offset visit) [243:44].

(5) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, endpoint visit, and the offset visit) [243:44].

(6) Physician's evaluation of total nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8 , Week 12, endpoint visit, and the offset visit) [243:44].

(7) Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit) [243:44].

(8) Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit) [243:44].

(9) Subject's self-evaluation of overall disease condition using the PAR 0-3

visit, and the offset visit [243:44].

(10) Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [243:44].

(11) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit and the offset visit [243:44].

(12) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [243:44].

(13) The proportion of 'symptom-free' days (i.e. total nasal symptom=0) during the entire treatment period (i.e. excluding baseline visit) [243:44].

Pollen counts were not collected in this study. Rescue medication use between the 3 treatment groups was not analyzed statistically but a frequency of rescue medication for all 3 treatment groups was tabulated, thus providing a general overview of differences in rescue medication use [244:317].

8.15.4. RESULTS

A total of 550 subjects with PAR were randomized into study I94-079, with 2 immediate drop-outs (1 subject in the mometasone group and 1 subject in the fluticasone group, respectively who did not receive any double-blind medication and were excluded from all analyses) [243:47], leaving 548 subjects evaluable in the ITT population [243:47]. One hundred and eighty one (181) subjects in the ITT population received mometasone treatment, 183 subjects received fluticasone, and 184 subjects received placebo [243:47]. An additional 89 subjects were excluded from efficacy analyses because of various protocol violations, leaving 459 subjects in the efficacy evaluable population [243:47].

The treatment groups in this study were comparable with regard to demographic and disease characteristics [243:49]. Again, for all 3 treatment groups, the majority of subjects were Caucasian, although approximately 28-30% of all subjects in each of the 3 treatment groups were Hispanic [243:49]. The distribution of male and female subjects in each of the treatment groups was approximately equal, with slightly more female than male subjects enrolled in all 3 treatment groups. Approximately 35-40% of the subjects had SAR in addition to PAR and the majority did not have the NARES syndrome (7 subjects total, 1 subject in the mometasone treatment group) [243:219-221]. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a statistically significant difference among the 3 treatment groups with the majority of subjects in all 3 groups having 'moderate' PAR symptoms at baseline [243:51].

Analysis of the primary efficacy variable for the ITT population demonstrated greater efficacy of both active treatment groups in decreasing total

nasal symptom score/unit change for the mometasone treatment group was 5.8 (with a -2.3 unit decrease in total nasal symptoms from baseline or a -37% change), compared with a raw total nasal symptom score of 4.5 (-1.3 unit decrease in total nasal symptoms or -17% change) for the placebo group ($p<.01$) [244:403], and a raw total nasal symptom score of 3.9 (-2.2 unit decrease in total nasal symptoms or -35% change) for the fluticasone treatment group ($p<.01$ for fluticasone vs. placebo) [244:403]. No statistically significant difference was noted between the mometasone and fluticasone treatment groups. Furthermore, no significant difference was noted between the a.m. and p.m. total nasal symptom scores or change in scores in the mometasone treatment group for the day 1-15 interval (mometasone group a.m. raw total nasal symptom score/change in raw score=3.9/-2.3 unit change vs. mometasone group p.m. raw total nasal symptom score/change in raw score=3.7/-2.3 unit change), once again supporting once daily dosing of mometasone [244:404-405]. Additionally, no significant difference in the primary efficacy variable was noted between the ITT and efficacy evaluable population [244:373, 403].

Sub-analysis of the primary efficacy variable (total nasal symptom scores) on a weekly basis for the efficacy evaluable population revealed a statistically significant response in the mometasone treatment group compared to placebo by week 1 of treatment ($p<0.01$) [244:442] and a continued decrement in the raw total nasal symptom score by week 2 of treatment which was statistically greater than that of the placebo group ($p<.01$) [244:442]. No statistically significant difference was noted between the 2 active drugs although fluticasone treated subjects had a slightly greater numerical response during weeks 1 and 2 of treatment, compared to the mometasone treatment group [244:442]. Again no significant difference between the a.m. and p.m. total nasal symptom scores (raw and change in raw scores) was noted for weeks 1 and 2 for the mometasone treatment group [244:443-444]. A summary of results for the primary and secondary efficacy variables is summarized in Table I. and Table II. below and overall, support the efficacy of mometasone in decreasing the symptoms of PAR. No significant difference in clinical efficacy was noted based on age, sex, or racial group with the exception that efficacy evaluable female subjects in the 2 active treatment groups showed a greater mean reduction in the total nasal symptom scores from baseline than did efficacy evaluable male subjects, and male subjects in the placebo group showed a greater mean reduction in total nasal symptom scores from baseline than did placebo group female subjects [243:53, 244:409]. In general, however, the number of subjects comprising the sub-groups were too small (i.e. age 12-17, age >64 or non-Caucasian subjects) to make any generalized conclusions [244:409] regarding possible differences in efficacy.

Analysis of subject and physician-rated individual nasal and non-nasal symptoms are summarized in Table III. below. Interestingly, in this PAR study mometasone treatment was noted to have an statistically significant effect on decreasing each individual nasal symptom, in particular nasal congestion--a

the other studies reviewed in this NDA submission. Mometasone treatment likewise demonstrated a very small numerical response in decreasing the individual non-nasal symptoms of PAR (Table III.), however these changes were not found to be statistically significant as compared with placebo. Analysis of the 'offset' visit indicates that for both the nasal and non-nasal, while not generally statistically significant, the mometasone treatment group did demonstrate a greater decrease in PAR symptoms than did placebo treated subjects one week after discontinuation of treatment. These findings suggest that mometasone (also fluticasone) continues to provide some relief of PAR symptoms 1 week after discontinuation of medication use and suggests that mometasone has a somewhat prolonged duration of action once subjects reach steady state dosing. Also, while numerically small, mometasone treatment increased the mean proportion of 'symptom-free' days for the entire study duration to 9.5 days, compared to 4.4 'symptom-free' days for placebo treated subjects ($p<.01$, no significant difference noted between the mometasone and fluticasone treatment groups) [244:400].

Analysis of rescue medication use (efficacy evaluable population) in the 3 treatment groups revealed lower rates of rescue medication use in the two active drug groups (53.9% of mometasone subjects, 57.3% of fluticasone subjects, and 71.0% of placebo subjects used rescue medication > 1 time during the study) [244:317-318]. A greater percentage of placebo group subjects tended to use rescue medication 11-15 times or more for the study duration than did subjects in either of the 2 active drug groups [244:317].

Table I. Primary Efficacy Variable of PAR and Treatment with Mometasone (ITT Population) [243:403]

	1° EFFICACY VARIABLE	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1	Subject evaluated mean Δ in Total Nasal Sx Score$_{\text{DAY 1-15}}$	*Yes

sx=Symptom

* Note: Statistically significant response for 1° efficacy variable in the efficacy evaluable population (ITT data not provided) carried by 3 of the 21 distinct study centers (i.e. 18/20 centers had a statistically non-significant response) [244:374-396]. 4 study centers (-009, -012, -013, and -022 had ≤ 10 efficacy evaluable subjects hence were combined as 1 single large center [243:41]).

Table II. Secondary Efficacy Variables of PAR and Treatment with Mometasone

(ITT Population, except where *otherwise noted). [244, 400, 403, 407, 246, 1495, 1498, 1527, 1528, 1537-1540]

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1	Subject evaluated mean Δ in Total Nasal Sx Score DAY 16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90	Yes:	All study intervals.	
2	Subject evaluated mean Δ in Endpoint Total Nasal Sx Score	Yes:	Endpoint visit.	
3	Subject evaluated mean Δ in Offset Total Nasal Sx Score	Yes:	Offset visit.	
4	Subject evaluated mean Δ in Total Sx Score DAY 1-15, DAY 16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90, Endpoint Visit, Offset Visit	Yes:	All study intervals and visits.	
5	Subject evaluated mean Δ in Total non-nasal Sx Score DAY 1-15, DAY 16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90, Endpoint Visit, Offset Visit	Yes:	Day 31-45, 61-75, Endpoint visit, Offset visit.	
		No:	Day 1-15, 16-30, 46-60, 76-90.	
6	Physician Evaluated Total Nasal Sx Score	Yes	Study visits:	Day 8, 15, 29, Week 8, Week 12, Endpoint visit.
		No:	Offset visit.	
7	Physician Evaluated Total Sx Score	Yes:	Study visit:	Day 8, 15, Week 8, Week 12, Endpoint visit.
		No:	Study visits:	Day 29, Offset visit.
8	Physician Evaluated Total non-nasal Sx Score	No:	All study visits	
9	Subject overall condition evaluation	Yes:	Study visits:	Day 8, 15, 29, Week 8, Week 12, Endpoint visit.
		No:	Study visits:	Offset visit.
10	Physician overall condition evaluation	Yes:	Study visits:	Day 8, 15, 29, Week 8, Week 12, Endpoint visit.
		No:	Study visits:	Offset visit.
11	Subject overall Rx Response evaluation	Yes:	Study visit:	All study visits.
12	Physician overall Rx Response evaluation	Yes:	Study visits:	All study visits.
13	*Proportion of symptom-free days for the entire treatment period (Total nasal sx score=0)	Yes		

Δ=Change, Sx=Symptom, Rx=Treatment Note: Analyses are for a.m. and p.m. combined symptom scores

ITT=Intent-to-Treat Population
*Otherwise noted=efficacy evaluable population

Table III. **Change in Individual PAR Symptoms (Subject and Physician Evaluated, a.m. and p.m. combined) with Mometasone Treatment** (ITT Population), {246.1501-1524, 1526-1528, 1529-1536}

PAR SYMPTOM	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
Subject Evaluated Individual Nasal Sx Score	Yes:	For all 4 nasal sxs: All study visits.	
Physician Evaluated Individual Nasal Sx Score	Yes:	Rhinorrhea:	Day 8, 15, 29, Week 8, 12, Endpoint visit.
		Congestion:	Day 8, 15, 29, Week 8, 12, Endpoint visit.
		Sneezing:	Day 8, 15, 29, Endpoint visit.
		Nasal Itch:	Week 8, Endpoint visit.
	No:	Rhinorrhea:	Offset visit.
		Congestion:	Offset visit.
		Sneezing:	Week 8 , Week 12, Offset visit.
		Nasal Itch:	Day 8, 15, 29, Week 12, Offset visit.
Subject Evaluated Individual non-nasal Sx Score	Yes:	Eye tear:	Day 31-45, Endpoint visit.
		Eye Itch:	Day 31-45, Endpoint visit.
		Ear/palate Itch:	Day 1-15, 31-45, 46-60, 61-75, Endpoint visit, Offset visit.
	No:	Eye tear:	Day 1-15, 16-30, 46-60, 61-75, 76-90, Offset visit.
		Eye redness:	All study visits..
		Eye Itch:	Day 1-15, 16-30, 46-60, 61-75, 76-90, Offset visit.
		Ear/palate Itch:	Day 16-30, 76-90.
Physician Evaluated Individual non-nasal Sx Score	No:	All 4 non-nasal Sxs:	All study visits.

Sx=Symptom

8.15.4.3. ADVERSE EVENTS:

The safety analysis was based on 548 subjects in the ITT population; 181 subjects were treated with mometasone 200 µg qd, 183 subjects were treated with with fluticasone 200 µg qd, and 184 subjects were treated with placebo [243:76, 245:615]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, and nasal examinations, and clinical laboratory tests relative to baseline [243:31-34, 246:1148-1165].

Adverse events were again similar for all three treatment groups, with viral infection and headache being the most frequently reported treatment-related adverse event. Overall, adverse events were reported in 75% of subjects in the mometasone group, 71% of subjects in the fluticasone treatment group, and 65% of subjects in the placebo group [243:77, 78, 245:615]. Viral infection was reported in 28% of subjects in the mometasone group, 19% of subjects in the fluticasone group, and 27% of subjects in the placebo group [243:78, 245:621, 249:5957-5980, 250:6253-6267, 6518-6538]. Headache was reported in 27% of mometasone and fluticasone subjects, compared to 24% of placebo subjects [243:78, 245:616, 249:5829-5873, 6135-6171, 250:6419-6457]. Reported next in frequency were pharyngitis and epistaxis; with 19% of subjects in the mometasone group, 21% of subjects in the fluticasone group, and 17% of placebo subjects reporting pharyngitis [243:78, 79, 245:622, 249: 6038-6052, 250:6334-6349, 6590-6605], and 19% of subjects in the mometasone group, 21% of subjects in the fluticasone group, and 13% of placebo subjects reporting epistaxis, respectively [243:78, 79, 245:621, 249:6003-6028, 250:6298-6321, 6559-6573]. As in other rhinitis studies in this NDA submission, episodes of epistaxis were generally mild and self-limited in duration. The third most frequent ADR was coughing, reported in 15% of mometasone subjects, 11% of fluticasone subjects, and 12% of placebo subjects [243:79, 245:621, 249:5985-6000, 250:6283-6295, 6546-6555]. Compared to the other PAR studies in this NDA submission, sinusitis was less frequent in study I94-079, being reported in 5% of mometasone treated subjects, 7% of fluticasone subjects, and 3% of placebo subjects [243:79, 245:621, 249:6064-6068, 250:6360-6365, 6622-6625].

There were no reports of nasal septal perforation in any of the 3 treatment groups but one mometasone treated subject was noted to have a left septal ulcer on Visit 7 (Week 12) of the study which was absent on screening (subject I94-079-06, #008) [251:7883] and one fluticasone treated subject was found to have a right nasal septal ulcer on Visit 7 (Week 12) of the study which was absent on screening (subject I94-079-06, #006) [251:7885]. Nasal ulcers were reported in 4 subjects in the mometasone group on Visit 7 of the study (subjects I94-079-04, #001, -05, #003, -06, #007, -011, #022) [252:7973, 7993, 8013, 8094], 2 subjects in the fluticasone group (1 report on Visit 6 and 1 report on Visit 7, subjects I94-079-25, #019 and -11, #018) [252:8101, 8290], and 2 subjects in the placebo group (1 report on Visit 3, subject I94-079-05, #020,[250:6634] and 1 report on Visit 7, subject I94-079-05, #011) [251:7881]. No assessment of glaucoma/cataract

deaths were reported in any of the 3 treatment groups.

In terms of infection, viral infection (see above) was reported as the most frequent ADR in all 3 treatment groups in this study. Herpes simplex infection was more prevalent in this PAR study with 2 subjects in the mometasone group (1% incidence), 5 subjects in the fluticasone group (3% incidence), and 2 subjects in the placebo group (1% incidence) reporting this adverse event [243:78, 245:621, 249:5954, 250:6250, 6517]. One subject in the fluticasone treatment group (subject I94-079-02, #026) was reported to have pneumonia during Visit 6 and Visit 7 of the study which was felt by the principal investigator to be unrelated to study medication [245:622, 250:6350]. One subject in the fluticasone treatment group was reported to have nasal candidiasis (right nares) on Visit 7 of the study (subject I94-079-17, #023) [252:8184]. No subjects in either of the three treatment groups were reported to have oral candidiasis on any clinic visits [245:621].

A total of 9 subjects discontinued treatment because of adverse events (3 subjects in the mometasone group, 4 subjects in the fluticasone group, and 2 subjects in the placebo group) [243:93]. Of the 3 subjects who discontinued treatment in the mometasone group (due to eczema, an upper respiratory infection (URI), and hyperglycemia from diabetes, respectively), none of these discontinuations were felt to be related to the study medication [243:93, 309, 311, 312].

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 3 treatment groups with the exception of several reports of a decrease in the WBC in mometasone treated subjects. Three subjects in the mometasone treatment group were noted to have a significant decrease in their WBC count on Visit 7 (Week 12) of the study to 2.46, 2.54, and 2.5 x 10^3/mL from a screening value of 5.33, 3.16, and 4.0 x 10^3/mL, respectively (subject I94-079-08, #024, I94-079-22, #001, and I94-079-23, #013) [243:95, 245:714-715]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change with the exception of a mild shift to the low normal range for the % neutrophil count in subjects of the 2 active drug groups, mometasone and fluticasone [245:988]. Adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects between 12-17 years and > 64 years of age was too small to draw meaningful conclusions.

8.15.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 12 weeks (plus 1 week off medication) in subjects with

2. In terms of individual PAR symptoms, mometasone treatment demonstrated a statistically significant effect in decreasing the PAR symptoms of rhinorrhea, nasal congestion, sneezing, and nasal itch; as compared with placebo. Mometasone did not show a statistically significant response in decreasing any of the non-nasal symptoms although a small degree of improvement was demonstrated in mometasone treated subjects, as compared with placebo for all 4 non-nasal symptoms.
3. Mometasone treatment demonstrated adequate duration of effect in treating PAR symptoms over 24 hours, supportive of once a day dosing.
2. While not specifically designed to evaluate efficacy, assessment of subject overall condition and response to treatment with mometasone over 52 weeks (by study subjects and their respective physicians), supports the efficacy of mometasone in doses of 100-400 µg qd for the treatment and maintenance treatment of symptoms of PAR.
3. A proportional increase incidence in overall adverse events with increasing mometasone dose (100, 200, and 400 µg qd); in particular, coughing, epistaxis, and sinusitis, was reported in study I93-018.

8.16. Trial 193-180 Assessment by Nasal Biopsy of Long-term Safety of Mometasone Furoate Aqueous Nasal Spray vs. Fluticasone Proprionate (Flixonase) in Perennial Rhinitis Patients (PAR).

Investigators: Stephen R. Durham, M.D., Robert J. Davies, M.D., and Valerie J. Lund, M.D.

Participating Centers: 3 Centers in the U.K.

8.16.1. OBJECTIVES:

1. To assess the effects of long-term treatment with mometasone furoate nasal spray (200 µg qd) vs. fluticasone propionate nasal spray (200 µg qd), on the nasal mucosa of PAR subjects, using nasal biopsy results.
2. To evaluate long-term efficacy of mometasone aqueous nasal spray in the treatment of symptoms of PAR (efficacy assessment was not the primary objective of this study).

8.16.2. STUDY DESIGN:

This was a randomized, multi center, open-label, active-controlled, parallel group trial in adult subjects with perennial allergic rhinitis to investigate the effect of mometasone 200 µg qd administered for 12 months on nasal mucosa. Nasal biopsies were performed pre- and post-treatment for both treatment groups; for each treatment subject one nostril was biopsied at baseline and the other was biopsied at the final visit. A separate group of healthy (i.e. non-allergic) subjects did not receive any treatment, but underwent nasal biopsy at baseline and after 12 months to assess biopsy sampling technique artifacts [283:10, 284:595].

8.16.3. PROTOCOL:

8.16.3.1.a. POPULATION:

Entry criteria for this study were the following: (1) age ≥ 18 years [283:14, 284:595, 597], (2) presence of IgE-mediated hypersensitivity to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 1 year of study entry via the prick testing or intradermal method [283:14, 284:597], and (3) a history of mild to moderate PAR for at least 1 year with sufficient symptoms at screening and baseline (i.e. a total nasal symptom score ≥ 4)[283:21-22, 284:596, 597]. Normal subjects must have been non-allergic by history in order to be study enrollable, with nasal mucosa of normal appearance on physical examination [283:12-13, 284:598].

8.16.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Tables

treatment subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Week 5 (Visit 3), 9 (Visit 4), 13 (Visit 5), 25 (Visit 6), 37 (Visit 7), and 53 (Visit 8) of therapy [283:11, 284:596, 601]. Normal control subjects were assessed at screening (Visit 1), baseline (Visit 2), and Week 53 (Visit 8) [283:10-11]. The discrepancy of the 1 week extension of this study compared with previous PAR studies was in order to account for the 1 additional week between the baseline nasal biopsy and the initiation of treatment (to allow time for healing of the nasal biopsy site) [283:11].

All subjects (active drug and normal control subjects) underwent routine screening during Visit 1 where a history and physical examination (including nasal exam), an assessment of the severity of subject PAR symptoms (according to a 0-3 severity scale, as per subject and physician evaluations), lab tests, and a screening ECG was performed [283:20-21, 284:603-604]. On the second study visit (baseline visit) approximately one week later, subject PAR symptom scores were re-evaluated, along with adverse events and concomitant medications. Study enrollable subjects were randomized to one of the following 4 treatment sequences, and along with normal control subjects, underwent a baseline nasal biopsy [283:21, 284:585, 605-607]:

		BIOPSY SITE SEQUENCE	
		BASELINE	FINAL VISIT
(A)	**Mometasone nasal spray 200 µg qd**	LEFT	RIGHT
(B)	**Mometasone nasal spray 200 µg qd**	RIGHT	LEFT
(C)	**Fluticasone nasal spray 200 µg qd**	LEFT	RIGHT
(D)	**Fluticasone nasal spray 200 µg qd**	RIGHT	LEFT

Subjects in the mometasone and fluticasone treatment groups began therapy, administered once daily each a.m., one week (7 days) following the baseline visit [283:22, 284:606]. The normal control subjects did not undergo any further testing or follow-up except for a follow-up nasal biopsy 12 months later [283:22, 284:606]. Subjects in the 2 active treatment groups were allowed use of rescue medication (not specified in protocol but to exclude all steroids) for relief of intolerable PAR symptoms [284:606]. Of note, eye examinations to assess glaucoma/cataract formation and assessments of HPA-axis suppression were not performed in this study. For study Visits 3-8, active treatment group subjects underwent routine re-assessment of their PAR status and any adverse events, along with a follow-up nasal exam, and on Visits 5-8, had follow-up lab tests [283:22-26, 284:607-609, 614-616]. Efficacy evaluation and overall condition of PAR was again based on a 0-3 severity scale [283:24, 284:610] and a 1-5 scale of therapeutic response [283:24, 284:610-611].

efficacy variables consisted of: (1) physician and (2) subject evaluations of overall condition and (3) physician and (4) subject evaluations of therapeutic response in the ITT population, as compared to baseline [283:35-36, 284:617]. Pollen counts were not collected in this study. Rescue medication use between the 2 treatment groups was not analyzed in any manner in this study (data not provided in the submission), thus making it difficult to reach any solid conclusions about clinical efficacy of the different treatments evaluated in this study.

A comparative (qualitative) study evaluating differences in nasal mucosal histology between steroid treated allergic subjects (mometasone and fluticasone subjects) and normal 'non-allergic' controls was performed in order to assess any long-term effects of mometasone treatment on nasal epithelium and the degree of study artifact (reason for normal control subjects). Using paraffin embedded, blinded, nasal biopsy specimens obtained from mometasone, fluticasone, and normal control subjects at baseline and at 12 months of the study, a number of histologic parameters were evaluated via light microscopy: (1) epithelial thickness, (2) cross-sectional area/mm of basement membrane, (3) epithelial phenotype: the percentage (%) of epithelium that was composed of basement membrane (BM) only, BM plus basal cells, BM plus columnar cells, and intact epithelium (including cilia), (4) degree of epithelial integrity, atrophy, and presence/absence of metaplasia, (5) extent of eosinophilia, and (6) extent of inflammatory cell infiltration (note: 'inflammatory' cells were defined in this study as comprising lymphocytes, monocytes, plasma cells, and neutrophils, in addition to eosinophils) [283:31-32, 35, 284:576-579, 611-612, 638-639]. For these parameters, a 2-way ANOVA extracting sources of variation due to treatment, center, and treatment by center interaction was used to compare treatment groups.

8.16.4. RESULTS

8.16.4.1.a. Efficacy

A total of 145 subjects with PAR were randomized into study I93-180, with 4 immediate dropouts after the baseline visit (3 subjects in the mometasone group and 1 subject in the fluticasone group; these subjects did not receive any study drug [283:38]), leaving 141 subjects in the ITT population [283:38]. Sixty-nine (69) subjects in the ITT population received mometasone and 72 subjects received fluticasone [283:38]. Six of the 30 normal control subjects were excluded from the study because they dropped out of the study immediately after the baseline visit [283:38-39]. The attrition rates for study subjects by Week 53 of study I93-180 were quite high, with 21.7% (15/69) of mometasone subjects, 19.7% (14/71) of fluticasone subjects, and 20% (6/30) of normal control subjects discontinuing treatment by this study endpoint [283:163, 170].

The treatment groups in this study were comparable with regard to demographic and disease characteristics with the exception of a statistically

with respect to age which nonetheless, did not affect treatment inferences (mean age of the mometasone subjects=30 years vs. mean age of the fluticasone subjects=34 years; p=0.02) [283:36, 40]. Again, for both active treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the 2 treatment groups was approximately equal. Approximately 50% or more of study subjects in both treatment groups had SAR in addition to PAR. The majority (76-84%) of study subjects were non-smokers. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a significant difference between the 2 treatment groups, with the majority of subjects in both groups having 'moderate' PAR symptoms at baseline [283:43].

Analysis of the efficacy variables for the ITT population showed that overall, subjects in the 2 active treatment groups demonstrated an improvement in symptoms which was maintained for the study duration. For the physician's evaluation of the overall condition of PAR, subjects in the mometasone and fluticasone treatment groups demonstrated an improvement by Week 5 of the study which was similar between the 2 treatment groups in terms of raw symptom scores and change in scores (and was additionally supported by the majority of subjects having 'mild' PAR symptoms) and this improvement was maintained through the Week 53 visit [283:163-164]. Since the study was not designed to determine clinical efficacy prior to the Week 5 visit, no conclusion can be made whether mometasone subjects might have demonstrated a statistically significant therapeutic response prior to Week 5 of treatment, as compared with placebo. Subjects' self-evaluation of the overall condition of PAR paralleled that of the physician evaluation; namely that improvement in symptoms was noted by Week 5 of the study (supported by the majority of subjects rating their overall PAR condition as 'mild') and was maintained throughout the study duration [283:170-171]. Both of these findings support maintenance of a therapeutic effect for mometasone and fluticasone throughout the open-treatment period. Physician evaluation of subjects' therapeutic response to treatment (1-5 scale) indicated that the majority of subjects in the 2 treatment groups experienced moderate-complete relief of PAR symptoms starting at Week 5 of the study and which continued throughout the open-treatment period, again providing evidence of maintenance of a therapeutic effect throughout the study duration [283:177-178]. Subjects' evaluation of the therapeutic response paralleled the physician evaluation of subjects' therapeutic response with the majority of study subjects reporting moderate-complete relief in PAR symptoms by Week 5 of treatment [283:182-183]. Again, this response was maintained for the study duration.

While this trial was not blinded and hence not designed to provide enough power to conduct inferences on efficacy, results of these supplementary analyses nonetheless provide supportive information that mometasone is effective in the treatment of symptoms of PAR. Results of the 4 efficacy variables for the mometasone and fluticasone treatment groups are summarized in Table 1 below:

Table 1. Efficacy Variables of PAR and Treatment with Mometasone 200 µg qd and Fluticasone 200 µg qd (ITT Population). [283:44-45, 47-48, 50-53, 163-164, 170-171, 177-178, 182-183]

EFFICACY VARIABLE		Improvement in PAR symptoms throughout study duration: Mometasone 200 µg qd: (Yes/No)	Improvement in PAR symptoms throughout study duration: Fluticasone 200 µg qd: (Yes/No)
1	Physician's evaluation of subject overall PAR condition compared to baseline	Yes	Yes
2	Subject self evaluation of overall PAR condition compared to baseline	Yes	Yes
3	Physician evaluated response to Rx compared to baseline	Yes	Yes
4	Subject self-evaluated response to Rx compared to baseline	Yes	Yes

sx=Symptom, Rx=Treatment, ITT=Intent-to-treat
Statistical analysis for between group differences performed using 2-way ANOVA

8.16.4.1.b. Nasal Biopsy Studies [283:67-78, 287:1606-1643]:

Analysis of nasal biopsy histology obtained from 101 active medication subjects pre- and post-treatment (46 mometasone subjects and 55 fluticasone subjects) and 24 normal control subjects indicates that overall there was no marked change in any of the parameters for the active treatment groups and no statistically significant difference between mometasone and fluticasone for any of the parameters examined. Furthermore, there appeared to be no inter-site differences in the appearance of the specimens, nor any differences with regard to gender or race in terms of the specific histologic features. Importantly, steroid (mometasone or fluticasone) treatment failed to demonstrate epithelial atrophy, and indeed appeared to improve epithelial integrity (epithelial 'intactness' which increased from 56.9% to 70.6% in the mometasone group and from 45.5% to 66.0% in the fluticasone group) following treatment for 12 months [283:73, 287:1609]. Mometasone treatment also appeared to normalize the epithelium of allergic rhinitis subjects to comprise a slightly higher % of ciliated stratified columnar epithelial cells and to decrease the degree of focal squamous metaplasia in nasal tissue after treatment [283:73, 287:1607, 1609]. For both mometasone and fluticasone treated subjects, the extent of intra-epithelial eosinophilia and inflammatory cell infiltration (lymphocytes, monocytes, plasma cells, and neutrophils) also decreased post-treatment at 12 months, consistent with known mechanisms of action of steroids in decreasing allergic inflammation (especially eosinophil and lymphocyte trafficking) [287:1609-1610]. A summary of nasal biopsy findings is summarized in Table 22 of the NDA submission [283:76-77] or Vol. 287:1609-1610.

8.16.4.3. ADVERSE EVENTS:

The safety analysis was based on 141 subjects in the ITT population: 69 subjects were treated with mometasone 200 µg qd and 72 subjects were treated with fluticasone [283:38, 188]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, an ECG (at screening only), physical, nasal, and clinical laboratory tests relative to baseline [283:25-26, 284:603-604].

Adverse events were similar for the 2 active treatment groups, with viral infection being the most frequently reported treatment-related adverse event. Overall, adverse events were reported in 90% of subjects in the mometasone 200 µg qd treatment group and 92% of subjects treated with fluticasone 200 µg qd treatment group [283:55, 188].

The most frequently reported adverse event was headache, reported by 43% of subjects in the mometasone treatment group and 49% of subjects in the fluticasone treatment group [283:56, 188, 286:1113-1134, 287:1271-1297]. Headache was followed by viral infection as the second most frequently reported adverse event; reported in 32% of mometasone subjects, compared to 38% of fluticasone subjects [283:57, 193, 286:1191-1199, 287:1353-1362]. Reported next in frequency was epistaxis; with 17% of subjects in the mometasone group and 14% of subjects in the fluticasone group recording this adverse event [283:57, 193, 286:1208-1213, 287:1368-1372]. Pharyngitis was reported in 14% of mometasone subjects, and 15% of fluticasone subjects [283:57, 194].

There were no reports of nasal septal perforation in either of the 2 active treatment groups although nasal ulcers were reported in one subject in the mometasone treatment group on Visit 6 (subject I93-180-02, #055) [289:2345] and 2 subjects in the fluticasone treatment group (subject I93-180-01, #004 and #032) on Visit 8 of the study [289:2270, 2291]. Again, no assessments of HPA-axis suppression or glaucoma/cataract formation were performed in this study. No deaths were reported in any of the 2 active treatment groups.

In terms of infection, viral infection was the second most frequently reported ADR in the study for both active treatment groups with a reported incidence of 32% in mometasone treated subjects and 38% in fluticasone treated subjects [283:59, 193]. In this study there was one report of herpes simplex labialis in a fluticasone treated subject (at Visit 5, no reports for mometasone subjects) and two reports of nasal candidiasis in mometasone treated subjects (subject I93-180-02, #051 at Visit 7 and subject I93-180-02, #038 at Visit 4) which were not recorded in the NDA submission as adverse events [283:59, 83, 193, 289:2309, 2331, 287:1345]. Furthermore, one subject in the mometasone treatment group was reported to develop pneumonia during Visit 6 of the study (subject I93-180-03, #008) which was not felt to be related to study medication by the principal investigator [283:193, 286:1220].

A total of 7 subjects discontinued treatment because of adverse events (4 subjects in the mometasone group, and 3 subjects in the fluticasone group) [283:65-66]. The most common reason for discontinuation that was considered

nasal burning. Otherwise, most subject discontinuations due to ADRs (arthritis, pneumonia) were considered unrelated to treatment by the principal investigator.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 2 treatment groups with the exception of several reports of elevated LFTs and one report of a decrease in the WBC. Two subjects total developed elevated LFTs; in 1 case this may have been possibly related to study medication (subject 193-180-01, #018 who received mometasone 200 µg qd and developed an increase in the SGOT from 43 IU/L at screening to 181 IU/L at Visit 7 (Week 37) with a decrease to 54 IU/L by the final visit (normal SGOT range 7-56 IU/L) [283:81, 284:310]. The other mometasone treated subject with normal LFTs on screening (subject 193-018-02, #005, SGOT at screening=31 IU/L and SGPT at screening=24 IU/L) developed an elevated SGOT and SGPT (to 192 IU/L and 372 IU/L, respectively) by Visit 6 of the study, which were attributed to alcohol consumption and which returned to within a normal range on re-testing 3 weeks later [283:81, 284:310]. One subject in the mometasone group (subject 193-180-02, #031) was reported to have a decreased WBC to 2.7 x 10^3/mm^3 (normal range: 3.5-10.8 x 10^3/mm^3) on Visit 7 from a screening value of 4.9 x 10^3/mm^3, which subsequently returned to within the normal range (5.4 x 10^3/mm^3) by Visit 8 [283:82, 284:310]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change with the exception of a slight shift in SGOT values to the high normal range for mometasone treated subjects as compared with fluticasone treated subjects (22% of mometasone subjects vs. 10% of fluticasone treated subjects [284:479]. Adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects <18 or > 65 years of age was too small to draw meaningful conclusions.

8.16.5. CONCLUSIONS:

1. The results of this study support the safety of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 52 weeks (1 year) in subjects with PAR.
2. While not specifically designed to evaluate efficacy, assessment of subject overall condition and response to treatment with mometasone over 52 weeks (by study subjects and their respective physicians), supports the efficacy of mometasone 200 µg qd for the treatment and maintenance treatment of symptoms of PAR.
3. Overall, long-term (12 month) treatment with mometasone did not demonstrate any histologic evidence of worsening nasal atrophy or ulcer formation. Indeed, treatment with mometasone (and fluticasone) appeared to improve nasal epithelial integrity and decrease the number of intra-epithelial eosinophils, lymphocytes, monocytes, plasma cells, and

however, is observational at best, and does not necessarily correlate with clinical benefit.

8.17. Trial C94-052. A Long-term Safety Study of Mometasone Furoate Aqueous Nasal Spray vs. Triamcinolone Acetonide (Nasacort) in Perennial Rhinitis (PAR).

Principal Investigator: Donald W. Aaronson, M.D.

Participating Centers: 20 Centers in the U.S.

8.17.1. OBJECTIVES:

1. To assess the safety effects of long-term treatment with mometasone furoate nasal spray (200 µg qd) vs. triamcinolone acetonide nasal spray (220 µg qd), on PAR subjects.
2. To evaluate long-term efficacy of mometasone aqueous nasal spray in the treatment of symptoms of PAR (efficacy assessment was not the primary objective of this study).

8.17.2. STUDY DESIGN:

This was a randomized, multi-center, open-label, active-controlled, parallel group trial in adult subjects with perennial allergic rhinitis to investigate the long-term safety profile of mometasone 200 µg qd administered for 12 months, focusing on HPA-axis suppression through evaluation of 24 hr urinary cortisol levels and serum cortisol levels 45-60 minutes post-Cortrosyn stimulation with 250 µg cosyntropin.

8.17.3. PROTOCOL:

8.17.3.1.a. POPULATION:

Entry criteria for this study were the following: (1) age ≥ 12 years [262:12, 14, 266:926, 928], (2) presence of IgE-mediated hypersensitivity to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 1 year of study entry via the prick testing or intradermal method [262:14, 20, 266:928], (3) a history of PAR for at least 2 years with sufficient symptoms at screening and baseline (i.e. a total nasal symptom score ≥ 5, nasal congestion and/or rhinorrhea score ≥ 2) [262:14, 20, 22, 24-45, 266:926, 928], (4) evidence at screening of a normal morning (8 a.m. ± 1 hour) cortisol level (≥ 5 µg/100 ml) and a positive response to Cortrosyn stimulation with 250 µg cosyntropin (defined as an increase in serum cortisol level ≥ 7 µg/100ml from baseline 45-60 minutes after Cortrosyn stimulation) [262:14, 266:928, 934, 935], and (5) at study sites -01, -05, -06, and -011, laboratory evidence of a creatinine level within normal limits in study enrollable subjects [262:14, 266:928].

8.17.3.1.b PROCEDURE:

of Trial C94-052 in the NDA submission [262:13, 266:965]. Mometasone and triamcinolone treatment subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Week 1 (Visit 3), 4 (Visit 4), 12 (Visit 5), 24 (Visit 6), 36 (Visit 7), and 52 (Visit 8) of therapy [262:12, 30, 266:927].

All subjects underwent routine screening during Visit 1 where a history and physical examination (including nasal exam), an assessment of the severity of subject PAR symptoms (according to a 0-3 severity scale, as per subject and physician evaluations), lab tests (including basal serum cortisol levels and serum cortisol levels post-Cortrosyn testing), and a screening ECG was performed [262:20-21, 266:927, 933-935]. At study sites -01, -05, -06, and -011, 24 hour urinary free cortisols and creatinine were additionally measured, along with plasma mometasone concentrations [262:21, 266:927, 934]. On the second study visit (baseline visit) approximately one week later, subject PAR symptom scores were re-evaluated, along with adverse events and concomitant medications, and study enrollable subjects were randomized to one of the following 2 treatments [262:15-18, 21-22, 266:926, 935-937]:

	TREATMENT
(A)	**Mometasone nasal spray 200 µg qd q a.m.**
(B)	**Triamcinolone nasal spray 220 µg qd q a.m.**

Subjects in the mometasone and triamcinolone treatment groups began therapy, administered once daily each a.m. [262:22, 266:927, 936-937]. Subjects in the 2 treatment groups were allowed use of rescue medication (not specified in the protocol but to exclude all steroids) for relief of intolerable PAR symptoms but were discouraged from taking other medications for their 'nasal' symptoms [262:19, 266:930-931]. For study Visits 3-8, subjects underwent routine re-assessment of their PAR status and any adverse events, along with a follow-up nasal exam, and on Visits 5-8, had follow-up lab tests, (including follow-up serum cortisol levels and post-Cortrosyn testing cortisol levels on Visits 5, 6 and 8, along with repeat plasma mometasone measurements) [262:22-23, 26-29, 31, 266:938-94-945]. Subjects at study sites -01, -05, -06, and -011 underwent repeat 24 hour urine collection prior to study Visits 5, 6, and 8 [262:23, 31-32, 266:940]. Efficacy evaluation and overall condition of PAR was again based on a 0-3 severity scale [262:24-25, 266:942] and a 1-5 scale of therapeutic response [262:25, 266:943].

A primary efficacy variable was not defined in this study, as assessment of clinical efficacy was not a primary objective of this study. Supplementary efficacy variables consisted of: (1) physician and (2) subject evaluations of overall condition and (3) physician and (4) subject evaluations of therapeutic response in the ITT population, as compared to baseline which were analyzed by 2-way ANOVA [262:37, 266:947]. Pollen counts were not collected in this study. Rescue

this study (data not provided in the submission), thus making it difficult to reach any solid conclusions about clinical efficacy of the different treatments evaluated in this study

Evaluation of plasma cortisol levels involved calculating the difference in plasma levels from screening [262:32, 266:946]. Analyses of urinary free cortisol levels were based on subjects (from centers -01, -05, -06, -011) whose creatinine value at a given visit was within 35% of the value at screening (subjects who failed this criterion were requested to collect another 24 hour urine for re-analysis) [262:31-21, 34, 266:940-941]. For the pre-cortrosyn value, post-cortrosyn value, the difference between post- and pre-cortrosyn values, and the change from screening in the difference between the post- and pre-cortrosyn values, treatment groups were compared using a 2-way ANOVA, extracting sources of variation due to treatment, center, and treatment by center interaction [262:36,266:946].

8.17.4. RESULTS

8.17.4.1.a. Efficacy

A total of 351 subjects with PAR were randomized into study C94-052, with no study dropouts, leaving 351 subjects in the ITT population [262:39]. One hundred and seventy-five (175) subjects in the ITT population received mometasone and 176 subjects received triamcinolone [262:39]. An efficacy evaluable population was not analyzed in this study [262:39]. The attrition rates for study subjects by Week 52 of study C94-052 were marginally acceptable, with 14.3% (25/175) of mometasone subjects and 13.1% (23/175) of triamcinolone subjects discontinuing treatment by this study endpoint [262:205].

The treatment groups in this study were comparable with regard to demographic and disease characteristics [262:40]. For both active treatment groups, the majority of subjects were Caucasian and female. Approximately 80% of study subjects in both treatment groups had SAR in addition to PAR. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a significant difference between the 2 treatment groups, with the majority of subjects in both groups having 'moderate' PAR symptoms at baseline [262:43].

Analysis of the efficacy variables for the ITT population showed that overall, subjects in the 2 active treatment groups demonstrated an improvement in PAR symptoms which was maintained for the study duration. For the physician's evaluation of the overall condition of PAR, subjects in the mometasone and triamcinolone treatment groups both demonstrated an improvement by Week 1 post-initiation of treatment which was very similar between the 2 treatment groups in terms of raw symptom scores and change in scores (and was additionally supported by the majority of subjects having 'mild' PAR symptoms) and this improvement was maintained through the Week 52 visit [262:205-206]. Subjects'

evaluation; namely that improvement in symptoms was noted by Week 1 of the study (supported by the majority of subjects rating their overall PAR condition as 'mild') and was maintained throughout the study duration [263:248-249]. Both of these findings support maintenance of a therapeutic effect for mometasone and triamcinolone throughout the open-treatment period. Physician evaluation of subjects' therapeutic response to treatment (1-5 scale) indicated that the majority of subjects in the 2 treatment groups experienced moderate-marked relief of PAR symptoms starting at Week 4 (Visit 4) of the study and which continued throughout the open-treatment period, again providing evidence of maintenance of a therapeutic effect throughout the study duration [263:289-290]. Subjects' evaluation of the therapeutic response paralleled the physician evaluation of subjects' therapeutic response with the majority of study subjects reporting moderate-complete relief in PAR symptoms by Week 4 of treatment [263:328-329]. Again, this response was maintained for the study duration.

While this trial was not blinded and hence not designed to provide enough power to conduct inferences on efficacy, results of these supplementary analyses nonetheless provide supportive information that mometasone is effective in the treatment of symptoms of PAR. Overall, subject and physician rated response of PAR symptoms to treatment were very similar between the mometasone and triamcinolone groups. Results of the 4 efficacy variables for the mometasone and triamcinolone treatment groups are summarized in Table I. below.

Table I. Efficacy Variables of PAR and Treatment with Mometasone 200 µg qd (ITT Population), [262:205-206, 263:248-249, 289-290, 329-329]

	EFFICACY VARIABLE	Improvement in PAR symptoms throughout study duration: Mometasone 200 µg qd: (Yes/No)	Improvement in PAR symptoms throughout study duration: Triamcinolone 220 µg qd: (Yes/No)
1	Physician's evaluation of subject overall PAR condition compared to baseline	Yes	Yes
2	Subject self evaluation of overall PAR condition compared to baseline	Yes	Yes
3	Physician evaluated response to Rx compared to baseline	Yes	Yes
4	Subject self-evaluated response to Rx compared to baseline	Yes	Yes

sx=Symptom, Rx=Treatment, ITT=Intent-to-treat
Statistical analysis for between group differences performed using 2-way ANOVA

8.17.4.1.b. Mometasone Bioavailability

Plasma mometasone levels were measured on the Screening Visit and on Visits 5, 6 and 8 (weeks 12, 24, and 52) in study subjects for study sites: -01, -05, -06, and -011 using a HPLC/mass spectrometry method (Phoenix International Life Sciences, Inc.) to determine the concentration of mometasone furoate in human plasma. The lower limit of quantitation of mometasone via this assay method was 50.1 pg/ml while the upper limit of quantitation was 5005 pg/ml [266:1222]. Based on this method, mometasone furoate levels were detected in 4 out of 169 plasma samples analyzed, 3 of which were near the limit of assay quantitation. In all other samples analyzed, mometasone concentrations were below the limit of quantitation [266:1246-1249]. Of note, all 3 subjects in whom mometasone levels were detected were from site -05. Subject findings are summarized in table II. below [262:83]:

Table II. Plasma Mometasone Concentration in PAR Subjects [262:83]:

SUBJECT	SAMPLE TIMEPOINT	Plasma Mometasone Concentration (pg/ml)
C94-052-05, #020	Week 12	58.7
C94-052-05, #023	Week 12	66.1
C94-052-05, #023	Week 24	57.1
C94-052-05, #013	Week 24	*1454

*Presumed pharmacokinetic outlier.

In summary, the levels of mometasone detected in subject plasma samples were less than twice the limit of quantitation in 3/4 subjects, thus providing evidence that systemic bioavailability of mometasone administered at a dose of 200 µg qd to PAR subjects had negligible bioavailability. These findings are consistent with mometasone's overall safety profile in adult SAR and PAR subjects along with previous human PK findings with mometasone administration, as reported in this NDA submission.

8.17.4.3. ADVERSE EVENTS:

The safety analysis was based on 351 subjects in the ITT population: 175 subjects were treated with mometasone 200 µg qd and 176 subjects were treated with triamcinolone 220 µg qd [283:38, 188]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, an ECG (at screening only), physical exam (including nasal exam), and clinical laboratory tests (including plasma cortisol levels pre- and post-cosyntropin stimulation prior to initiation of steroid treatment) on the Screening visit and on Weeks 12, 24, and 52 post-treatment along with a measurement of 24 hour urinary free cortisol levels in a subset of study subjects at these same respective study visits (at study sites -01,

Adverse events were similar for the 2 active treatment groups, with headache being the most frequently reported treatment-related adverse event. Overall, adverse events were reported in 88% of subjects in the mometasone 200 µg qd treatment group and 88% of subjects in the triamcinolone 220 µg qd treatment group [262:55, 263:367].

The most frequently reported adverse event was headache, reported by 45% of subjects in the mometasone treatment group and 41% of subjects in the triamcinolone treatment group [262:55, 263:368, 269:2404-2505, 270:2837-2942]. Headache was followed by upper respiratory infection as the second most frequently reported adverse event; reported in 30% of mometasone subjects, compared to 36% of triamcinolone subjects [262:56, 263:376, 270:2755-2773, 271:3182-3206]. Reported next in frequency was sinusitis; with 26% of subjects in the mometasone group and 16% of subjects in the triamcinolone group recording this adverse event [262:56, 263:376, 270:2737-2751, 271:3164-3175]. Viral infection was reported in 23% of mometasone subjects and 19% of triamcinolone subjects [262:56, 263:375, 269:2657-2668, 271:3089-3100]. Epistaxis and pharyngitis were reported in 17% of mometasone subjects, and in 13% and 14%, respectively of triamcinolone subjects [262:56, 263:375, 376, 271:2696-2706, 2717-2726, 271:3121-3129, 3141-3151]. Interestingly, for this study musculoskeletal pain was reported in 18% of mometasone subjects and in 15% of triamcinolone subjects [262:55, 253:372, 269:2588-2611, 271:3025-3045].

There were no reports of nasal septal perforation in either of the 2 treatment groups although an erosion of the right nasal septum was reported in one subject in the mometasone treatment group on Visit 8 (Week 52) (subject C94-052-13, #002) [272:4275] and a minimal abrasion of the left nasal septum was reported in 1 additional mometasone subject on Visit 8 of the study (subject C94-052-14, #014) [272:4279]. No assessments of glaucoma/cataract formation were performed in this study. No deaths were reported in any of the 2 active treatment groups.

In terms of infection, viral infection was reported in 23% in mometasone treated subjects and 19% in triamcinolone treated subjects [262:56], hence comparable in frequency to the incidence cited for the other PAR studies in this NDA submission. In this study there were 2 reports of herpes simplex labialis in triamcinolone treated subjects (no reports for mometasone subjects) and no reports of oral or nasal candidiasis in any study subjects that were associated with treatment [263:374]. Furthermore, 1 subject in both the mometasone and the triamcinolone treatment group were reported to develop pneumonia (subject C94-052-02, #016 and -10, #008) however, these occurred during the baseline visit and were not felt to be related to study medication by the principal investigator(s) [270:2727, 271:3152].

A total of 10 subjects discontinued treatment because of adverse events (4 subjects in the mometasone group, 6 subjects in the triamcinolone group)

probably related' to mometasone treatment involved headache, epistaxis, or rhinitis.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal septal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 2 treatment groups with the exception of one report of hyperglycemia (glucose=265 mg/dL on week 24, subject C94-052-01, #018) in a non-insulin dependent diabetic and 1 report of a decrease in the WBC (to 2.88 x $10^3/\mu L$ on week 24 though the subject's screening WBC was the same value, subject C94-052-13, #002) in mometasone treatment subjects [262:81-82, 264.516]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change with the exception of a slight shift in glucose values to the normal-high range for triamcinolone treated subjects as compared with mometasone treated subjects (7% of triamcinolone subjects vs. 3% of mometasone treated subjects [262:80, 265:773] and a slight shift in the WBC to the low-normal range in both treatment groups [265:791]. Adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects <18 or > 65 years of age was too small to draw meaningful conclusions.

8.17.4.3.b. Hypothalamic Pituitary Adrenal (HPA) Axis Suppression Studies [263:472-473, 264:496-497]:

Analysis of HPA function was performed using 2 methods in this study: (1) Cortrosyn testing (cosyntropin stimulation) after baseline plasma cortisol levels were obtained and (2) 24 hour free urinary free cortisol levels pre- and post-treatment with mometasone and triamcinolone. Of note, if a subject's creatinine value at a given visit was not within 35% of the value at screening, then the subject was excluded from the analyses of urinary free cortisol for that visit [262:32].

Cortrosyn stimulation tests revealed small but inconsistent changes in the plasma cortisol post-stimulation with cosyntropin, as compared to screening values for both treatment groups in pooled data for all subjects tested which are summarized in Table III. [263:472]. Furthermore, no statistically significant difference was detected between the 2 steroid treatments. Analysis of the distribution of plasma cortisol levels between the 2 treatment groups showed that similar to screening plasma values post-cosyntropin, the majority (i.e. > 90%) of subjects demonstrated a $\geq$ 7 μg/100 ml increase in plasma cortisol levels post-cosyntropin administration, indicating that for pooled data, no evidence of HPA-axis suppression was evident at either week 12, 24, or 52 of the study [263:473]. The sponsor states that 1-2 subjects per treatment group had an abnormal response in Cortrosyn stimulation testing post-initiation of treatment but no subject had more than one abnormal response [262:78]. An important flaw and limitation in analysis of pooled data is that pooling tends to obscure abnormal response to Cortrosyn testing in individual subjects which may have laboratory evidence of

positive effect on the HPA-axis in these subjects.

Table III. **Cortrosyn Stimulation Test Result Summary**: Mean Plasma Cortisol Levels, Pre- and Post-Treatment with Mometasone and Triamcinolone and Mean Change (Δ) from Screening (ITT) [262:78, 263:472]

	MOMETASONE			TRIAMCINOLONE			
	n	Mean Plasma Cortisol (µg/dL)	Δ from screening (µg/dL)	n	Mean Plasma Cortisol (µg/dL)	Δ from screening (µg/dL)	[1]P-value
Screening	168	Pre 16.60 Post 31.93	NA	168	Pre 16.70 Post 32.31	NA	0.64
WEEK 12	167	Pre 17.39 Post 31.85	-0.88	167	Pre 17.12 Post 32.03	-0.71	0.81
WEEK 24	158	Pre 17.71 Post 33.16	0.05	162	Pre 17.44 Post 33.14	0.15	0.97
WEEK 52	148	Pre 17.69 Post 31.66	-1.48	152	Pre 16.80 Post 31.12	-1.15	0.33
ENDPOINT	168	Pre 17.38 Post 31.42	-1.30	168	Pre 16.76 Post 31.39	-0.98	0.51

NA=Not applicable
[1]P-value for mometasone vs. placebo, α=0.05, 2-way ANOVA

Evaluation of the 24 hour urinary free cortisol levels at study sites -01, 05, 06, and -011 using pooled data from these sites also failed to reveal an effect or a consistent trend post-treatment in decreasing urinary cortisol levels [264:496], although again pooling of data would be less likely to capture abnormal HPA-axis function in individual subjects. Also of note, a number of subjects failed to have a creatinine value at the respective study visit during which 24 hour urinary free cortisols were collected that was 35% of the value at screening, hence these subjects were excluded from data analysis of the 24 hour urinary free cortisol levels for that visit. As discussed with Ms. Paula Rinaldi, Regulatory Affairs of Schering Plough, Inc. on 08/29/97, the mean screening value for 24 hour urinary free cortisol values was modified to reflect only those subjects that were used in the data analysis for that study visit, i.e. those subjects with a serum creatinine ≥ 35% of the screening value. Results of these modified 24 hour urinary free cortisol levels (taking into account screening 24 hour urinary free cortisol values based on subjects with serum creatinine's ≥ 35% of the screening value) are summarized in Table IV.

Table IV. **24 Hour Urinary Free Cortisol Analysis:** Mean and Mean Change from Screening (ITT Population, study C94-052)
[264:496, FAX Schering Plough, Inc., 08/29/97]

	MOMETASONE		TRIAMCINOLONE		
	n	Mean Urinary Cortisol (µg/day)	n	Mean Urinary Cortisol (µg/day)	[1]P-value
Screening (all subjects)	44	25.63	42	24.17	0.53
Screening	31	25.13	23	23.61	
WEEK 12	31	28.52	23	20.61	0.41
Change	31	3.38	23	-3.00	0.43
Screening	28	23.76	27	26.16	
WEEK 24	28	22.90	27	26.22	0.27
Change	28	-0.85	27	0.06	0.52
Screening	24	20.21	24	22.32	
WEEK 52	24	20.07	24	21.49	0.48
Change	24	-0.15	24	-0.83	0.83
Screening	27	20.05	28	21.95	
ENDPOINT	27	20.80	28	22.45	0.45
Change	27	0.75	28	0.49	0.94

Study performed at sites -01, -05, -06, and -11. Only subjects with a creatinine ≤ 35% of the screening value were used to determine the screening mean 24 hour urinary free cortisol level used to calculate the change in 24 hour urinary free cortisol.
[1]P-value for mometasone vs. triamcinolone (for treatment difference), α=0.05, 2-way ANOVA.

Review of the subject line listings submitted 07/14/97 per FDA request by the Sponsor indicates that a total of 10 mometasone treatment group subjects failed to have a > 7 µg/dL increase in plasma cortisol post-cosyntropin stimulation after having received at least 12 weeks (or more) of mometasone treatment (13 triamcinolone treated subjects had similar findings) Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, Study Report C94-052, p. 1-55]. Nonetheless, in 9 of the 10 mometasone subjects, all plasma cortisol levels were > 18 µg/dL, indicative of adequate adrenal function. In one subject (subject C94-052-16, #008), plasma cortisol levels pre and post-ACTH stimulation were 15.7 µg/dL and 12.9 µg/dL, respectively, indicative of a blunted adrenal response (of note, one triamcinolone subject (subject C94-052-16, #002) also had a blinded adrenal response). Overall, however, these data indicate that for the majority of subjects, treatment with mometasone 200 µg qd is unlikely to result in either subclinical or clinically significant adrenal suppression.

8.17.5. CONCLUSIONS:

1. The results of this study support the safety of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 52 weeks (1 year) in subjects with PAR.
2. While not specifically designed to evaluate efficacy, assessment of subject overall condition and response to treatment with mometasone over 52 weeks (by study subjects and their respective physicians), supports the efficacy of mometasone 200 µg qd for the treatment and maintenance treatment of symptoms of PAR.
3. Mometasone administration for up to 52 weeks in PAR subjects did not appear to cause HPA-axis suppression in mometasone treated subjects collectively as a group, as assessed via Cortrosyn stimulation testing of adrenal function and via 24 hour urinary cortisol levels on pooled data.
4. Plasma levels of mometasone in PAR subjects from 4 study sites at steady state were undetectable in the majority of subjects analyzed. Of those subjects who were found to have measurable mometasone levels, in 3 of these 4 subjects these were minimally higher than the lower limit of quantitation.

APPEARS THIS WAY
ON ORIGINAL

8.18. Trial C94-092. Safety and Efficacy of Mometasone Furoate Nasal Spray vs. Placebo in the Treatment of Elderly Patients with Perennial Allergic Rhinitis (PAR).

Principal Investigator: None (Multi-center study)

Participating Centers: 24 centers in the U.S.

8.18.1. OBJECTIVES:

1. To evaluate the safety and efficacy of mometasone furoate aqueous nasal spray 200 μg qd in the treatment of symptoms of perennial allergic rhinitis (PAR) in elderly (≥ 65 years of age) subjects.

8.18.2. STUDY DESIGN:

The study was a phase III, randomized, multicenter, double-blind, placebo-controlled, parallel group study with a single-blind, placebo run-in phase (7-14 days) to determine the safety and efficacy of mometasone furoate 200 μg administered intranasally once daily (qd) vs. placebo for a total of 12 weeks for the treatment of perennial allergic rhinitis in subjects ≥ 65 years of age.

8.18.3. PROTOCOL:

8.18.3.1.a. POPULATION:

Entry criteria for this study were the following: (1) age ≥ 65 years [229:13, 15, 231:791], (2) presence of IgE-mediated hypersensitivity to a relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 2 years of study entry via the prick testing or intradermal method (wheal size ≥ 3 mm larger than diluent control (diluent not specified) for prick testing and ≥ 7 mm larger than diluent control for intradermal testing) [229:13, 15, 231:791], and (3) presence of PAR symptoms of sufficient severity (a nasal congestion score at least moderate in severity (≥ 2), a total symptom score ≥ 5 at both screening and baseline, and a nasal congestion score ≥ 2 during 4 of the last 7 days prior to the baseline visit), in order to begin study drug treatment [229:15, 25-26, 31, 231:789, 791, 808].

8.18.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1. of Trial C94-092 in the NDA submission [229:14, 231:819] and is similar to the study design of previous PAR studies reviewed in this NDA submission. Subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Day 8 (Visit 3), 15 (Visit 4), 29 (Visit 5), and Weeks 8 (=Day 56, Visit 6), and 12 (=Day 84, Visit 7) of therapy [229:13, 24, 32, 231:796]. Day 1 was designated as the start of

discussed for the mometasone SAR and PAR studies [229:19-21, 231:793-795], and subjects were not allowed to use rescue medication (including systemic antihistamines) for intolerable PAR symptoms for the duration of the study [229:20, 231:795].

After the screening visit, subjects participated in a 1-2 week single-blind placebo run-in period during which they self-administered a nasal spray from a placebo bottle each morning [229:23, 231:789]. On re-evaluation during the baseline visit (Visit 2), subjects who met all inclusion criteria were randomized to one of the following 2 treatment groups, received diary cards to record symptoms reflectively over the previous 12 hours (upon awakening, before the a.m. dose and before retiring (p.m. recording)) and began therapy with study drug administered every a.m. [229:17, 19, 231:802-803]:

(A) Mometasone aqueous nasal spray 200 µg qd	
a.m. dosing:	Mometasone 200 µg
p.m. dosing	NONE
(B) Placebo (0 µg qd)	
a.m. dosing	Mometasone placebo
p.m. dosing:	NONE

Subjects underwent clinical efficacy and safety evaluation (including nasal exam) during each study visit [229:22-25, 27-29, 231:798-809, 811-813]. Efficacy evaluation was again based on a 0-3 severity scale [229:26, 231:808], a 0-3 scale of the overall condition of PAR [229:25, 231:808], and a 1-5 scale of therapeutic response [229:26, 231:809].

The primary efficacy variable [229:38, 231:815] was defined as: the mean change from baseline (the mean of the a.m. and p.m. baseline scores and the a.m. and p.m. scores from the 7 prior consecutive days) in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject diaries) where the:

Mean Change in Total nasal symptom score= 15 Day Interval Score[(Nasal a.m. average $_{\text{Day 1-15}}$) + (Nasal p.m. average$_{\text{Day 1-15}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

and the **total nasal symptom score=[discharge+ stuffiness+ sneezing+ itching].**

Secondary efficacy variables consisted of the following [229:38, 231:815-816]:

averaged over Days 16-30 (a.m. and p.m. combined), Days 31-45, Days 46-60, Days 61-75, and Days 76-90 [229:38].

Mean Change in Total nasal symptom score$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$**=Day 16-30 (or Day 31-45, Day 46-60, Day 61-75, Day 76-90) Interval Score**[(Nasal a.m. average $_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$) + (Nasal p.m. average$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

(2) Endpoint total nasal symptom score (a.m. and p.m. combined): Endpoint score defined as the last available post-baseline value for each study subject, pooled across the 24 participating centers [229:38].

(3) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit) [229:38].

(4) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit) [229:38].

(5) Physician's evaluation of total nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit) [229:38].

(6) Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit) [229:38].

(7) Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit) [229:38].

(8) Subject's self-evaluation of overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, and the endpoint visit [229:38].

(9) Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, and the endpoint visit [229:38].

(10) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, and the endpoint visit [243:44].

(11) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, and the endpoint visit [243:44].

(12) The number of 'symptom-free' days (i.e. total nasal symptom=0) during the entire treatment period (i.e. excluding baseline visit) [229:38].

Pollen counts were not collected in this study.

9.1.8.4 RESULTS

092 and comprised the ITT population (no subject drop-outs) [229:41]. One hundred and seventy (170) subjects in the ITT population received mometasone treatment, while 164 subjects received placebo [229:41]. An additional 20 subjects were excluded from efficacy analyses because of various protocol violations, leaving 314 subjects in the efficacy evaluable population [229:41].

The 2 treatment groups in this study were comparable with regard to demographic and disease characteristics [229:43]. Again, for both treatment groups, the majority of subjects were Caucasian [229:43]. The distribution of male and female subjects in each of the 2 treatment groups was approximately equal. Greater than 50% of the subjects had SAR in addition to PAR. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a significant difference between the 2 treatment groups with the majority of subjects in both groups having 'moderate' PAR symptoms at baseline [229:46].

Analysis of the primary efficacy variable for the ITT population demonstrated greater efficacy of mometasone treatment in decreasing total nasal symptoms for the day 1-15 interval, compared with placebo. The raw total nasal symptom score/unit change for the mometasone treatment group was 4.7 (with a -1.1 unit decrease in total nasal symptoms from baseline or a -16% change), compared with a raw total nasal symptom score of 5.0 (-0.7 unit decrease in total nasal symptoms or -11% change) for the placebo group ($p=.02$) [229:280]. No significant difference was noted between the a.m. and p.m. total nasal symptom scores or change in scores in the mometasone treatment group for the day 1-15 interval (mometasone group a.m. raw total nasal symptom score/change in raw score=4.8/-1.1 unit change vs. mometasone group p.m. raw total nasal symptom score/change in raw score=4.6/-1.0 unit change), once again supporting once daily dosing of mometasone [231:1105-1106]. Additionally, no significant difference in the primary efficacy variable was noted between the ITT and efficacy evaluable population [229:252, 280] (of note: in both subject populations, 4 study centers with ≤ 5 subjects/center were pooled into one center). A summary of results for the primary and secondary efficacy variables is summarized in Table I. and Table II. below and overall, support the efficacy of mometasone in decreasing the symptoms of PAR. No significant difference in clinical efficacy was noted based on age subgroup analysis into subjects age 65-69 and age ≥ 70 years, sex, or racial group [229:282-283]. In general, however, the number of subjects comprising the sub-groups were too small to make any generalized conclusions regarding possible differences in efficacy. Interestingly, in comparison with total nasal symptom scores evidenced in other PAR studies in this NDA submission, those recorded by elderly subjects in study C94-092 were lower, with a small degree of change in total nasal symptoms (numerical and % change). These results are suggestive of anecdotal evidence that SAR and PAR generally decrease in severity with elderly age due to a waning immune response.

Analysis of subject and physician-rated individual nasal and non-nasal

numerically lower for mometasone treated elderly subjects, in comparison with placebo treated subjects, a statistically significant difference was not noted for any physician rated scores and absent in most subject rated scores. This lack of a statistically significant response in elderly subjects was again, in contrast to findings for subjects age 12-64 in the previous PAR studies. Particularly striking was the lack of statistical significance when mometasone treated subjects were compared with placebo group subjects in subject self-evaluated overall response to treatment at all study visits, in contrast to findings of all previous PAR studies. The implications of these findings in elderly subjects (subjects ≥ 65 years of age) is unknown, but aside from speculation that elderly subjects may not have as severe PAR symptoms as younger subjects, a longer duration of underlying perennial rhinitis in elderly subjects (mean duration 29 and 28 years for mometasone and placebo subjects, respectively [229:43] as compared with a mean duration of PAR of 16-20 years in subjects age 12-64 years) was another distinguishing feature between the two age groups. It is also possible that rhinitis symptoms in some of these older individuals may, in part, have been attributable to other underlying medical conditions (*Reference: Liston SL, Siegel LG, Nasal and sinus disorder in the elderly: which ones are life-threatening?, Geriatrics. 1981; 36(2):91-102*) or medications taken for other underlying medical conditions (e.g. antihypertensives). The number of 'symptom-free' days for the entire study duration, while listed as a secondary efficacy variable, was not included by the Sponsor in the efficacy analysis. A review of subject responses however suggests that the majority of mometasone subjects experienced moderate to marked improvement in PAR symptoms by Visit 7 of treatment (as did the placebo group subjects), with a smaller percentage of subjects (≤ 10%) experiencing complete relief of PAR symptoms [230:415].

In summary, while elderly PAR subjects did not appear numerically (and in terms of percent change) to have the same degree of response in PAR symptom scores with mometasone treatment as did subjects (generally, age 12-64 years) evaluated in the other PAR studies, response to treatment was demonstrable and for some efficacy variables statistically significant compared to placebo. Based on statistically significant efficacy for the primary efficacy variable and an overall trend of lower symptom scores for all secondary efficacy variables in mometasone treated subjects, as compared with placebo; mometasone was overall shown to demonstrate efficacy in decreasing PAR symptoms in elderly subjects.

Table I. Primary Efficacy Variable of PAR and Treatment with Mometasone (ITT Population) [229 280]

1° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1	Subject evaluated mean Δ in Total Nasal Sx Score$_{DAY\ 1-15}$	*Yes

sx=Symptom

* Note Statistically significant response for 1° efficacy variable in the efficacy evaluable population (ITT data not provided) carried by 2 of the 21 distinct study centers (i.e. 19/20 centers had a statistically non-significant response) [229 253-273] 4 study centers (-014, -016, -017, and -019 had ≤ 5 efficacy evaluable subjects hence were combined as 1 single large center [229 273])

Table II. Secondary Efficacy Variables of PAR and Treatment with Mometasone (ITT Population, except where *otherwise noted), [229:279-280, 357-358, 230:378-379, 399-400, 414-415, 231:1105-1147]

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1	Subject evaluated mean Δ in Total Nasal Sx Score$_{DAY\ 16-30\ DAY\ 31-45\ DAY\ 46-60\ DAY\ 61-75\ DAY\ 76-90}$	No:	All study visits.	
2	Subject evaluated mean Δ in Endpoint Total Nasal Sx Score	Yes:	Endpoint visit.	
3	Subject evaluated mean Δ in Total Sx Score$_{DAY\ 1-15\ DAY\ 16-30\ DAY\ 31-45\ DAY\ 46-60\ DAY\ 61-75\ DAY\ 76-90\ Endpoint\ Visit,\ Other\ Visit}$	Yes: No:	Day 1-15, Endpoint visit. Day 31-45, 46-60, 61-75, 76-90.	
4	Subject evaluated mean Δ in Total non-nasal Sx Score$_{DAY\ 1-15\ DAY\ 16-30\ DAY\ 31-45\ DAY\ 46-60\ DAY\ 61-75\ DAY\ 76-90\ Endpoint\ Visit,\ Other\ Visit}$	No:	All study visits.	
5	Physician Evaluated Total Nasal Sx Score	No:	All study visits.	
6	Physician Evaluated Total Sx Score	No:	All study visits.	
7	Physician Evaluated Total non-nasal Sx Score	No:	All study visits.	
8	*Subject overall condition evaluation	Yes: No:	Study visits: Study visits:	Week 8. Day 8, 15, 29, Week 8, Week 12, Endpoint visit.
9	*Physician overall condition evaluation	No:	All study visits.	
10	*Subject overall Rx Response evaluation	Yes: No:	Study visit: Study visit:	Endpoint visit. Day 8, 15, 29, Week 8, Week 12.
11	*Physician overall Rx Response evaluation	No:	All study visits.	
12	Proportion of symptom-free days for the entire treatment period (Total nasal sx score=0)	DATA NOT PROVIDED.		

Δ=Change, Sx=Symptom, Rx=Treatment Note: Analyses are for a.m. and p.m. combined symptom scores
ITT=Intent-to-Treat Population

Table III. Change in Individual PAR Symptoms (Subject and Physician Evaluated, a.m. and p.m. combined) with Mometasone Treatment (ITT Population). [231.1113, 1116, 1119, 1122, 1125, 1128, 1131, 1134, 1140-1147]

PAR SYMPTOM	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
Subject Evaluated Individual Nasal Sx Score	Yes:	Rhinorrhea:	Endpoint visit.
		Congestion:	Endpoint visit
		Sneezing:	Day 1-15.
	No:	Rhinorrhea:	Day 1-15, 16-30, 31-45, 46-60, 61-75, 76-90.
		Congestion:	Day 1-15, 16-30, 31-45, 46-60, 61-75, 76-90.
		Sneezing:	Day 16-30, 31-45, 46-60, 61-75, 76-90, Endpoint visit.
		Nasal Itch:	All study visits.
Physician Evaluated Individual Nasal Sx Score	Yes:	Congestion:	Endpoint visit.
		Sneezing:	Week 8.
	No:	Rhinorrhea:	All study visits.
		Congestion:	Day 8, 15, 29, Week 8, Week 12.
		Sneezing:	Day 8, 15, 29, Week 12, Endpoint visit.
		Nasal Itch:	All study visits.
Subject Evaluated individual non-nasal Sx Score	Yes:	Eye tear:	Day 1-15, Endpoint visit.
		Eye redness:	Day 1-15, Endpoint visit.
	No:	Eye tear:	Day 1-15, 16-30, 76-90, Endpoint visit.
		Eye Itch:	All study visits.
		Eye redness:	Day 16-30, 31-45, 46-60, 76-90.
		Ear/palate Itch:	All study visits.
Physician Evaluated individual non-nasal Sx Score	No:	For all 4 non-nasal sxs:	All study visits.

Sx=Symptom

8.18.4.3. ADVERSE EVENTS:

The safety analysis was based on 334 elderly subjects in the ITT population, 170 subjects were treated with mometasone 200 µg qd and 164 subjects were treated with placebo [229:41]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, and nasal examinations, and clinical laboratory tests relative to baseline [229:22-29, 231:798-807, 811-813].

Adverse events were again similar for both treatment groups, and were similar in frequency and profile to those observed in subjects ≤ 65 years of age in the other clinical studies in this NDA submission. Overall, adverse events were reported in 76% of subjects in both the mometasone and the placebo group [229:68, 70, 230:430]. Again, the most frequently reported adverse event was headache, reported in 24% of mometasone subjects and 20% of placebo subjects [229:68, 69-60, 230:430, 233:3635-3675, 3909-3944]. Headache was followed by pharyngitis as the second most common adverse event, reported in 20% of mometasone subjects and 13% of placebo subjects [229:69, 230:436, 233:3818-3834, 234:4060-4069]. This was followed by cough and epistaxis as the next most frequent adverse events (with 16% of mometasone subjects and 10% of placebo subjects, and 13% of mometasone subjects and 9% of placebo subjects reporting cough and epistaxis, respectively) [229:69, 230:436, 233:3791-3805, 234:4031-4041, 4044-4053]. As in other rhinitis studies in this NDA submission, episodes of epistaxis were generally mild and self-limited in duration. Viral infection was reported in 15% of subjects in the mometasone group and 12% of subjects in the placebo group [229:72, 230:436, 233:3758-3766, 234:4016-4022]. Compared to the other PAR studies in this NDA submission, reports of sinusitis in elderly subjects in study C94-092 were less frequent, being reported in 5% of mometasone treated subjects and 7% of placebo subjects [229:73, 230:437].

There were no reports of nasal septal perforation in either of the 2 treatment groups but 3 mometasone treated subjects were noted to have nasal septal ulcerations on various visits during the study which were absent on screening and baseline (subjects C94-092-08, #001, #008, and #23) [233:3815-3816]. Nasal ulcers were reported in 2 subjects in the mometasone group on Visit 7 of the study (subjects C94-092-08, #034 and -06, #002) [233:4746, 4841] and not reported in any placebo group subjects. No assessment of glaucoma/cataract formation or suppression of the HPA-axis was performed in this PAR study. No deaths were reported in either of the 2 treatment groups.

In terms of infection, viral infection (see above) was reported as one of the more frequent adverse events in the 2 treatment groups in this study. Herpes simplex infection was reported in only 1 subject in the mometasone group on Visit 6 (1% incidence) and in no placebo group subjects [229:72, 230:435, 233:3755]. One subject in the placebo treatment group (subject C94-092-23, #002) was reported to have pneumonia during Visit 4 of the study which was felt by the

No subjects in either of the 2 treatment groups were reported to have nasal or oral candidiasis on any clinic visits [229:72, 230:436].

A total of 11 subjects discontinued treatment because of adverse events (4 subjects in the mometasone group and 7 subjects in the placebo group) [229:83]. Of the subjects who discontinued treatment in the mometasone group, most of these discontinuations were felt to be unrelated to the study medication [229:84].

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in either of the 2 treatment groups. One subject (subject C94-092-17, #004) in the mometasone treatment group was noted to have an elevated SGPT following mometasone treatment (84 IU/L, Visit 7) which increased from a screening value of 17 IU/L and which was attributed to Voltaren use. Discontinuation of Voltaren and re-evaluation of the SGPT 5 days post-discontinuation yielded a decreasing value of 55 IU/L [229:87, 230:433, 504, 233:3725]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change in the 2 subject groups. Adverse events did not appear to differ significantly based on sex or race, although the number of non-Caucasian subjects was too small to draw meaningful conclusions [230:568-688].

8.18.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis in elderly subjects with PAR (age ≥ 65 years of age), as assessed for up to 12 weeks.
2. Mometasone treatment demonstrated a statistically significant effect in decreasing PAR symptoms for the primary efficacy variable and at least some additional study timepoints. Although a numerical difference in response was noted between mometasone and placebo treated subjects for most secondary efficacy variables; for most endpoints, these differences were not statistically significant. In general, the response of elderly subjects to mometasone treatment was somewhat less consistent for the duration of the entire study, as compared with subjects analyzed in the other PAR studies.
3. Mometasone treatment demonstrated adequate duration of effect in treating PAR symptoms over 24 hours, supportive of once a day dosing.
4. Elderly subjects treated with mometasone did not develop an increased rate of infections (bacterial or viral) and overall demonstrated a similar adverse event frequency and profile as subjects age 12-64 years treated with mometasone.

8.19. Trial I93-221. Six Month Safety Study of Mometasone Furoate Nasal Spray in Perennial Allergic Rhinitis (PAR) Patients

Principal Investigator: Angel Alonso, M.D.

Participating Centers: 23 international centers (Canada, Latin America, Europe, and Australia).

8.19.1. OBJECTIVES:

1. To characterize the safety profile of mometasone furoate nasal spray in doses ranging from 100-400 µg qd (depending on the subject's therapeutic response) for a period of 6 months.
2. To evaluate efficacy of mometasone aqueous nasal spray in the treatment of symptoms of PAR (efficacy assessment was not the primary objective of this study).

8.19.2. STUDY DESIGN:

This was a randomized, multi center, non-comparative, non-placebo controlled trial in adult subjects with perennial allergic rhinitis in which 6 month safety and efficacy data on the use of variable dose mometasone (100, 200, or 400 µg qd) in the treatment of PAR was analyzed.

8.19.3. PROTOCOL:

8.19.3.1.a. POPULATION:

Entry criteria for this study after completion of a washout period (up to 7 days) were essentially the same as those for the majority of PAR studies in this NDA submission, namely: (1) age ≥ 12 years (with the exception of age ≥ 18 in the Netherlands and age ≥ 18 for female subjects in France, [291:13-14, 293:846-847], (2) presence of IgE-mediated hypersensitivity to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 2 years of study entry via the prick testing or intradermal method; or in the absence of a positive skin test, history of chronic, perennial allergy documented by nasal eosinophilia [291:13, 293:846, 848], and (3) sufficient severity of PAR symptoms at both screening and baseline to qualify for study randomization (i.e. nasal rhinorrhea and/or congestion scores each ≥ 2 at both screening and baseline and during 4 of the last 7 days (a.m. or p.m.) just prior to the baseline visit and a total nasal symptom score ≥ 5 at both screening and baseline [291:13, 293:846, 848, 861].

8.19.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1. of Trial I93-221 in the NDA submission [291:12, 293:869]. Subjects were

(Visit 4), 12 (Visit 5), and 26 (Visit 6) of therapy [291:11, 293:847, 853].

At screening, in addition to routine history and physical examination, subjects at study sites 18 and 20 underwent measurement of plasma cortisol levels at 8 a.m. ± 1 hour [291:19, 293:839] as a rough screening method to assess underlying adrenal function in potential study subjects prior to treatment with mometasone.

Subjects entered a washout phase (up to 14 days) between the screening and baseline visit, during which they took no medications except for rescue medication (note: no restrictions outlined in the protocol with regard to the type of rescue medication that could be used by a subject with the exception of corticosteroid use), as prescribed by the principal investigator for relief of intolerable PAR symptoms prior to initiation of the open-label treatment [291:16, 18-20, 293:851-852]. On re-evaluation at the baseline visit, subjects who met all inclusion criteria were assigned to one treatment group, received diary cards to record symptoms reflectively over the previous 12 hours and began therapy with mometasone (initiated at 200 µg qd, with the option to increase (to 400 µg qd) or lower (to 100 µg qd) the dose as necessary to treat PAR symptoms) administered once daily in the a.m. [291:14-16, 847, 293:857, 859]:

(A)	**Mometasone aqueous nasal spray 100, 200 or 400 µg qd** (VARIABLE DOSE)-subjects started treatment with mometasone 200 µg qd

Subjects underwent clinical efficacy and safety evaluation (including nasal exam) during each study visit [291:19-22, 24-27, 293:854-860, 863-865]. While eye examinations to assess glaucoma/cataract formation were not performed in this study, a rough assessment of HPA-axis suppression in mometasone treated subjects at 2 study sites was performed via serial a.m. plasma cortisol measurements at the Screening, Week 12 (Visit 5), and Week 26 (Visit 6) visits (-018 and -020) [291:22, 293, 293:838]. Efficacy evaluation was again based on a 0-3 severity scale [291:23, 293:861] and a 1-5 scale of therapeutic response [291:24, 293:862].

Subjects started mometasone treatment at 200 µg qd but were allowed to lower the medication dose to 100 µg qd if nasal symptoms were well controlled or to increase the dose to 400 µg qd in order to improve control of nasal symptoms [291:14-15, 293:853]. Dose titrations were not to be done more frequently than bi-weekly, and an intermediate dose of 300 µg qd was not allowed [291:14-15, 293:857]. Rescue medication use was allowed throughout the study duration, excluding steroid formulations (nasal, inhaled, etc.)[291:17-18, 293:851-852].

A primary efficacy variable was not defined in this study. Supplementary efficacy variables consisted of: (1) physician and (2) subject evaluations of overall condition and (3) physician and (4) subject evaluations of therapeutic response (ITT population) [291:30, 293:866]. Pollen counts were not collected in this study. Rescue medication use was [illegible]

8.19.4. RESULTS

A total of 333 subjects with PAR were randomized into study 193-221, with 2 immediate drop-outs (the subjects did not receive any study drug)[291:32], leaving 331 subjects for the ITT population all of whom received mometasone treatment by virtue of the study design [273:36]. The majority of subjects had PAR; only 2 subjects had a diagnosis of non-allergic rhinitis with eosinophilia (NARES) [291:32]. The attrition rate for study subjects by Week 26 of study 193-221 was approximately 9% (30 dropouts out of 330 subjects) [291:149], an acceptable value.

The treatment groups in this study were comparable with regard to demographic and disease characteristics [291:33]. The majority of mometasone treated subjects were Caucasian, however a sizeable proportion of study subjects (36%) were Hispanic. The distribution of male and female subjects was approximately equal. Approximately 29% study subjects had SAR in addition to PAR.

Analysis of the efficacy variables for the ITT population showed that overall, subjects demonstrated an improvement in symptoms which was maintained for the study duration. For the physician's evaluation of the overall condition of PAR, subjects demonstrated an improvement by Week 4 (Visit 3) of the study (as supported by the majority of subjects having 'mild' PAR symptoms) and this improvement was maintained through the Week 26 visit [291:37-38, 149, 174]. Subjects' self-evaluation of the overall condition of PAR was very similar to that of the physician evaluation; namely that improvement in symptoms was noted by Week 4 of the study (supported by the majority of subjects rating their overall PAR condition as 'mild') and was maintained throughout the study duration [291:39, 183, 206]. In fact, PAR symptom scores for the pooled ITT population were identical between subject and physician rated symptoms. Both of these findings support maintenance of a therapeutic effect for mometasone throughout the open-treatment period. Physician evaluation of subjects' therapeutic response to treatment (1-5 scale) indicated that mometasone treated subjects experienced marked relief in PAR symptoms starting at Week 4 of the study (with concomitant decrease in PAR symptom scores) [291:40-41, 215], which continued throughout the open-treatment period, again providing evidence of maintenance of a therapeutic effect throughout the study duration [291:239]. Subjects' evaluation of therapeutic response, again, was almost identical in terms of symptom scores to the physician evaluation of subjects' therapeutic response with the majority of study subjects reporting marked relief in PAR symptoms by Week 4 of treatment [291:42, 246, 270]. Again, this response was maintained for the study duration.

Regarding the dose distribution for mometasone treated subjects at the time of the last dose in this study, 59/331 (17.8%) of subjects received mometasone 100 µg qd, 211/331 (63.7%) of subjects received mometasone 200 µg qd, and 61/331 (18.4%) of subjects received mometasone 400 µg qd [293:785] The majority of subjects either remained at the initial 200 µg qd dose

and maintained that dosage level for the remainder of the study (17.5% were titrated upwards to 400 µg qd and 17.5% were titrated downwards to 100 µg qd) [293:786]. The remaining 7.9% of subjects changed their mometasone dose more than once during the study [293:786]. Similar to other 'variable dose' mometasone studies (e.g. C93-014, I93-018) these data suggest that the most effective dose of mometasone for the control of PAR symptoms was 200 µg qd. A gradual increase in dose of mometasone over the course of study I93-221 was not observed.

While this trial was uncontrolled and hence not designed to provide enough power to conduct inferences on efficacy, results of these supplementary analyses nonetheless provide supportive information that mometasone is effective in the treatment of symptoms of PAR. Results of the 4 efficacy variables for the 2 mometasone treatment groups are summarized in Table I. below.

Table I. Efficacy Variables of PAR and Treatment with Mometasone (100, 200, or 400 µg qd) (ITT Population), [291:149, 174, 183, 206, 215, 239, 246, 270]

EFFICACY VARIABLE		Improvement in PAR symptoms throughout study duration: Mometasone 100-400 µg qd: (Yes/No)
1	Physician's evaluation of subject overall PAR condition compared to baseline	Yes
2	Subject self evaluation of overall PAR condition compared to baseline	Yes
3	Physician evaluated response to Rx compared to baseline	Yes
4	Subject self-evaluated response to Rx compared to baseline	Yes

sx=Symptom, Rx=Treatment, ITT=Intent-to-treat
Statistical analysis for between group differences performed using 2-way ANOVA
NOTE The majority of subjects received mometasone 200 µg qd for the duration of the study

8.19.4.3. ADVERSE EVENTS:

The safety analysis was based on 331 subjects in the ITT population all of whom received mometasone treatment. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical exam (including nasal exam), and clinical laboratory tests relative to baseline (including a.m. plasma cortisol levels at two designated centers in 37 subjects) [291:19-27].

Adverse events were similar to those noted in other SAR and PAR studies of mometasone. Overall, adverse events were reported in 78% of mometasone treated subjects [291:278].

Headache was the most common adverse event, reported in 36% of

(reported in 27% of subjects [291:284, 295:2163-2194], pharyngitis (15% of mometasone subjects)[291:285, 295:2281-2299], and epistaxis (13% of mometasone subjects) [291:284, 295:2245-2265]. In this study one case of decreased plasma glucocorticoid (1% incidence, subject I93-221-019, #005 [292:391]) and one case of hypothyroidism (1% incidence, subject I93-221-010, #013 [295:2052]) were reported with mometasone use [291:280]. In the subject (a 12 year old male receiving mometasone 200 µg qd) with a reported decreased a.m. plasma cortisol on week 12 of the study (to 104.0 µg/dL, normal range: 219.7-367.8 µg/dL), mometasone treatment was nonetheless continued and follow-up a.m. plasma cortisol levels approximately 3 and 12 weeks later were within normal limits (319.8 and 272.2 µg/dL, respectively) [292:391, 295:2051].

Regarding serious adverse events, one case of spontaneous abortion occurred approximately two weeks after a subject discontinued the study (after 9 weeks of treatment with mometasone) but was felt by the principal investigator to be unrelated to study medication [291:57, 292:391]. One death was reported, however was felt to be unrelated to study drug treatment with 200 µg qd of mometasone (subject I93-221-05, #001, a 67 year old male developed edema and renal dysfunction, and died secondary to arrhythmia and myocardial infarction approximately 7.5 months after the start of the trial) [291:57, 292:390].

There did not appear to be a dose relationship in the overall incidence of ADRs for the different doses of mometasone noted for the study duration (overall incidence of ADRs for mometasone 100 µg qd group=60%, overall incidence of ADRs for mometasone 200 µg qd group=71%, overall incidence of ADRs for mometasone 400 µg qd group=66% [291:62, 292:371]). ADRs which exhibited a mild dose response for the varying doses of mometasone were viral infection (13%, 20%, and 21% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose, respectively [292:382]), pharyngitis (6%, 10%, and 14% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose, respectively [292:384]), epistaxis (8%, 10%, and 10% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose, respectively [292:383]), and myalgia (1%, 2%, and 5% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose of, respectively) [292:379]. A similar increased incidence in epistaxis and pharyngitis with increased mometasone dose was likewise noted in the other variable dose mometasone studies (e.g. I93-018). Nonetheless, the relatively small number of study subjects in the variable dose mometasone groups, especially the 100 µg (n=83) and 400 µg (n=86) groups, precludes any definitive conclusion regarding the mometasone dose-relationship of adverse events [292:371].

There were no reports of nasal septal perforation in any mometasone treated subjects, however nasal ulcers were reported in 7 subjects total (4 subjects at Visit 3 (Week 4 post-initiation of treatment) [295:2329, 296:3269, 3272, 297:3318] and 3 subjects at Visit 5 (Week 12 post-initiation of treatment)) [296:3274, 3279, 3285].

In terms of infection, viral infection was the second most frequently

was one report of oral candidiasis (Week 26 of treatment) [291:284, 295:2197] and one report of nasal candidiasis (Week 12 of treatment) [296:3314] in mometasone treated subjects.

A total of 12 subjects discontinued treatment because of adverse events [291:56]. The most common reason for discontinuation that was considered 'possibly or related' to study medication involved headache, epistaxis, or coughing. Otherwise, most subject discontinuations due to ADRs were considered unrelated to treatment by the principal investigator.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted with the exception of several reports of elevated LFTs. Three subjects developed elevated LFTs (SGOT, SGPT, or total bilirubin) which were not clearly related to study medication [291:59, 292:685-686]. Two subjects receiving mometasone (subject I93-221-02, #014 and #018) developed an increase in serum alkaline phosphatase to the 300-400 IU/L range during Visits 5 and 6 (normal alkaline phosphatase range: 68-160 IU/L) which were not commented on the in the investigator's case report form [291:59] and 1 additional subject (I93-221-01, #001) [295:2106] developed an increase in serum alkaline phosphatase which was not ascribed a laboratory value or described in the abnormal laboratory reports section of the NDA. From the data provided in the NDA submission, it cannot be concluded that these increases in alkaline phosphatase were not related to mometasone treatment. In the latter case, the subject was a 12 year old female whose laboratory abnormality was felt by the principal investigator to be possibly related to treatment.

No significant change in the mean a.m. plasma cortisol level for the endpoint visit as compared to baseline was detected for pooled subjects from the study sites 18 and 20 (n=37) [292:416], however minor changes consisting of: (1) a small increase (17-18% increase from baseline (screening) value) in a.m. plasma cortisol levels at endpoint were detected in subjects age 12-17 years of age (n=2) [292:449] and in female subjects (n=20) [292:545] and (2) a small decrease (~ 13% increase from baseline (screening) value) in a.m. plasma cortisol levels at endpoint were detected in male subjects (n=17) [292:577]. These discrepancies may represent chance findings and because of the small number of subjects, no conclusions can be drawn regarding these observations. Individual line listings of subject a.m. plasma cortisol levels were not submitted by the Sponsor. Flag shift distributions of laboratory values failed to reveal any significant patterns of change, although for a.m. plasma cortisol levels (n=37), most subject flag shifts from the baseline to endpoint visit were in the normal to the high normal range [292:674]. Aside from the discussion above, adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects <18 or > 65 years of age was too small to draw meaningful conclusions.

8.19.5. CONCLUSIONS:

1. The results of this study support the safety of mometasone 100 µg, 200 µg and 400 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 26 weeks (6 months) in subjects with PAR. The use of a.m. cortisol levels to test HPA-axis suppression did not reveal any signals based on the pooled data provided by the Sponsor. Nonetheless, two shortcomings of the methodology used: (1) the inability evaluate subjects' individual responses with treatment in order to screen for subject 'outliers' and (2) use of a crude test of HPA-axis suppression, limit the inferences that can be made from these results.
2. While study 193-221 was not specifically designed to evaluate efficacy or assess the impact of rescue medication use among the 3 different mometasone dosage groups, assessment of subject overall condition and response to treatment with mometasone for up to 26 weeks (by study subjects and their respective physicians), supports the efficacy of mometasone in doses of 100-400 µg qd for the treatment and maintenance treatment of symptoms of PAR.
3. The majority of subjects, given the opportunity to titrate the dose of mometasone up to 400 µg qd, nonetheless chose to remain on a dose of 200 µg qd of mometasone. Some subjects were eventually able to titrate down the dose of medication to 100 µg qd. Based on these findings, the most appropriate starting dose and maintenance dose of mometasone for the treatment of PAR would be 200 µg qd.

8.20 Trial I94-078. Efficacy and Safety of Mometasone Furoate Nasal Spray vs. Budesonide Aqueous Nasal Spray, and vs. Placebo in the Treatment of Perennial Allergic Rhinitis (PAR).

Principal Investigator: None (Multi-center study)

Participating Centers: 25 centers in North, Central, and South America, and in Western Europe, Africa, and Australia.

8.20.1. OBJECTIVE:

1. To investigate the safety and efficacy of mometasone furoate aqueous nasal spray 200 µg qd in the treatment of symptoms of perennial allergic rhinitis (PAR).

8.20.2. STUDY DESIGN:

The study was a phase III, randomized, multi-center, double-blind, double-dummy, active- and placebo-controlled, parallel group study to determine the safety and efficacy of mometasone furoate 200 µg administered intranasally once daily (qd), vs. the active control, budesonide (Rhinocort Aqua) 400 µg administered once daily (qd), and vs. placebo for a total of 12 weeks for the treatment of perennial allergic rhinitis (plus 1 additional week of observation at the end of the double-blind treatment period (the 'offset' or Week 13 visit) [A51.1:15, A51.1:16, 38, A51.4:1062].

8.20.3. PROTOCOL:

8.20.3.1.a. POPULATION:

Entry criteria for this study were very similar to those for all other PAR studies, namely: (1) age ≥ 12 years (with the exception of age ≥ 18 years at sites -03 and -05 in Canada, site -08 in Denmark, site -021 in Norway, and site -022 in South Africa) [290:3, 20-21, 23, A51.1:16, 18, A51.4:1061, 1063], (2) presence of IgE-mediated hypersensitivity to a relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 2 years of study entry via the prick testing or intradermal method; or in the absence of a positive skin test, a diagnosed or suspected history of non-allergic rhinitis with eosinophilia syndrome (NARES) which had been corroborated by nasal cytology demonstrating eosinophilia [290:21, 23, 32, A51.1:16, 18, A51.4:1061, 1064, 1075-1076], and (3) presence of PAR symptoms of sufficient severity (nasal rhinorrhea and/or congestion scores at least moderate in severity (≥ 2), a total symptom score ≥ 5 at both screening and baseline, and rhinorrhea and/or congestion scores ≥ 2 during 4 of the last 7 days prior to the baseline visit), in order to begin study drug treatment [290:3-4, 21, 23, 42, A51.1:18, 28, 38, A51.4:1061-1062, 1064, 1078].

8.21.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1 of Trial I94-078 and in an amendment (Volumes A51.1-A51.4, submitted by the Sponsor, Schering Plough, Inc. to the Pulmonary Division, HFD-570 on 04/16/97) to the NDA submission [290:55, A51.1:17, A51.4:1102], and is similar to the study design of PAR studies I92-293 and I94-079. Subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Day 8 (Visit 3), 15 (Visit 4), 29 (Visit 5), and Weeks 8 (=Day 57, Visit 6), and 12 (=Day 85, Visit 7) of therapy [290:4, 29, 31-33, A51.1:16, 38, A51.4:1062, 1072, 1076-1077]. Subjects were also evaluated at Week 13 at the end of the 'off-set' period (Visit 8) when subjects were no longer receiving double-blind medication in order to assess duration of effect of each treatment in decreasing PAR symptoms [290:29, A51.1:16, 38, A51.4:1062]. Day 1 was designated as the start of treatment date [A51.1:16, 38]. Medication restrictions consisted of those previously discussed for the mometasone SAR and PAR studies [290:25-28, A51.1:24-26, A51.4:1067-1070], although subjects were allowed to use a rescue medication (loratadine, up to 10 mg po qd maximum dose) for intolerable PAR symptoms starting with the screening visit (the 7-14 day 'run-in' phase) and continuing for the duration of the study, including the offset period [290:31, 33, 45, A51.1:22, 28, A51.4:1063, 1069, 1073, 1077, 1081, 1091].

Subjects who met all inclusion criteria were randomized to one of the following 3 treatment groups, received diary cards to record symptoms reflectively over the previous 12 hours (upon awakening, before the a.m. dose and before retiring (p.m. recording)) and began therapy with study drug every a.m. and p.m. (4 bottles utilized for this double dummy design--each active drug had a matching placebo) [290:21-22, 34-37, A51.1:20-21, A51.4:1062-1063, 1071-1072, 1079-1081]:

(A) Mometasone aqueous nasal spray 200 µg qd		
a.m. dosing:	Bottle 1: Mometsone 200 µg	Bottle 2: Budesonide Placebo
p.m. dosing	NONE	
(B) Budesonide nasal spray (Rhinocort Aqua) 400 µg qd		
a.m. dosing:	Bottle 1: Mometasone Placebo	Bottle 2: Budesonide 400 µg
p.m. dosing:	NONE	
(C) Placebo (0 µg qd)		
a.m. dosing:	Bottle 1: Mometasone placebo	Bottle 2: Budesonide Placebo
p.m. dosing:	NONE	

Subjects underwent clinical efficacy and safety evaluation (including nasal exam on Visits 2 (baseline) and 7 (Week 12) during each study visit [290:22, 37

41, 46-48, A51.1:29-36, 47-48, A51.4:1077-1094]. Efficacy evaluation was again based on a 0-3 severity scale [290:42, A51.1:31-32, A51.4:1087], a 0-3 scale of the overall condition of PAR [290:42-43, A51.1:32, A51.4:1088], and a 1-5 scale of therapeutic response [290:43, A51.1:33, A51.4:1088-1089].

The primary efficacy variable [290:22, 50, A51.1:41, 45, A51.4:1097-1098] was defined as: the mean change from baseline (the mean of the a.m. and p.m. baseline scores and the a.m. and p.m. scores from the 7 prior consecutive days) in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject diaries) where the:

Mean Change in Total nasal symptom score= 15 Day Interval Score[(Nasal a.m. average $_{\text{Day 1-15}}$) + (Nasal p.m. average$_{\text{Day 1-15}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

and the **total nasal symptom score=[discharge+ stuffiness+ sneezing+ itching].**

Secondary efficacy variables consisted of the following [290:51, A51.1:46, A51.4:1098]:

(1) The mean change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30 (a.m. and p.m. combined), Days 31-45, Days 46-60, Days 61-75, and Days 76-90, [A51.1:46]:

Mean Change in Total nasal symptom score$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$**=Day 16-30 (or Day 31-45, Day 46-60, Day 61-75, Day 76-90) Interval Score**[(Nasal a.m. average $_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$) + (Nasal p.m. average$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

(2) Endpoint total nasal symptom score (a.m. and p.m. combined): Endpoint score defined as the last available post-baseline value for each study subject, pooled across the 24 participating centers [A51.1:46].

(3) Mean change in the total nasal symptom score for the 'offset' (Week 13) visit [A51.1:46].

(4) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, endpoint visit, and the offset visit) [A51.1:46].

(5) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, endpoint visit, and the offset visit) [A51.1:46].

(6) Physician's evaluation of total nasal symptoms (for the Baseline visit, Day

[A51.1:46]

(7) Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit) [A51.1:46].

(8) Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit) [A51.1:46].

(9) Subject's self-evaluation of overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [A51.1:46].

(10) Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [A51.1:46].

(11) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [A51.1:46].

(12) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [A51.1:46].

(13) The proportion of 'symptom-free' days (i.e. total nasal symptom=0) during the entire treatment period (i.e. excluding baseline visit) [A51.1:46].

Pollen counts were not collected in this study. Rescue medication use between the 3 treatment groups was not analyzed statistically but a frequency of rescue medication for all 3 treatment groups was tabulated, thus providing a general overview of differences in rescue medication use. Centers with 15 or fewer efficacy evaluable subjects were combined as a single large center for the purpose of efficacy analysis [A51.1:42]. Furthermore, since treatment-by-center interactions were not statistically significant (p=0.11), pooling of data across centers to obtain an overall assessment of treatment differences was considered acceptable [A51.1:44].

8.20.4. RESULTS

A total of 523 subjects with PAR were randomized into study I94-078, with no immediate drop-outs, leaving 523 subjects evaluable in the ITT population [A51.1:49]. One hundred and seventy one (171) subjects in the ITT population received mometasone treatment, 179 subjects received budesonide, and 173 subjects received placebo [A51.1:49]. An additional 60 subjects were excluded from efficacy analyses because of various protocol violations, leaving 463 subjects in the efficacy evaluable population [A51.1:43, 49].

The treatment groups in this study were comparable with regard to demographic and disease characteristics [A51.1:50]. Again, for all 3 treatment groups, the majority of subjects were Caucasian, although approximately 32-35%

Approximately 1.5-2 times the number of female than male subjects per treatment group were enrolled in this study [A51.1:51]. Approximately 25% of the subjects had SAR in addition to PAR and the majority did not have the NARES syndrome (15 subjects total were diagnosed with NARES; 4 subjects in the mometasone treatment group, 7 subjects in the budesonide group, and 4 in the placebo group) [A51.1:53, 206-208]. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a statistically significant difference among the 3 treatment groups with the majority of subjects in all 3 groups having 'moderate' PAR symptoms at baseline [A51.1:53]. Numerically, a slightly greater percentage of 'severe' PAR subjects comprised the budesonide and placebo treatment groups [A51.1:53].

Analysis of the primary efficacy variable for the ITT population demonstrated greater efficacy of both active treatment groups in decreasing total nasal symptoms for the day 1-15 interval, compared with placebo. The raw total nasal symptom score/unit change for the mometasone treatment group was 4.1 (with a -2.4 unit decrease in total nasal symptoms from baseline or a -34% change), compared with a raw total nasal symptom score of 4.9 (-1.6 unit decrease in total nasal symptoms or -23% change) for the placebo group ($p<.01$) [A51.2:310], and a raw total nasal symptom score of 3.8 (-2.7 unit decrease in total nasal symptoms or -39% change) for the budesonide treatment group ($p<.01$ for budesonide vs. placebo) [A51.2:310]. No statistically significant difference was noted between the mometasone and budesonide treatment groups, although a greater numerical response in total nasal symptoms was noted in budesonide treated subjects. Furthermore, no significant difference was noted between the a.m. and p.m. total nasal symptom scores or change in scores in the mometasone treatment group for the day 1-15 interval (mometasone group a.m. raw total nasal symptom score/change in raw score=4.2/-2.5 unit change vs. mometasone group p.m. raw total nasal symptom score/change in raw score=4.1/-2.3 unit change), again supporting once daily dosing of mometasone [A51.2:337, 339]. Additionally, no significant difference in the primary efficacy variable was noted between the ITT and efficacy evaluable population [A51.2:310, 344].

A summary of results for the primary and secondary efficacy variables is summarized in Table I. and Table II. below and overall, support the efficacy of mometasone in decreasing the symptoms of PAR. While no statistically significant difference was demonstrable between mometasone and budesonide treatment, in general, budesonide treated subjects demonstrated greater numerical decreases in their respective symptom scores than did mometasone treated subjects.

No significant difference in clinical efficacy was noted based on age or gender, with the exception that ITT female subjects in the 18-64 year age range for the 2 active treatment groups showed a greater mean reduction in the total nasal symptom scores from baseline than did ITT male subjects or ITT female subjects 12-17 years or >64 years of age [A51.2:350]. Nonetheless, the number of subjects comprising the sub-groups were too small (i.e. age 12-17 or >64 years) to make

group analyses were not performed in this study.

Analysis of subject and physician-rated individual nasal and non-nasal symptoms are summarized in Table III. below. Results of this study are similar to previous PAR studies; namely, that mometasone treatment was more effective in decreasing the nasal symptoms of PAR than non-nasal symptoms. Interestingly, in this PAR study (similar to study 194-079) mometasone treatment was noted to have a statistically significant effect on nasal congestion--a symptom generally shown to be minimally affected by mometasone treatment in the other studies reviewed in this NDA submission. Mometasone treatment likewise demonstrated a very small numerical response in decreasing the individual non-nasal symptoms of PAR (Table III.), however these changes were not always found to be statistically significant as compared with placebo. Analysis of the 'offset' visit indicates that for nasal symptoms, the mometasone subjects, while not always statistically significant, did demonstrate a greater decrease in PAR symptoms than did placebo treated subjects one week after discontinuation of treatment. These findings suggest that mometasone (also budesonide) continues to provide some relief of PAR symptoms 1 week after discontinuation of medication and suggests that mometasone has a somewhat prolonged duration of action once subjects reach steady state dosing. Also, while numerically small, mometasone treatment increased the mean proportion of 'symptom-free' days for the entire study duration to 13.1 days, compared to 5.2 'symptom-free' days for placebo treated subjects ($p<.01$, no significant difference noted between the mometasone and budesonide treatment groups) [A51.2:341].

Analysis of rescue medication use (ITT population) in the 3 treatment groups revealed lower rates of rescue medication use in the two active drug groups (30% of mometasone subjects, 31% of budesonide subjects, and 34% of placebo subjects used rescue medication > 1 time during the study) [A51.2:305]. A greater percentage of placebo group subjects tended to use rescue medication > 6 times throughout the study duration than did subjects in either of the 2 active drug groups [A51.2:305].

Table I. Primary Efficacy Variable of PAR and Treatment with Mometasone (ITT Population) [A51.2.310]

1° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1	Subject evaluated mean Δ in Total Nasal Sx Score$_{DAY\ 1-15}$	*Yes

sx=Symptom

* Note Statistically significant response for 1° efficacy variable in the efficacy evaluable population (ITT data not provided) carried by 2 of the 25 distinct study centers (i.e. 23/25 centers had a statistically non-significant response although 2 of these 23 centers were close to being statistically significant) [A51.2.311-335] Centers 001, 002, 008, 015, and 023 were combined into a single large center for analysis because each center had ≤ 10 subjects [A51.1.65]

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Table II. Secondary Efficacy Variables of PAR and Treatment with Mometasone (ITT Population), [A51.2:310, 341, 354, 383, 387, 390, 392, 415-416, 452-453, 489-490, 516-517]

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1	Subject evaluated mean Δ in Total Nasal Sx Score DAY1-15 DAY 16-30 DAY 31-45 DAY 46-60 DAY 61-75 DAY 76-90	Yes:	All study intervals.	
2	Subject evaluated mean Δ in Endpoint Total Nasal Sx Score	Yes:	Endpoint visit.	
3	Subject evaluated mean Δ in Offset Total Nasal Sx Score	Yes:	Offset visit.	
4	Subject evaluated mean Δ in Total Sx Score DAY 1-15 DAY16-30 DAY 31-45 DAY 46-60 DAY 61-75 DAY 76-90 Endpoint Visit, Offset Visit	Yes: No:	Day 1-15, 16-30, 61-75, 76-90, Endpoint visit. Day 31-45, 46-60, Offset visit.	
5	Subject evaluated mean Δ in Total non-nasal Sx Score DAY 1-15 DAY16-30 DAY 31-45 DAY 46-60 DAY 61-75 DAY 76-90 Endpoint Visit, Offset Visit	No:	All study intervals.	
6	Physician Evaluated Total Nasal Sx Score	Yes No:	Study visits: Study visits:	Day 8, 15, 29, Week 12, Endpoint and Offset visit. Week 8.
7	Physician Evaluated Total Sx Score	Yes: No:	Study visit: Study visits:	Day 8, 15, Week 12, Endpoint visit. Day 29, Week 8, Offset visit.
8	Physician Evaluated Total non-nasal Sx Score	No:	All study visits	
9	Subject overall condition evaluation	Yes: No:	Study visits: Study visits:	Day 8, 15, 29, Week 12, Endpoint visit, Offset visit. Week 8.
10	Physician overall condition evaluation	Yes: No:	Study visits: Study visits:	Day 29, Week 8, Week 12, Endpoint, visit, Offset visit. Day 8, 15.
11	Subject overall Rx Response evaluation	Yes:	Study visit:	All study visits.
12	Physician overall Rx Response evaluation	Yes:	Study visits:	All study visits.
13	Proportion of symptom-free days for the entire treatment period (Total nasal sx score=0)	Yes		

Δ=Change, Sx=Symptom, Rx=Treatment Note: Analyses are for a.m. and p.m. combined symptom scores. ITT=Intent-to-Treat Population.

Table III. Change in Individual PAR Symptoms (Subject and Physician Evaluated, a.m. and p.m. combined) with Mometasone Treatment (ITT Population).
[A51.2:395-398, 400-403, 405-408, 410-413]

PAR SYMPTOM	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
Subject Evaluated Individual Nasal Sx Score	Yes:	Rhinorrhea:	Day 1-15, 16-30, 31-45, 61-75, 76-90, Endpoint visit, Offset visit.
		Congestion:	All study intervals.
		Sneezing:	Day 1-15, 16-30, 31-45, 46-60, 61-75, 76-90, Endpoint visit.
		Nasal Itch:	Day 1-15, 16-30, 76-90, Endpoint visit.
	No:	Rhinorrhea:	Day 46-60.
		Sneezing:	Offset visit.
		Nasal Itch:	Day 31-45, 46-60, 61-75, Offset visit.
Physician Evaluated Individual Nasal Sx Score	Yes:	Rhinorrhea:	Week 12, Endpoint visit.
		Congestion:	All study intervals.
		Sneezing:	Week 12, Endpoint visit.
		Nasal Itch:	Day 8, 15, Week 8, Week 12, Endpoint visit, Offset visit.
	No:	Rhinorrhea:	Day 8, 15, 29, Week 8, Offset visit.
		Sneezing:	Day 8, 15, 29, Week 8, Offset visit.
		Nasal Itch:	Day 29.
Subject Evaluated individual non-nasal Sx Score	Yes:	Ear/palate Itch:	Day 16-30.
	No:	Eye tear:	All study intervals.
		Eye redness:	All study intervals.
		Eye Itch:	All study intervals.
		Ear/palate Itch:	Day 1-15, 31-45, 46-60, 61-75, 76-90, Endpoint visit, Offset visit.
Physician Evaluated individual non-nasal Sx Score	Yes:	Ear/Palate Itch:	Day 15, Week 12, Endpoint visit.
	No:	Eye tear:	All study visits.
		Eye redness:	All study visits.
		Eye Itch:	All study visits.
		Ear/Palate Itch:	Day 8, 29, Week 8, Offset visit.

Sx=Symptom

8.20.4.3. ADVERSE EVENTS:

The safety analysis was based on 523 subjects in the ITT population: 171 subjects were treated with mometasone 200 µg qd, 179 subjects were treated with with budesonide 200 µg qd, and 173 subjects were treated with placebo [A51.1:78]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, and nasal examinations, and clinical laboratory tests relative to baseline [A51.1:33-36, A51.4:1076-1086].

Adverse events were again similar for all three treatment groups, with headache, closely followed by viral infection being the most frequently reported treatment-related adverse events. Overall, adverse events were reported in 61% of subjects in the mometasone group, 66% of subjects in the budesonide treatment group, and 53% of subjects in the placebo group [A51.1:78-79, A51.2:544]. Headache was reported in 18% of mometasone subjects and 19% of budesonide subjects, compared to 21% of placebo subjects [A51.1:80, A51.2:545]. Viral infection was reported in 15% of subjects in the mometasone group, 20% of subjects in the budesonide group, and 18% of subjects in the placebo group [A51.1:81, A51.2:550]. Reported next in frequency were epistaxis and pharyngitis; with 13% of subjects in the mometasone group, 16% of subjects in the budesonide group, and 7% of placebo subjects reporting epistaxis [A51.1:81, A51.2:551], and 9% of subjects in the mometasone group, 13% of subjects in the budesonide group, and 11% of placebo subjects reporting pharyngitis, respectively [A51.1:81, A51.2:551]. In terms of the demographic distributions of adverse events, headache and pharyngitis were noted to be reported more frequently in females than males. Headache, epistaxis, and pharyngitis were less frequent in subjects < 18 years of age (n=74) than in subjects 18-64 years of age. Viral infection, epistaxis and pharyngitis were more frequent in Caucasians than in Hispanics [51.2:573-633]. While noted, none of these differences were likely clinically significant.

There were no reports of nasal septal perforation in any of the 3 treatment groups but again, several subjects in both active drug treatments were noted to have nasal ulcerations post-treatment (individual subject line listings of nasal examinations were not submitted with the study report for I94-078). No assessment of glaucoma/cataract formation or suppression of the HPA-axis was performed in this PAR study. No deaths were reported in any of the 3 treatment groups but one case of spontaneous abortion in a 32 year old female > 30 days after completion of the study was reported in a mometasone treatment subject (subject I94-078-21, #019) [290:10, A51.1:95, A51.3:636]. This event was felt not to be related to study medication by the principal investigator, as the subject was using an intrauterine device (IUD) as a contraceptive throughout the study and at the time of conception which may have contributed to and/or resulted in spontaneous abortion.

In terms of infection, viral infection (see above) was reported as the most frequent ADR in all 3 treatment groups in this study. Herpes simplex infection

or placebo group) [A51.2:550]. No subjects in either of the three treatment groups were reported to have nasal or oral candidiasis on any clinic visits [A51.2:550].

A total of 11 subjects discontinued treatment because of adverse events (1 subject in the mometasone group, 5 subjects in the budesonide group, and 5 subjects in the placebo group) [A51.1:93]. The one mometasone subject (subject I94-078-02, #010) discontinued the study because of a severe facial rash which was felt to be 'probably' related to study drug [A51.1:94, 295].

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 3 treatment groups with the exception of one report of an increased SGPT (from 12 U/L at screening to 92 U/L by Week 12 (Visit 7), subject I94-078-07 , #001) [A51.1:97, A51.3:640] and one report of a decrease in the WBC (from 4.04 x 10^3/mm^3 at screening to 2.5 x 10^3/mm^3 by Week 12, subject I94-078-09, #008) [A51.1:97, A51.3:640] in mometasone treated subjects. Flag shift distributions of laboratory values failed to reveal any significant patterns of change in any of the 3 treatment groups or for any of the demographic sub-groups.

8.20.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 12 weeks (plus 1 week off medication) in subjects with PAR.
2. In terms of individual PAR symptoms, mometasone treatment demonstrated a statistically significant effect in decreasing the PAR symptoms of rhinorrhea, nasal congestion, sneezing, and nasal itch for most study visits, as compared with placebo. Mometasone did not show a statistically significant response in decreasing the non-nasal symptoms of PAR although a small degree of improvement was demonstrated in mometasone treated subjects, as compared with placebo for all 4 non-nasal symptoms.
3. Mometasone treatment demonstrated adequate duration of effect in treating PAR symptoms over 24 hours, supportive of once a day dosing. Mometasone treatment also appeared to continue to provide efficacy in the treatment of PAR symptoms for at least one week after discontinuation of treatment.

9.0. INTEGRATED SUMMARY OF EFFICACY

The clinical program for mometasone furoate (Sch 32088) nasal spray evaluated efficacy for 3 major clinical indications: (1) seasonal allergic rhinitis (SAR), (2) prophylaxis of seasonal allergic rhinitis, and (3) perennial allergic rhinitis (PAR), in adult subjects ≥ 12 years of age. A total of 20 clinical studies were reviewed for efficacy in NDA 20-762.

9.1. Summary of Efficacy Studies for each indication reviewed in NDA 20-762:

(1) The database of efficacy for seasonal allergic rhinitis (SAR) was generated from 8 studies (U.S. and international) in NDA 20-762, which consisted of the following:

(A) Four (4) phase III randomized, multi-center, double-blinded, active- and placebo-controlled trials of mometasone 200 µg qd in adult SAR subjects at least 2 weeks in duration (studies C93-013 (pivotal SAR study), I92-200, I94-001, and C94-145).

(B) One (1) phase II, randomized, multi-center, placebo-controlled, parallel group, dose ranging study of mometasone nasal spray (50, 100, 200, and 800 µg qd) vs. placebo for 2 weeks for the treatment of adult SAR (study C92-011).

(C) One (1) phase III randomized, double-blinded, placebo-controlled, parallel group, two-arm mometasone onset of action study of mometasone 200 µg qd vs. placebo for the treatment of adult SAR (study C93-184).

(D) Two phase II, randomized, double-blinded, placebo-controlled, parallel group nasal provocation studies with allergens investigating mometasone pre-treatment on early and late phase allergic inflammation in adult subjects with SAR (studies C93-[illegible] and I94-139).

(2) For prophylaxis of seasonal allergic rhinitis in adult subjects ≥ 12 years of age, two (2) studies (one U.S. (study C93-215, the pivotal prophylaxis study) and the other, an international (study I93-133)) were submitted in NDA 20-762 and reviewed. Both studies were randomized, multi-center, active- and placebo-controlled.

(3) The efficacy database for perennial allergic rhinitis (PAR) in adult subjects ≥ 12 years of age consisted of a total 10 studies, 9 of which were submitted to NDA 20-762 at the time of filing (October 1, 1996). Four (4) of these 10 studies were randomized, placebo-controlled trials (studies C92-280 (pivotal PAR study), I92-293, I94-079, and I94-078). Another 4 studies (C93-014, I93-018, I93-180, and C94-052) were active- but not placebo

controlled and one (1) study (I93-221) was a 6 month open label, noncomparative (no placebo group) study. One additional study (study C94-092) was a placebo controlled study that assessed the response of PAR symptoms in elderly subjects (defined as age ≥ 65 years).

The general trial design and subject accounting for the intent-to-treat (ITT) population (the population generally used in this review to assess efficacy, in addition to safety) for the 20 studies reviewed in the efficacy database for mometasone furoate nasal spray is summarized below in Tables I.-III.

Table I. Seasonal Allergic Rhinitis (SAR) Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)	
Phase III, active- and placebo controlled	C93-013 (Pivotal SAR),	4 weeks	C93-013: Mometasone (200 µg qd)	112
			Beclomethasone (168 µg bid)	116
			Placebo (0 µg qd)	116
	I92-200	• • •	I92-200: Mometasone (100 µg qd)	126
			Mometasone (200 µg qd)	125
			Beclomethasone (200 µg bid)	125
			Placebo (0 µg qd)	121
Phase III, active- and placebo controlled	I94-001,	2 weeks	I94-001: Mometasone (200 µg qd)	104
			Fluticasone (200 µg qd)	104
			Placebo (0 µg qd)	103
	C94-145	• • •	C94-145: Mometasone (200 µg qd)	176
			Mometasone (200 µg qd) + Loratadine (10 mg po qd)	169
			Loratadine (10 mg po qd)	181
			Placebo	179
Phase III, dose ranging, placebo controlled	C92-011	4 weeks	C92-011: Mometasone (50 µg qd)	95
			Mometasone (100 µg qd)	95
			Mometasone (200 µg qd)	95
			Mometasone (800 µg qd)	95
			Placebo (0 µg qd)	95
Phase III, onset of action, placebo controlled	C93-184	2 weeks	C93-184: Mometasone (200 µg qd)	101
			Placebo (0 µg qd)	99
Phase III, placebo controlled, 2-period crossover, nasal provocation studies.	C93-193	2 weeks	C93-193: Mometasone (200 µg qd)	20
			Placebo (0 µg qd)	21
	I94-139	• • •	I94-139: Mometasone (200 µg qd)	24
			Placebo (0 µg qd)	24

Table II. Prophylaxis of SAR Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)
placebo controlled	(Pivotal Prophylaxis of SAR),	8 weeks total, (4 week prophylaxis period, followed by a 4 week ragweed period assessment)	C93-215 Mometasone (200 µg qd) 116 Beclomethasone (168 µg bid) 116 Placebo (0 µg qd) 115
	I93-133		I93-133 Mometasone (200 µg qd) 168 Budesonide (400 µg qd) 172 Placebo (0 µg qd) 173

Table III. Perennial Allergic Rhinitis (PAR) Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)
Phase III active- and placebo controlled	C92-280 (Pivotal PAR),	12 weeks	C92-280 Mometasone (200 µg qd) 164 Beclomethasone (168 µg bid) 163 Placebo (0 µg qd) 163
	I92-293	12 weeks	I92-293 Mometasone (200 µg qd) 143 Beclomethasone (200 µg bid) 146 Placebo (0 µg qd) 138
	I94-079	12 weeks (+ 1 week off treatment offset period)	I94-079 Mometasone (200 µg qd) 181 Fluticasone (200 µg qd) 183 Placebo (0 µg qd) 184
	I94-078	12 weeks (+ 1 week off treatment offset period)	I94-078 Mometasone (200 µg qd) [illegible] Fluticasone (200 µg qd) 179 Placebo (0 µg qd) 173
Phase III active controlled	C93-014 F/U of C92-280	Up to 52 weeks	C93-014 Mometasone (200 µg qd) 100 Mometasone (100 [illegible] 95 Beclomethasone (168 µg bid) 96
	[2]I93-018 (1 yr. F/U of I92-293	Up to 52 weeks (1 year)	C94-145 Mometasone (200 µg qd) [illegible] Mometasone (100-[illegible] 80 Beclomethasone (200 µg bid) 71
	[2]I93-180 (Nasal bx study)	Up to 52 weeks (1 year)	I93-180 Mometasone (200 µg qd) 69 Fluticasone (200 µg qd) 72
	[2]C94-052 (HPA study)	Up to 52 weeks (1 year)	C94-052 Mometasone (200 µg qd) 175 Triamcinolone (220 µg qd) 176
Phase III, placebo controlled [illegible]	[illegible]	12 weeks	C94-032 Mometasone (50 µg [illegible] [illegible] [illegible] 74
Noncomparative (no placebo)	[2]I93-221	26 weeks (6 months)	C93-184 Mometasone (100, 200 or 400 µg qd) 321

[1]Study I94-078 was amended to the original NDA for mometasone

[2]Safety assessment (and not efficacy) was the primary objective of these studies. Hence, these [illegible] were not designed to statistically demonstrate efficacy [illegible]

In summary, greater than 3000 (a total of 3381) mometasone treated subjects (all doses) comprised the ITT population for efficacy evaluation for the 3 clinical indications assessed in NDA 20-762. For the SAR indication, 812 mometasone treated subjects were evaluated in active- and placebo-controlled trials, and of these 812 subjects, 517 received mometasone 200 µg qd. A total of 2[illegible] mometasone treated subjects were evaluated in active- and placebo-controlled trials for the prophylaxis of SAR indication, all of whom were treated with mometasone 200 µg qd. A total of 829 mometasone 200 µg qd treated subjects were evaluated in placebo controlled trials for the PAR indication, and of these 829 mometasone subjects, 659 were evaluated in active- and placebo-controlled trials. Nine hundred and twenty seven (927) mometasone subjects were evaluated in uncontrolled trials for the PAR indication.

9.2. Study Design Issues and Efficacy Results

9.2.1. Seasonal Allergic Rhinitis (SAR)

9.2.1.a. Study Design

The study design of all SAR studies (including the pivotal study C93-013) were overall similar with minor modifications from study to study. Study subjects were to have a history of SAR to aeroallergens (trees, grass, pollen) for at least 2 years (confirmed by skin prick or intradermal skin testing) and were to be symptomatic at the screening and baseline visits. The SAR symptoms assessed in all studies consisted of nasal (rhinorrhea, congestion, sneezing, and nasal itch), non-nasal (eye redness, eye itch, eye tearing, and ear and/or palatal itch), and total (nasal plus non-nasal) SAR symptoms which were rated on a 0-3 (no, mild, moderate and severe) symptom severity scale. Subjects rated their SAR symptoms retrospectively over the previous 12 hours in the a.m. and p.m. (twice daily). Instantaneous symptom scores were not recorded. Additionally, subjects overall condition (rhinitis) and therapeutic response to treatment were rated using a 0-3 and 1-5 point scale, respectively. Rescue medication use was only allowed in 3 of the 4 active- and placebo-controlled trials (C93-013, I92-200, and I94-001). Subjects received study medication for at least 2 weeks total in all SAR studies submitted in NDA 20-762.

The primary efficacy endpoint for 3 of the 4 active- and placebo-controlled trials (C93-013, C94-145, and I94-001) was defined as the subject rated mean change in the total nasal symptom score over the initial 15 day study period for combined a.m. and p.m. scores. Study I92-200 defined the primary efficacy variable as the subject rated mean change in the total nasal symptom score over the first week for combined a.m. and p.m. scores. For the dose-ranging study (C92-011) the primary efficacy variable was prospectively defined as the physician rated mean change in the total nasal symptom score over the initial 15 day study period for combined a.m. and p.m. scores, however the subject rated mean change in total nasal symptom scores for days 1-15 was also examined [illegible]

study (C93-184), the primary efficacy variable was defined as the clock time (in hours) from the start of treatment that the subject first experienced 'moderate' relief of total nasal symptoms, 'moderate' being defined as a therapeutic response score ≥ 3 (as per the 1-5 rating system discussed above). For this study as well, the subject rated mean change in total nasal symptom scores for days 1-15 was also examined. And while the [illegible] of the two nasal provocation studies (C93-193 and 194-039) was to evaluate nasal lavage levels of specific chemical mediators of allergic rhinitis before and after treatment with mometasone and not to determine clinical efficacy per se, these 2 studies did nonetheless evaluate total and individual nasal symptom scores.

9.2.1.b. SAR Efficacy Results

Analysis of efficacy for the 8 SAR trials indicates that mometasone administered once daily was more effective in decreasing SAR symptoms than placebo and was not statistically significantly different from the active comparator(s) in terms of efficacy in those studies which incorporated an active control arm.

9.2.1.b.1. Active- and Placebo- Controlled Studies

Results of the 4 active- and placebo-controlled trials which includes the pivotal SAR study (C93-013) are summarized below in Table IV. and support the conclusion that mometasone was statistically significantly more effective in decreasing subject rated mean total nasal symptom scores for the initial 15 day study period (the primary efficacy endpoint), as compared with placebo.

Table IV. Efficacy of Mometasone vs. Placebo in the Treatment of SAR: Primary Efficacy Variable for the ITT Population for Active- and Placebo-Controlled Trials in NDA 20-762

STUDY	MOMETASONE 200 µg qd: (unless otherwise specified): [1]Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	PLACEBO: Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	[2]P-Value
C93-013	-2.3 (-25%)	-1.5/(-16%)	<.01
I92-200	Mometasone 100 µg qd -4.3/(-52%)	-2.7/(-35%)	<.01
	Mometasone 200 µg qd -4.7/(-58%)	-2.7/(-35%)	<.01
I94-001	-2.8/(-36%)	-1.0/(-11%)	<.01
C94-145	Mometasone 200 µg qd: -2.7/(-32%)	-1.3/(-13%)	<.01
	Mometasone 200 µg qd + Loratadine 10 mg po qd: -3.0/(-35%)	-1.3/(-13%)	Direct comparison not performed

Δ = Change, [1]Study I92-200 the primary efficacy variable was defined for Week 1 of treatment, not days 1-15
[2]P-value is for comparison of mometasone vs. placebo using 2-way ANOVA.
NOTE: Total nasal symptom score for a.m. and p.m. combined

In general, mometasone treated subjects demonstrated a 2.3-4.7 unit decrease in total nasal [illegible] decrease for the primary efficacy variable compared with [illegible] decrease [illegible]. For study C94-145, addition of the antihistamine loratadine to mometasone treatment demonstrated a small, additive effect in decreasing total nasal symptom scores for the day 1-15 study period but in this study, the majority of efficacy was carried by mometasone treatment.

Analysis of the a.m. total nasal symptom scores (end of dosing interval) and separate a.m. and p.m. symptom scores for these 4 active- and placebo-controlled studies demonstrated that mometasone treatment had statistically greater efficacy in the a.m. than placebo (supporting a 24 hour duration of action), with no significant difference in a.m. vs. p.m. symptom scores. [illegible] nasal symptoms, rhinorrhea (nasal discharge) was the only nasal symptom which consistently demonstrated a statistically significant decrease post-mometasone treatment. While nasal congestion also showed a statistically significant decrease with mometasone, as compared to placebo treatment (especially in the pivotal SAR study C93-013), this was not consistently shown in all SAR studies.

Review of the total and individual non-nasal symptoms for these 4 studies revealed that mometasone treatment did not show a consistent effect in decreasing non-nasal symptoms although a slight numerical advantage (though not statistically significant) for mometasone treatment was evident in decreasing non-nasal symptoms compared with placebo at some study timepoints.

Review of rescue medication use in these 4 studies revealed that mometasone treated subjects (also active comparator subjects) used less rescue medication and used it less frequently than placebo treated subjects, although the studies did not perform a statistical comparison of these treatment group differences.

9.2.1.b.2. Nasal Provocation Studies

Inclusion of the 2 nasal provocation studies (C93-193 and I94-139) as supportive studies of efficacy confirmed the findings of the other SAR studies; namely that mometasone treatment resulted in a statistically significant difference in the mean change in total nasal symptom scores post-treatment during nasal challenge with allergen, as compared with placebo.

Analysis of subject SAR response to treatment by demographics (age, gender, and race) overall failed to reveal any consistent pattern of differential response. Worth noting only because it was a pivotal study, was the greater response in SAR symptoms of female subjects over male subjects in study C93-013. This treatment by gender interaction most likely represents sampling variation as there are no known or reported gender differences in nasal mucosa or the allergic response that would account for a different response in female subjects (Also, refer to Statistical Review and Evaluation, Dr. James Gebert, NDA 20-762, p. 4). This pattern of response was not noted in any of the other 7 SAR studies individually although a post-hoc pooled analysis of total nasal symptom scores for [illegible] SAR studies (C93-013, C93-184, I94-001, and C94-145) revealed that [illegible] had a -3.0 unit decrease in total nasal symptom score (-30% decrease) from baseline to study period, compared to a -2.5 unit decrease in total nasal symptom score from baseline (-29% decrease) in male subjects for the initial 14 days of therapy [302:43-44].

9.2.1 b.3. Mometasone Dose Ranging Results in SAR

One phase II, dose ranging study of mometasone (C92-011) was conducted to determine the optimum dose of mometasone in the treatment of SAR in adult subjects, although one other study (I92-200) for the SAR indication in NDA 20-762 compared two doses of mometasone (100 and 200 µg qd) against an active comparator (beclomethasone), and against placebo.

The phase II dose ranging study of mometasone treatment compared doses of 50, 100, 200, and 800 µg qd of mometasone against placebo, administered for [illegible] weeks. All doses of mometasone [illegible] decrease in physician (the primary efficacy variable) and subject rated total nasal

symptom scores by Day 7 of treatment. Whereas doses of 50 and 100 µg qd of mometasone showed less consistent effectiveness on Days 3 and 7 of treatment, the 200 µg qd dose provided consistent and statistically significant efficacy compared with placebo for the 4 weeks of the study. In summary, the 200 µg qd dose of mometasone demonstrated the most favorable dose response, with a decrease in physician and subject rated total nasal symptom scores similar, if not superior at Day 3, 7, 14, 21, and 28 of treatment to the 800 µg qd dose of mometasone. In other words, the 800 µg qd dose of mometasone offered no additional efficacy in reducing SAR symptoms than did the 200 µg qd dose. Review of the response of non-nasal SAR symptoms at the different doses of mometasone likewise revealed a less consistent numerical response of the 50 and 100 µg qd doses in decreasing non-nasal symptoms than the 200 µg qd dose, with no added benefit seen with the 800 µg qd dose. A.m. vs. p.m. SAR symptom scores were not assessed in this study, hence no comment can be made regarding end of dosing interval efficacy in study C92-011.

Results for the different demographic subgroups (age, gender, and race), were similar in inference for the different doses of mometasone, with no significantly different patterns of response noted across these subgroups.

Evaluation of the 100 µg qd dose of mometasone vs. the 200 µg qd dose of mometasone in the treatment of total nasal symptoms of SAR (Study 192-200) revealed more consistent efficacy of the 200 µg qd dose of mometasone in numerically decreasing total nasal symptoms during the first week of treatment, although statistical significance in efficacy was reached by both doses of mometasone, as compared with placebo. Both doses showed that after Day 3 of treatment, a.m. total nasal symptom scores were statistically significantly lower than placebo, thus supporting maintenance of activity during once daily dosing of mometasone.

5.1.1.4 Mometasone Onset of Action Results for SAR

[redacted] action of mometasone 200 µg qd vs. placebo, where treatments were administered to SAR subjects over 14 days. Analysis of the primary efficacy variable of time to onset of 'noticeable' relief of SAR symptoms in hours post-initiation of treatment with mometasone or placebo in subjects who were 'censored' or excluded from data analysis at 72 hours if they did not notice any improvement in nasal symptoms showed that the mean and median (50%) onset time to relief of symptoms was 39.2 and 35.9 hours, respectively, for the mometasone 'responder' subjects, and 53.4 and >72 hours, respectively, for placebo subjects (p-value <0.0001 for mometasone vs. placebo via the log-rank test). Based on a different endpoint evaluated in this study but using the same 'censored' subjects--the 'percentage' of subjects experiencing at least moderate relief of SAR symptoms; results obtained from this study indicated that for most mometasone treated subjects, onset of action occurred somewhat later (at 1.5 days (or 39.2 hours)). At day 3 of treatment, slightly greater than 50% of mometasone treated subjects experienced

moderate SAR symptom relief, compared with approximately 30% of placebo subjects. The onset of 'moderate' nasal symptom relief data for mometasone vs. placebo treated subjects are summarized in Table I. below. Comparison of the a.m. and p.m. symptom scores and the proportion of subjects experiencing at least 'moderate' symptom relief in the mometasone treatment group revealed a statistically significant response of mometasone [illegible] compared with placebo treatment, once again, indicating a 24 hour duration of action of mometasone and supporting once daily dosing of mometasone. Greater efficacy of mometasone in decreasing non-nasal symptoms of SAR, as compared with placebo, was not demonstrated in this study. Again, no significant demographic differences in response based on age, gender, or race were demonstrable in this study.

Table I: Percentage and Proportion of Subjects Experiencing at Least Moderate Relief (Efficacy Population), Study C93-184 [175: 47, 122]

	Mometasone (200 µg)	Placebo	*P-Value
Day 1			
-a.m.	-	-	-
-p.m.	28.4% (27/95)	12.8% (12/95)	0.01
Day 2			
-a.m.	29.2% (28/96)	18.8% (18/96)	0.13
-p.m.	41.2% (40/96)	19.8% (19/96)	<0.01
[illegible]			
[illegible]	52.1% (50/96)	[illegible]	[illegible]
[illegible]	59.1% [illegible]	32.5% (26/80)	<0.01
Day 4			
-a.m.	59.5% (47/79)	27.3% (21/77)	<0.01
-p.m.	-	-	-

* Fisher's exact test

Review of total nasal symptoms for the efficacy population (ITT not available in NDA 20-762) for Days 1-8 (data for days 5-8 not depicted in Table II. below) of treatment in study C93-184 indicates that although a greater numerical decrease in the total nasal symptom score in mometasone treated subjects was demonstrable by 12 hours post-initiation of treatment, as compared with placebo [175: 126], a statistically significant mean change in the total nasal symptom score [illegible] treated subjects, as compared with placebo was only seen in the

a.m. of Day 2--the 24 hour interval post-initiation of treatment. More importantly, this decrease in total nasal symptoms was only consistently statistically significantly lower for the mometasone treated subjects (as compared with placebo) by the a.m. of Day 3, or approximately 2 days after initiation of treatment [175:125]. After this time point, subsequent measurements of the mean change in total nasal symptoms for mometasone treated subjects demonstrated a statistically significant decrease, as compared with placebo. A summary of these data are summarized for days 1-4 of the treatment period in Table II. below.

Evaluation of the onset of action of mometasone 200 µg qd vs. placebo, in the treatment of the total nasal symptoms of SAR was also examined in the pivotal SAR study C93-013, using ITT population data generated from primary SAS Datafiles by Dr. James Gebert, Biostatistics, FDA. These results are summarized in Table III. below and indicate that a statistically significant mean change in total nasal symptoms (a -2.1 mean change in total nasal symptoms in mometasone treated subjects vs. a -1.1 mean change in total nasal symptoms in placebo subjects, p=0.01) was demonstrable in mometasone treated subjects by the Day 2 p.m. score (approximately 60 hours or 2.5 days), as compared to placebo subjects. Thus these onset of action results for mometasone are consistent with the onset of action data of study C93-184.

In summary, based on studies C93-184 and C93-013, statistically significant and consistent efficacy of mometasone 200 µg qd in decreasing total nasal symptoms of SAR (i.e. onset of action), as compared with placebo, appears to be between 2.0-2.5 days after initiation of treatment, although some subjects may experience SAR symptom relief earlier than this time point.

Table II: Total Nasal Symptom Scores and Mean Change in Total Nasal Symptom Scores for Mometasone vs. Placebo Treatment; Days 1-4, Post-Initiation of Treatment (Efficacy Population), Study C93-184 [175:125-126]

		Mometasone (200 µg)	Placebo	*P-Value
Baseline				
--a.m.		8.5	8.5	0.82
--p.m.		8.2	8.6	0.21
Day 1				
--a.m.	RAW	-	-	-
	CHANGE	-	-	-
[illegible]	RAW	6.9	[illegible]	[illegible]
	CHANGE	-1.4	-0.7	0.09
Day 2				
[2]--a.m.	RAW	7.1	8.0	0.01
	CHANGE	-1.3	-0.6	0.01
--p.m.	RAW	6.4	7.1	0.06
	CHANGE	-1.8	-1.5	0.35
Day 3				
--a.m.	RAW	6.3	7.4	<.01
	CHANGE	[illegible].2	-1.1	<.01
--p.m.	RAW	5.6	6.8	0.01
		[illegible]	1.8	0.05
Day 4				
--a.m.	RAW	5.8	7.1	<.01
	CHANGE	-2.7	-1.4	<.01
--p.m.	RAW	5.2	6.8	0.01
	CHANGE	-3.0	-1.8	0.05

*P-values are from 2-way ANOVA and LSMeans pairwise comparisons between mometasone treatment and placebo.

[1]DAY 1, p.m. score represents the 12 hour dosing interval

[2]DAY 2, a.m. score represents the 24 hour dosing interval

Table III: Total Nasal Symptom Scores and Mean Change in Total Nasal Symptom Scores for Mometasone vs. Placebo Treatment; Days 1-5, Post-Initiation of Treatment (ITT Population), SAR Study C93-013 [SAS Datafiles, C93-013, Dr. James Gebert]

		Mometasone (200 µg)	Placebo	*P-Value
Baseline				
--a.m.		7.7	7.7	0.98
--p.m.		7.5	7.4	0.74
Day 1				
--a.m.	RAW	-	-	-
	CHANGE	-	-	-
--p.m.	RAW	6.7	-	0.54
	CHANGE	-0.8	-0.6	0.47
Day 2				
[2]--a.m.	RAW	6.9	7.0	0.79
	CHANGE	-0.8	-0.7	0.77
--p.m.	RAW	6.0	6.3	0.46
	CHANGE	-1.5	-1.1	0.29
Day 3				
--a.m.	RAW	6.3	6.6	0.48
	CHANGE	-1.4	-1.1	0.46
--p.m.	RAW	5.5	6.4	0.01
	CHANGE	-2.1	-1.1	-
Day 4				
--a.m.	RAW	5.8	6.6	-
	CHANGE	-1.9	-1.1	0.03
--p.m.	RAW	5.3	6.5	<.01
	CHANGE	-2.1	-1.0	<.01

*P-values are from 2-way ANOVA and LSMeans pairwise comparisons between mometasone treatment and

--p.m. score represents the 12 hour dosing interval

[2]DAY 2, a.m. score represents the 24 hour dosing interval

9.2.2. Prophylaxis of Seasonal Allergic Rhinitis (SAR)

9.2.2.a. Study Design

Two studies (C93-215 and I93-133) were conducted to assess whether prophylaxis with mometasone treatment 4 weeks prior to the anticipated onset of the allergy season would statistically significantly decrease SAR symptoms compared with placebo prophylaxis. An important flaw in the design of both studies was the omission of a mometasone treatment group at the start of the allergy season which would allow a direct comparison of the mometasone prophylaxis group with mometasone treatment initiated at the onset of the allergy season.

Important inclusion criteria for both studies included an asymptomatic clinical status for study subjects, defined as a total nasal symptom score ≤ 2 on a 0-3 symptom severity scale. Again, subject rated SAR symptoms (nasal and non-nasal) reflectively over the previous 12 hours, twice daily (in the a.m. and p.m.). Rescue medication use was not allowed in study C93-215 (the pivotal study) but was allowed in I93-133 (loratadine, up to 10 mg po qd). Subjects were treated for up to 8 weeks total with study medication in both studies (4 weeks of prophylaxis treatment and 4 weeks of continued treatment during the 'pollen' season). The primary efficacy variable for both studies was defined as the mean proportion of minimal symptom days (total nasal symptom score ≤ 2 for combined a.m. and p.m. scores) from the start of the pollen season, through the last day of treatment. An assessment of the total nasal symptom score for the day 1-15 interval during the pollen season was also performed and comprised one of the many supplementary efficacy variables in both studies.

9.2.2.b. Prophylaxis of SAR Efficacy Results

A summary of the efficacy results for the primary efficacy variable and the mean change in the total nasal symptom score for days 1-15 of the pollen season (analogous to the primary efficacy variable in the SAP studies) for studies C93-215 and I93-133 are summarized in Table V and Table VI below.

On Original

Table V. **Primary Efficacy Variable Analysis for Mometasone vs. Placebo in Prophylaxis of SAR:** Proportion of 'Minimal' Symptom Days During the Pollen Season (defined as a Total Nasal Symptom Score ≤ 2), ITT Population.

STUDY	MOMETASONE 200 µg qd:	PLACEBO:	[1]P-Value
C93-215	0.84	0.63	<.01
I93-133	0.84	0.65	<.01

[1]P-value is for comparison of mometasone vs. placebo using 2-way ANOVA and LSMeans pairwise comparisons
NOTE: Total nasal symptom score for a.m. and p.m. combined

Table VI. **Efficacy of Mometasone vs. Placebo in the Prophylaxis of SAR:** Mean Change in the Total Nasal Symptom Score for Days 1-15 of the Pollen Season, ITT Population.

STUDY	MOMETASONE 200 µg qd:	PLACEBO:	[2]P-Value
	Mean Δ in total nasal symptom score day 1-15 of pollen season (% Δ)	Mean Δ in total nasal symptom score day 1-15 (% Δ)	
C93-215	0.4/(86.6% increase in symptoms from the prophylaxis period)	1.6 /(367% increase in symptoms from the prophylaxis period)	<.01
[1]I93-133	0.3/(149% increase in symptoms from the prophylaxis period)	1.2/(230% increase in symptoms from the prophylaxis period)	<.01

ITT population unless otherwise noted (study I93-133), efficacy evaluable subset analysis
[2]P-value is for comparison of mometasone vs. placebo using 2-way ANOVA and LSMeans pairwise comparisons
NOTE: Total nasal symptom score for a.m. and p.m. combined

In both studies, mometasone treated subjects demonstrated a statistically significantly greater proportion of minimal symptom days with treatment and a lower increase in the total nasal symptom score with onset of the pollen season, compared with placebo treated subjects. Again, lack of a mometasone treatment arm at the onset of the pollen season does not allow for any conclusions as to whether pretreatment with mometasone would afford greater overall efficacy than treatment with mometasone at the onset of the pollen season. Based on the onset of action of mometasone (< 1 week), pre-treatment for 1 week should afford adequate SAR prophylaxis. Indeed, in both studies a number of mometasone subjects did not receive the full 4 weeks of mometasone treatment, but rather received 2-3 weeks of prophylaxis. These subjects did not overall exhibit a different efficacy response with onset of the pollen season than did subjects pre-treated for a longer period of time. No significant difference in clinical response

was noted for any of the demographic groups (based on age, gender, and race) evaluated in either study. Rescue medication use in the one study where it was allowed (C92-280), again showed that mometasone treated subjects used less rescue medication and used it less frequently than placebo treated subjects.

Like the SAR studies, analysis of the separate a.m. and p.m. symptom (nasal and non-nasal) scores for the prophylaxis studies revealed no significant difference between a.m. and p.m. scores and efficacy at the end of dosing interval (the a.m. score) for mometasone treated subjects, compared with placebo. Again, this supports once a day dosing of mometasone for the treatment of SAR symptoms.

Review of the response of non-nasal symptoms to mometasone prophylaxis indicates a somewhat greater numerical response in decreasing non-nasal symptoms than noted in the SAR studies discussed previously where subjects received mometasone only during the pollen season. For the pivotal prophylaxis study C93-215, this response in non-nasal symptoms was statistically significant compared with placebo, however the active comparator arm (beclomethasone [illegible]) demonstrated a statistically significant effect in decreasing non-nasal symptoms.' An explanation for this differential effect of prophylaxis is not readily apparent based on the pathophysiology of allergic rhinitis or the mechanism of and onset of action of mometasone and again, this response may be the result of subject sampling variation. Thus, based on data in the NDA submission regarding mometasone's onset of action and results of these 2 prophylaxis studies prophylaxis with mometasone 2-4 weeks prior to onset of the allergy season was found to be effective in decreasing SAR symptoms with onset of the allergy season, compared with placebo treatment.

9.2.3. Perennial Allergic Rhinitis (PAR)

9.2.3.a. Study Design

The PAR studies evaluated in this NDA submission were similar in design to the SAR studies with the exception of a longer duration of treatment and longer duration of assessment of nasal and non-nasal SAR symptoms (12 to 52 weeks). In order to qualify for study enrollment, subjects were to be allergic to a perennial allergen (dust mite, cockroach, mold, or animal dander), and were to have clinical evidence of active symptoms at both the screening and baseline visits. Symptom scores for nasal and non-nasal symptoms were rated on a 0-3 severity scale, overall condition of rhinitis was rated on a 0-3 scale, and therapeutic response to treatment was rated on a 1-5 scale, same as the symptom rating scores [illegible] prophylaxis SAR studies. With the exception of study C94-092 (PAR study in elderly subjects), rescue medication use was allowed for all PAR studies in NDA 20-762.

For the 4 active- and placebo controlled PAR studies (C92-280, I92-293, [illegible]) and the [illegible] studies (C94-[illegible]) the primary efficacy variable was the same as that in the SAR studies: the mean

change in the total nasal symptom score for the initial 15 day study period for the ITT population (for a.m. and p.m. combined scores). For the 4 open label studies (I93-014, I93-018, I93-180, I93-221), a primary efficacy variable was not defined, as assessment of clinical efficacy was not a primary objective of these studies. Supplementary efficacy variables for the open label studies consisted of 4 distinct endpoints: (1) physician and (2) subject evaluations of overall nasal condition, and (3) physician and (4) subject evaluations of therapeutic response for the ITT population which were based on the scoring system previously defined.

Duration of treatment for the 4 active- and placebo-controlled PAR studies was 12 weeks; with 2 of the 4 studies, study I94-079 and I94-078, having an additional 13th or 'offset' week to assess the duration of effect of mometasone in decreasing PAR symptoms post-discontinuation of treatment at week 12 of the study. The geriatric study was likewise 12 weeks in duration. The open label studies, whose primary goal it was to assess safety of mometasone treatment, were up to 52 weeks in duration. One additional safety study (I93-221) was 6 months in duration.

9.2.3.b. PAR Efficacy Results

9.2.3.b.1. Active- and Placebo- Controlled PAR Studies

Results of the 10 PAR studies reviewed in NDA 20-762 indicate that mometasone treatment was effective in decreasing and maintaining a decrease in PAR symptoms. For most of the PAR studies, additional decrease in PAR symptoms was gained from the 3rd-12th, or to the 52nd week, respectively, of mometasone treatment, in addition to efficacy achieved by the second week of mometasone treatment. Primary efficacy variable results for the 4 active- and placebo-controlled PAR studies are summarized in Table VII. below and indicate that mometasone treatment in general, decreased total nasal symptoms for the initial 15 day period of treatment by [redacted] units (a 20-37% decrease in total nasal symptoms), compared with a [redacted] decrease (13-23%) in total nasal symptoms in placebo treated subjects. Again, no significant difference was noted in these studies in total nasal symptom scores for the a.m. vs. the p.m. Additionally, a.m. total nasal symptom scores of the mometasone treated subjects demonstrated a statistically significant decrease in mean change in scores for the 15 day period, compared with placebo, supporting once daily dosing of mometasone. For the individual nasal symptoms, mometasone treatment consistently decreased the rhinorrhea score and overall demonstrated the greatest decrement in this parameter. Nasal congestion scores were significantly decreased in 2 of these 4 studies, but again, the overall response in nasal congestion was not consistent across all 4 studies reviewed.

Table VII. Efficacy of Mometasone vs. Placebo in the Treatment of PAR: Primary Efficacy Variable for the ITT Population for Active- and Placebo-Controlled Trials in NDA 20-762

STUDY	MOMETASONE 200 µg qd:	PLACEBO:	[1]P-Value
	Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	
C92-280	-1.5/(-20%)	-1.0/(-13%)	0.02
I92-293	-1.7 (-26%)	-1.0/(-13%)	<.01
I94-079	-2.3/(-37%)	-1.3/(-17%)	<.01
I94-078	-2.4/(-34%)	-1.6/(-23%)	<.01

[1] P-value is for comparison of mometasone vs. placebo using 2-way ANOVA

NOTE: Total nasal symptom score for a m and p m combined

Analysis of the non-nasal symptom scores for the 4 active- and placebo-controlled trials revealed that mometasone treatment decreased the numerical score of many of the non-nasal symptoms, as compared with placebo, however these differences were not generally statistically significant. In summary, mometasone's effect on non-nasal symptoms was inconsistent, with no particular pattern of response (or trend in response) noted for the individual non-nasal symptoms. Subject rescue medication use was lower (no statistical comparison performed in these studies between treatment groups for rescue medication use) in the mometasone treatment group (also lower in the active comparator groups), as compared with the placebo treatment group. No significant demographic differences in treatment response were identified, based on age, gender, or race.

9.2.3.b.2. Placebo-controlled Study in Elderly Subjects (Age ≥ 65 years) (C92-280, n=334, ITT population) was specifically performed to assess any differences in efficacy or safety of mometasone treatment in this population, as compared to subjects age 18-64. The study design was essentially identical to the 4 active- and placebo controlled trials with the exception that no active comparator group was included.

Overall, elderly subjects demonstrated a statistically significant decrease in the primary efficacy variable of total nasal symptoms over the initial 15 day period with mometasone treatment, however numerically this decrease was lower than that seen in the elderly subgroups in the other PAR studies and lower than that seen for subjects age 12-64 in the 4 active- and placebo-controlled PAR studies. Primary efficacy variable results for elderly subjects are summarized in Table VIII.

Table VIII. Efficacy of Mometasone vs. Placebo in the Treatment of PAR: Primary Efficacy Variable for the ITT Population for the Placebo-Controlled Trial in Elderly Subjects (Age ≥ 65 years) in NDA 20-762.

STUDY	MOMETASONE 200 µg qd:	PLACEBO:	[1]P-Value
	Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	
C94-092	-1.1 (-16%)	-0.7 (-11%)	p .02

[1] P-value is for comparison of mometasone vs. placebo using 2 way ANOVA

NOTE: Total nasal symptom score for a.m. and p.m. combined

The meaning of this small numerical difference in total nasal symptom scores (which was also noted for the non-nasal symptom scores) is not clear and these results represent those of only one study. Similar to the gender by treatment interaction noted for the pivotal SAR study C93-013, these results may simply represent sampling variation and if enough placebo-controlled studies in elderly subjects were performed, different numerical differences in symptom scores might be obtained.

9.2.3.b.3. Open label (no placebo group) PAR studies

A total of 5 open label studies for PAR were evaluated in NDA 20-762. Because the main objective of these studies was safety monitoring and not efficacy, no comparison with placebo was provided. Thus, any conclusions gained from these studies are only supportive of those shown in active- vs placebo-controlled PAR studies discussed in section 9.4.1.b.1 above. Results of supplementary efficacy variables of physician and subject evaluations of PAR condition compared to baseline and physician and subject evaluations of treatment compared to baseline, indicate that for all 5 studies [illegible] PAR symptoms were evident throughout the study duration for mometasone treated subjects. Clinical findings in these 5 open label studies thus support the efficacy of mometasone in decreasing PAR symptoms.

9.2.3.b.4. PAR Dose Ranging Data for Mometasone

Three of the 5 open label PAR mometasone studies included a 'variable dose' mometasone group in which subjects [illegible] with mometasone 200 µg qd and were given the option [illegible] PAR symptoms, or decrease this dose to 100 µg qd for well-controlled PAR symptoms. Because of the study design of these 3 trials, the variable dose group [illegible] for the different doses of mometasone. Thus, the information obtained from the variable dose mometasone group is limited from the perspective of [illegible]

comparison of efficacy between the 100, 200, and 400 µg qd dose of mometasone.

Nonetheless, for all 3 studies, the majority of study subjects remained on mometasone 200 µg qd throughout the study with approximately 60% of study subjects for all 3 studies remaining on 200 µg qd of mometasone at the time of completion of the trials, 10-18% of study subjects remaining on 100 µg qd of [illegible] remaining on 400 µg qd of mometasone at the time of completion of the trials. A gradual increase in the dose of mometasone over the course of the study was not observed in either of the 3 studies.

9.3 CONCLUSION:

Results of the SAR, prophylaxis of SAR, and PAR studies in adult subjects summarized in this integrated summary of efficacy support the efficacy of mometasone for these clinical indications. Mometasone treatment demonstrated an adequate 24 hour duration of activity, supporting once a day dosing via nasal spray. A statistically significant and consistent onset of action of mometasone was shown to be between 2.0 and 2.5 days of treatment with maximal benefit of total nasal symptom relief achieved by 2 weeks of treatment with mometasone, based on the data reviewed in the clinical studies of NDA 20-762. The most appropriate dose of mometasone for the treatment of rhinitis is adult subjects is 200 µg qd, although lower doses of mometasone (50 and 100 µg qd) also demonstrated a statistically significant decrease in rhinitis symptoms, as compared with placebo. At the 50 µg qd and 100 µg qd doses of mometasone, decrease in rhinitis symptoms were not as consistent during the first few days of treatment as with the 200 µg qd dose of mometasone. Conversely, a higher dose of mometasone, given as 800 µg qd did not provide a statistically or consistently numerically greater efficacy response in reducing rhinitis symptoms, than the 200 µg qd dose of mometasone. No significant demographic differences, based on age, gender, or race were seen in the SAR (except for the minor treatment by [illegible] effect in the pivotal SAR study C93-013), prophylaxis of SAR, or PAR with mometasone, although the number of subjects in the different demographic subgroups for the individual studies were too small to [illegible]

10.0 INTEGRATED SUMMARY OF SAFETY:

The clinical program for mometasone furoate (SCH 32088) nasal spray evaluated safety in greater than 3000 subjects age 12 years or older exposed to mometasone treatment for at least one visit post-baseline. Although a total of 20 [illegible] safety in NDA 20-[illegible], pooling of safety data was performed only on those studies (19 total) submitted to NDA 20-762 at the time of filing. Thus, the data that forms the basis of this safety summary are taken from the Integrated Summary of Safety (ISS) originally supplied in the Mometasone NDA, as well as from the 120 day safety update, which likewise is a single document submitted to the Mometasone NDA. These documents include summaries of safety data from 10 U.S. and 10 non-U.S. studies. All studies which form this safety database were performed with the 'to-be-marketed' formulation of mometasone nasal spray , thus there are no formulation differences in the mometasone used from study to study. Likewise, placebo tested in these trials had the same chemical formulation as mometasone furoate nasal spray minus the active ingredient, mometasone (i.e. the same excipients, humectants, etc.).

Although similar to the database presented in the medical officer's 'Integrated Summary of Efficacy', the subject safety database which comprised [illegible] ITT subjects is summarized in Tables. I-IV. below and incorporates phase I studies (human HPA-axis suppression studies) submitted with NDA 20-762.

Table I. Phase I Mometasone Studies (HPA Axis Assessment)

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)	
[illegible]se I, active- and [illegible]bo controlled HPA study	[illegible]-F64	[illegible]	C93-21[illegible] [illegible]etasone [illegible]0, 2000, 4000 µg qd nasal spray, and 2000, 4000, 8000 µg po qd)	16
			Dexamethasone (200, 40[illegible]	[illegible]
			Placebo [illegible]	24
	C92-022	29 days	C92-022 Mometasone (400 and 1200 µg qd nasal spray)	24
			Prednisone (10 mg po qd)	12
			Placebo (0 µg qd)	12
	C93-196	36 days	C93-196 Mometasone (200 and 400 µg qd nasal spray)	32
			Prednisone (10 mg po qd)	16
			Placebo (0 µg qd)	16
Phase I	C91-101-102/-103/-328 (combined into 1 study report)	Single dose	C91-101 Mometasone 200 µg qd nasal spray, Mometasone 1000 µg po/I.V. qd	6 30
Phase I	C95-050	[illegible]	[illegible] Mometasone 400 µg qd nasal spray, Mometasone [illegible] µg po qd	6 [illegible]

Table II Phase II and Phase III Studies: Seasonal Allergic Rhinitis (SAR) Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)		
Phase III, active- and [illegible]	C93-013 [illegible]	4 weeks	C93-013	Mometasone (200 µg qd)	112
				[illegible]	[illegible]
	I92-200	. . .	I92-200	**Mometasone (100 µg qd)**	126
				Mometasone (200 µg qd)	125
				Beclomethasone (200 µg bid)	125
				Placebo (0 µg qd)	121
[illegible]	I94-001	2 weeks	I94-001	Mometasone (200 µg qd)	104
				Fluticasone (200 µg qd)	104
				Placebo (0 µg qd	103
	C94-145	. . .	C94-145	Mometasone (200 µg qd)	176
				Mometasone (200 µg qd) + Loratadine (10 mg po qd)	169
				Loratadine (10 mg po qd)	18*
				Placebo (0 µg qd)	[illegible]
Phase II, dose ranging, placebo controlled	C92-011	4 weeks	C92-011	Mometasone (50 µg qd)	9[illegible]
				Mometasone (100 µg qd)	95
				Mometasone (200 µg qd)	98
				Mometasone (800 µg qd)	95
				Placebo (0 µg qd)	95
Phase III, onset of action, placebo controlled	C93-184	2 weeks	C93-184	**Mometasone (200 µg qd)**	101
				Placebo (0 µg qd)	99
Phase III, placebo controlled, 2-period crossover, nasal provocation studies	C93-193	2 weeks	C93-193	**Mometasone (200 µg qd)**	20
				Placebo (0 µg qd)	21
	I94-139		I94-139	Mometasone (200 µg qd)	24
				Placebo (0 µg qd)	24

[illegible] SAR St[illegible]

[illegible] TYPE	[illegible] Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)		
[illegible] III, active- and placebo controlled	C93-215 (Pivotal Prophylaxis of SAR),	8 weeks total, (4 week prophylaxis period, followed by a 4 week ragweed period assessment)	C93-215	Mometasone (200 µg qd)	116
				Beclomethasone (168 µg bid)	116
				Placebo (0 µg qd)	115
	I93-133	. . .	I93-133	Mometasone (200 µg qd)	169
				[illegible]	[illegible]
				Placebo (0 µg qd)	173

Table IV Phase III Perennial Allergic Rhinitis (PAR) Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)		
Phase III active placebo controlled	C92-280 (1 yr total PAR)	[illegible]	[illegible]	Beclomethasone (168 µg bid)	163
				Placebo (0 µg qd)	163
	I92-293	12 weeks	I92-293	Mometasone (200 µg qd)	143
				Beclomethasone (200 µg bid)	146
				Placebo (0 µg qd)	138
	[illegible]	12 weeks (+ 1 week off treatment offset period)	I94-079	Mometasone (200 µg qd)	181
				Fluticasone (200 µg qd)	183
				Placebo (0 µg qd)	184
	I94-078	12 weeks (+ 1 week off treatment offset period)	I94-078	Mometasone (200 µg qd)	171
				Budesonide (200 µg qd)	179
				Placebo (0 µg qd)	173
Phase III active controlled (no placebo)	[illegible] (1 yr [illegible] 280)	[illegible] 1 year	[illegible]	Mometasone [illegible] µg qd	[illegible]
				Beclomethasone (168 µg bid)	95
			C94-145	Mometasone (200 µg qd)	77
	I93-018 (1 yr F/U of I92-293)	Up to 52 weeks (1 year)		Mometasone (100-400 qd)	80
				Beclomethasone (200 µg bid)	71
	I93-180 (Nasal bx study)	Up to 52 weeks (1 year)	I93-180	Mometasone (200 µg qd)	69
				Fluticasone (200 µg qd)	72
	C94-052 (HPA study)	Up to 52 weeks (1 year)	C94-052	Mometasone (200 µg qd)	175
				Triamcinolone (220 µg qd)	176
Phase III, placebo controlled geriatric [illegible] yrs)	C94-092	12 weeks	C94-092	Mometasone (200 µg qd)	170
				Placebo (0 µg qd)	164
[illegible]	[illegible] 221	[illegible] weeks (6 months)	C93-184	Mometasone (100 [illegible] 400 µg qd)	33[illegible]

[illegible]8 was amended to the original NDA for mometasone

[illegible]ent (and not efficacy) was the primary objective of these studies. Hence these placebo [illegible]trolled studies [illegible] designed to statistically evaluate efficacy of mometasone

Excluding PAR study I94-078 which was submitted to NDA 20-762 after the filing date, a total of 3210 subjects comprised the ITT population for mometasone. Of these 3210 subjects from phase II and III studies, a total of 3120 distinct subjects received treatment with mometasone and had at least 1 follow-up evaluation for safety. Thus, in most instances, the evaluation of safety is based on the 3210 subjects, as subjects in the 2 PAR studies C92-280 and I92-293 could re-enroll for long-term treatment, up to 1 year, in the 'rollover' studies C93-014 and I93-018. Because treatment assignment in the 2 'roll-over' [illegible] was re-randomized, subjects were counted separately for most safety measures. The 2 exceptions were for calculation of the [illegible] adverse events grouped by duration of treatment. Subjects who received treatment in the

'rollover' studies were counted only once and exposure/duration was considered cumulative.

10.1. Demographics of the Exposed Population

The demographic profiles of 'all mometasone dose' subjects, the mometasone 200 µg qd subjects, and placebo subjects were overall similar. Most subjects were 18-64 years of age ('all doses of mometasone' group=83%, mometasone 200 µg qd group=82%, and placebo group=78%) and the remainder were generally balanced between 12-17 years and ≥ 65 years of age. One female subject (in the 'all doses of mometasone' group) was < 12 years of age.

The proportion of male and female subjects were likewise balanced in all 3 groups ('all doses of mometasone' group=45% male subjects vs. 55% female subjects, mometasone 200 µg qd group=47% male subjects vs. 53% female subjects, and placebo group=46% male subjects vs. 54% female subjects) and across the 3 main age categories (12-17 years, 18-64, and ≥ 65 years) within each group. The majority of study subjects were Caucasian (all doses of mometasone group=85%, mometasone 200 µg qd group=88%, and placebo group=85%). Of the non-Caucasian subjects, the majority were of Hispanic origin. A summary of the demographic data for mometasone treated subjects, all active comparator groups, and placebo for the ITT population is presented in Table H8 of the Integrated Summary of Safety in the NDA submission [302:40]. Salient demographic data for the mometasone and placebo group are summarized below in Table V.

Table V. Summary of Demographic Data for Mometasone and Placebo Subjects (Pooled Safety Population, Controlled and Uncontrolled Studies[1]) [302:4, 131-141].

Variable	All Mometasone Doses	Mometasone 200 µg qd	Placebo
Total subject # (n)	3210	2103	1671
Age:			
< 12 years	1	0	0
12-17 years	335	191	181
18-64 years	2671	1714	1305
≥ 65 years	203	198	185
Gender:			
Female	1453	993	764
Male	1757	1110	907
Gender within Age:			
< 12 years			
female	1	0	0
male			
12-17 years			
female	120	63	59
male	215	128	122
18-64 years			
female	1221	822	607
male	1450	892	698
≥ 65 years			
female	111	108	98
male	92	90	87
Race:			
Caucasian	2732	1841	1428
Non-Caucasian	478	262	243

[1]Excludes study C94-078

Duration of Subject Exposure/Subject Disposition

The extent of exposure to mometasone and placebo treatment for all subjects in the phase II and phase III (controlled and uncontrolled studies) pooled safety population is summarized in Table VI. Greater than 3000 'distinct' study subjects received the various doses of mometasone once daily for at least 2 weeks, approximately 1300 mometasone subjects were treated for at least 12 weeks, and 350 mometasone subjects were treated for at least 1 year. At least 2/3 of these subjects received mometasone 200 µg qd, the recommended dosage.

Subjects exposed to mometasone 400 µg qd in the PAR studies C93-014, I93-018 and I93-221 comprised 144 subjects treated for at least 2 weeks and 105 subjects treated for at least 12 weeks. Of the 506 subjects who participated in these 'variable-dose' studies, 54% (275 subjects) did not change the dose of mometasone from 200 µg qd, 21% (107 subjects) increased the mometasone dose to 400 µg qd at some point in the studies, and 15% (76 subjects) decreased the mometasone dose to 100 µg qd and maintained it, and 10% (48 subjects) changed the mometasone dose more than once.

Table VI. Subject Exposure to Mometasone Treatment (Pooled Safety Population, [1]Controlled and Uncontrolled Studies) [302.42, 143]

Length of Exposure	All Doses of Mometasone	Mometasone 50 µg qd	Mometasone 100 µg qd	Mometasone 200 µg qd	Mometasone 400 µg qd	Mometasone 800 µg qd	Placebo
≥ 1 Dose	3120	96	220	2018	153	95	1665
≥ 1 Week	3094	91	216	2004	153	93	1638
≥ 2 Weeks	3018	88	205	1955	144	89	1553
≥ 4 Weeks	2370	82	177	1511	140	84	1121
≥ 8 Weeks	1595	0	0	1187	117	0	776
≥ 12 Weeks	1315	0	0	838	105	0	460
≥ 26 Weeks	712	0	0	363	42	0	0
≥ 52 Weeks	372	0	0	349	23	0	0
52 - 69 Weeks	350	0	0	273	2	0	0
Unknown	26	0	1	20	*	0	6

* There were 5 subjects in the pooled variable dose group whose extent of exposure could not be calculated; hence they could not be assigned to any particular dose

[1]NOTE: This table does not depict the 169 subjects in the mometasone + loratadine group for study C94-145 and the 21 cross-over mometasone vs. placebo subjects in study C93-193, which are accounted for in the 'all doses of mometasone' column .

10.3. Adverse Events (AE's)

The overall incidence of all adverse events were generally similar among the treatment groups, including placebo. The most frequent adverse events across all studies reviewed in NDA 20-762 were [illegible] viral infection, pharyngitis, [illegible].

A summary of all reported adverse events (treatment emergent, i.e. occurring during treatment) for all doses of mometasone in controlled and uncontrolled trials (n=3210 mometasone subjects) are summarized in Table VII. A summary of all reported adverse events ('treatment emergent', i.e. occurring during treatment) for subjects treated with the 200 µg qd dose of mometasone in all controlled trials (n=2103) and in placebo group subjects in controlled studies of NDA 20-762 are summarized in Table VIII. Again, based on these 2 tables, most adverse events in mometasone treated subjects were not generally significantly different in frequency from placebo subjects. The most frequently reported adverse event in mometasone 200 µg qd treated subjects was headache (26%), followed by viral infection (14%), and pharyngitis (12%). Adverse events relating to the upper or lower respiratory tract were slightly more frequent in mometasone treated subjects than in placebo, in particular epistaxis. The incidence of epistaxis was [illegible] several percentage points higher with mometasone and the active comparator treatments than with placebo treatment. Other adverse events slightly

more prevalent in mometasone treated subjects, as compared with placebo controlled subjects were the following: headache, musculoskeletal pain, dysmenorrhea (in female subjects), viral infection, coughing, pharyngitis, sinusitis, and upper respiratory tract infection.

Table VII. Adverse Event (AE) Frequency:
AE's ≥ 1% in Mometasone Treated Subjects (All doses combined) by Organ System and Preferred Term, Pooled Safety Population, n=3210 Mometasone Subjects for Controlled and Uncontrolled Trials [302:151-185, 303:310-326].

BODY SYSTEM	Preferred Term	Mometasone n (%)
All Systems	Any AE	2049 (64%)
Autonomic Nervous System Disorders	Dry Mouth	20 (1%)
Body as a Whole	Chest Pain	46 (1%)
	Edema	17 (1%)
	Fatigue	53 (2%)
	Fever	84 (3%)
	Headache	***882 (27%)***
	Influenza-like Symptoms	114 (4%)
	Injury, Accidental	19 (1%)
	Malaise	18 (1%)
CNS and PNS Disorders	Dizziness	51 (2%)
	Dysphonia	31 (1%)
Gastro-intestinal System Disorders	Abdominal Pain	49 (2%)
	Diarrhea	54 (2%)
	Dyspepsia	70 (2%)
	Gastritis	32 (1%)
	Gastroenteritis	20 (1%)
	Nausea	81 (3%)
	[illegible]	70 (2%)
	[illegible]	37 (1%)
Hearing and Vestibular Disorders	Ear Disorder NOS	17 (1%)
	Earache	105 (3%)
Musculoskeletal System Disorders	Arthralgia	63 (2%)
	Musculoskeletal Pain	***169 (5%)***
	Myalgia	98 (3%)
Psychiatric Disorders	Depression	17 (1%)
	Insomnia	40 (1%)
	Somnolence	21 (1%)
Reproductive Disorders, Female	Dysmenorrhea	***72 (5%)***
	Vaginitis	8 (1%)
Resistance Mechanism Disorders	Infection	19 (1%)
	Bacterial Infection	27 (1%)
	Viral Infection	***431 (13%)***

Note: AE's ≥ 1% frequency are bolded in bold-face italic type.

Table VII. CONTINUED:
Adverse Event (AE) Frequency ≥ 1% in Mometasone Treated Subjects:
(All mometasone doses combined) by Organ System and the Preferred Term for Controlled and Uncontrolled Trials, (Pooled Safety Population, n=3210 Mometasone Subjects) [302:151-185, 303:310-326].

BODY SYSTEM	Preferred Term	Mometasone n (%)
Respiratory System Disorders	Asthma	62 (2%)
	Asthma Aggravated	24 (1%)
	Bronchitis	69 (2%)
	Coughing	***234 (7%)***
	Dyspnea	39 (1%)
	Epistaxis	***315 (10%)***
	Nasal Burning	64 (3%)
	Nasal Congestion	35 (1%)
	Nasal Irritation	84 (3%)
	Pharyngitis	***371 (12%)***
	Respiratory Disorder	36 (1%)
	Rhinitis	129 (4%)
	Sinusitis	***154 (5%)***
	Sneezing	68 (2%)
	Tonsillitis	19 (1%)
	Upper Respiratory Tract Infection	***159 (5%)***
	Wheezing	43 (1%)
Skin and Appendages Disorders	Pruritus	51 (2%)
	Urticaria	32 (1%)
Special Senses Other, Disorders	Taste Perversion	30 (1%)
Urinary System Disorders	Urinary Tract Infection	20 (1%)
[illegible] Disorders	Migraine	44 (1%)
Vision Disorders	Conjunctivitis	122 (3%)
	[illegible]	
	Eye(s) Dry	
White cell and RES Disorders	Lymphadenopathy	19 (1%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' italic type.

Table VIII. Treatment Emergent Adverse Event (AE) Frequency:
AE's ≥ 1% in Mometasone 200 µg qd Treated Subjects for All Controlled Clinical Trials. Pooled Placebo Subjects from all [1]Controlled Trials Included for Comparison [302:187-235, 303:261-307].

BODY SYSTEM	Preferred Term	Mometasone 200 µg qd (n=2103)	Placebo (n=1671)
		n (%)	n (%)
All Systems	Any AE	1344 (64%)	979 (59%)
Autonomic Nervous System Disorders	Mouth Dry	11 (1%)	9 (1%)
Body as a Whole	Chest Pain	38 (2%)	10 (1%)
	Edema	11 (1%)	9 (1%)
	Fatigue	32 (2%)	32 (2%)
	Fever	50 (2%)	26 (2%)
	Headache	***551 (26%)***	***366 (22%)***
	[illegible]	[illegible] (4%)	51 (3%)
	Injury Accidental	12 (1%)	7 (<1%)
	Malaise	15 (1%)	5 (<1%)
CNS and PNS Disorders	Dizziness	31 (1%)	28 (2%)
	Dysphonia	18 (1%)	10 (1%)
Gastro-intestinal System Disorders	Abdominal Pain	31 (1%)	19 (1%)
	Diarrhea	36 (2%)	19 (1%)
	Dyspepsia	41 (2%)	24 (1%)
	Gastritis	13 (1%)	3 (<1%)
	Gastroenteritis	12 (1%)	1 (<1%)
	Nausea	56 (3%)	29 (2%)
	Tooth Disorder	48 (2%)	13 (1%)
Hearing and Vestibular Disorders	Ear Disorder *NOS	15 (1%)	8 (<1%)
	Earache	71 (3%)	40 (2%)
Musculoskeletal System Disorders	Arthralgia	40 (2%)	21 (1%)
	Musculoskeletal Pain	***112 (5%)***	***50 (3%)***
	Myalgia	77 (4%)	[illegible]
Psychiatric Disorders	Depression	12 (1%)	1 (<1%)
	Insomnia	30 (1%)	25 (1%)
	Somnolence	14 (1%)	14 (1%)
Reproductive Disorders, Female	***Dysmenorrhea***	***50 (5%)***	***26 (3%)***
Resistance Mechanism Disorders	Infection	15 (1%)	7 (<1%)
	Bacterial Infection	16 (1%)	2 (<1%)
	Viral Infection	***292 (14%)***	***181 (11%)***

NOTE: All AEs ≥ 5% in frequency are denoted in 'bold-face italic' type.
[1] Excludes PAR study 094-078, which was submitted after the [illegible] date for NDA 20-762.
*NOS: Not otherwise specified.

Table VIII. CONTINUED:
Treatment Emergent Adverse Event (AE) Frequency:
AE's ≥ 1% in Mometasone 200 µg qd Treated Subjects for All Controlled Clinical Trials. Pooled Placebo Subjects from all [1]Controlled Trials Included for Comparison [302-187-235, 303-261-307]

BODY SYSTEM	Preferred Term	Mometasone 200 µg qd (n=2103)	Placebo (n=1671)
		n (%)	n (%)
Respiratory System Disorders	Asthma	39 (2%)	18 (1%)
	Asthma Aggravated	17 (1%)	11 (1%)
	Bronchitis	41 (2%)	20 (1%)
	Coughing	***155 (7%)***	***97 (6%)***
	Dyspnea	20 (1%)	17 (1%)
	Epistaxis	***223 (11%)***	***104 (6%)***
	Laryngitis		
	Nasal Burning		
	Nasal Congestion	25 (1%)	14 (1%)
	Nasal Irritation	52 (2%)	53 (3%)
	Pharyngitis	***246 (12%)***	***162 (10%)***
	Respiratory Disorder	28 (1%)	11 (1%)
	Rhinitis	82 (4%)	56 (3%)
	Sinusitis	***114 (5%)***	***58 (3%)***
	Sneezing	38 (2%)	64 (4%)
	Upper Respiratory Tract Infection	***136 (6%)***	***40 (2%)***
	Wheezing	26 (1%)	12 (1%)
Skin and Appendages Disorders	Pruritus	31 (1%)	20 (1%)
	Rash	30 (1%)	19 (1%)
	Urticaria	24 (1%)	17 (1%)
Special Senses Other, Taste	Taste Perversion	2	0
Urinary System Disorders	Urinary Tract Infection	12 (1%)	3 (<1%)
Body as a Whole - General Disorders		31 (1%)	7 (<1%)
Vision Disorders	Conjunctivitis	74 (4%)	32 (2%)
	Eye Pain	22 (1%)	16 (1%)
	Eyes, Dry	17 (1%)	6 (<1%)
White cell and RES Disorders	Lymphadenopathy	13 (1%)	5 (<1%)

Note: All AE's ≥ 1% in frequency are listed in descending order.
[1]Excludes PAR study C94-078, which was submitted after the filing date for NDA 20-762

10.3.1. Adverse Events Due to Viral and Fungal Infections

Since several reports of viral and fungal infections (herpes simplex, varicella, oral and/or nasal candidiasis) were noted in mometasone treated subjects on review of the individual studies in the NDA submission, a pooled analysis of the incidence of these resistance mechanism disorders for mometasone and placebo group subjects by dose of mometasone was performed using the sponsor's database for controlled clinical trials in the mometasone NDA. Results are summarized in Table IX. below and indicate that the majority of resistance mechanism disorders were prevalent in the 200 µg qd mometasone group and comprised herpes simplex infection. No obvious dose response in resistance mechanism disorder AE frequency was noted except that almost no subjects receiving > 200 µg qd mometasone group reported any of these adverse events. Overall, no significant difference between the different doses of mometasone and placebo were found regarding these selective viral and fungal infections.

Table IX. Incidence of Selective Viral and Fungal Infections: Mometasone Treated Subjects (Stratified by Dose) compared with Placebo Treated Subjects for all [1]Controlled Clinical Trials in NDA 20-762, Pooled Safety Population [302-217-219, 303-290-292]

Resistance Mechanism Disorder AE	Mometasone 50 µg qd (n=96)	Mometasone 100 µg qd (n=221)	Mometasone 200 µg qd (n=2103)	Mometasone 100-400 µg qd (n=506)	Mometasone 800 µg qd (n=95)	Placebo (n=1671)
Herpes Simplex	[illegible]	[illegible]	[illegible]	1 (<1%)	[illegible]	8 [illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1 (<1%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0 (0	[illegible]
Measles	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
[illegible]	[illegible]	[illegible]	[illegible]	1 (<1%)	0 (0%)	0 (0%)
[illegible]	[illegible]	[illegible]	[illegible]	0 (0%	0 (0%)	0 (0%)
Varicella	0 (0	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

[1]Excludes PAR study I94-078, which was submitted after the filing date for NDA 20-762

Review of the individual uncontrolled studies for NDA 20-762 however revealed an [illegible] reports of oral candidiasis in [illegible] enrolled in [illegible] reports of [illegible] candidiasis (no reports [illegible] placebo subjects). Importantly, these subjects all received mometasone for [illegible] months of treatment

10.3.2. Nasal Perforation and Nasal Ulcer Frequency

Regarding nasal perforation and nasal ulcer frequency in mometasone treated subjects vs. placebo treated subjects, there were no reports of nasal [illegible] in this NDA submission or in placebo group subjects. Nasal ulcers, however, were noted in slightly higher frequency in mometasone treated subjects (and other steroid active comparator groups) as compared with placebo treated subjects on physical examinations during follow-up study visits (these were not submitted as part of the adverse event reports, and thus are not included in the AE database submitted by the sponsor). While nasal ulcers were not rated by the examining physician in terms of the extent of involvement of the nasal mucosa, of the 42 reports of nasal ulcer in mometasone treated subjects, only one (1) subject receiving mometasone 800 µg qd was noted to have a nasal ulcer of 'moderate' severity. Of mometasone treated subjects with nasal ulcers, 4 subjects were noted to have [illegible] may be more prone to perforate (of note, 3 out of 4 of these subjects were [illegible] years). A tabulation of nasal ulcer frequency in mometasone and placebo subjects for all SAR, prophylaxis of PAR and PAR studies (excluding study 194-078) is summarized in Table X. The denominators for the percentages were 3210 mometasone subjects and 1692 placebo subjects.

Table X. Incidence of Nasal Ulcers
Mometasone Treated Subjects vs. Placebo for all [1]Controlled and Uncontrolled Trials in NDA 20-762, ITT Population (n=3210 for mometasone subjects, n=1692 for placebo subjects), [Compiled from the Medical Officer Review of Adverse Events for Individual Studies in NDA 20-762]

	Mometasone [illegible]			Placebo		
	Controlled Trials (n=2283)	Uncontrolled Trials (n=927)	ALL TRIALS n (%)	Controlled Trials (n=1692)	Uncontrolled Trials	ALL TRIALS n (%)
SAR	7	NA	7	2	NA	2
Prophylaxis of SAR	0	NA	0	2	NA	2
PAR	11	24	35	5	NA	5
[illegible]	1	[illegible]	[illegible] (1.3%)	[illegible]	NA	[illegible] 0.5%

[1]Excludes PAR study 194-078 which was submitted after the filing date for NDA 20-762. NA=Not applicable
NOTE: Although all doses of mometasone were included in this analysis, review of the individual cases indicate that [illegible] only of subjects were [illegible] mometasone 200 µg qd.

While sub-analysis of mometasone associated nasal ulcers [illegible] by dose (i.e. 50, 100, 200 µg qd, etc.) because physical examination [illegible]

dose" mometasone subjects (uncontrolled PAR studies C93-014, 193-018, and 193-221) was not recorded by the dose of mometasone (with the exception of treatment emergent adverse events), review by the medical officer of data for all mometasone studies excluding the 'variable dose' studies indicate that all nasal ulcers were reported in subjects taking the 200 µg qd dose of mometasone. Based on these reports, the incidence of nasal ulcers associated with mometasone use was low but higher than the incidence reported in placebo subjects. Furthermore, nasal ulcers were more prevalent in subjects receiving a longer course of mometasone treatment, as noted in the virtual absence of nasal ulcers in SAR subjects (treated less than 4 weeks). A review of the individual nasal ulcer cases for the PAR studies indicates that the majority of nasal ulcers occurred at or later than 4 weeks (Visit 3) post-initiation of mometasone treatment. Subjects who presented with nasal ulcers during the screening or baseline visit (pre-treatment) were discounted from these analyses.

Additionally, of the 35 PAR subjects who were found to have nasal ulcers, 5 of these were elderly subjects who received mometasone 200 µg qd in study C94-092 (incidence=2.9% (5/170)), compared with no findings of nasal ulcers in placebo treated elderly subjects (incidence=0%). Although based on a small number of elderly subjects which make it impossible to draw meaningful conclusions, the incidence of nasal ulcers in elderly subjects in this study was approximately twice that in the 'all ages combined' group of subjects summarized in Table X. above.

10.3.2. Adverse Event Stratification By Duration of Treatment

A longer duration of treatment with mometasone generally resulted in an increased incidence of adverse events, in particular adverse events related to the upper and lower respiratory tract and increased nasal ulcer formation discussed above in Section 10.3.2. Nonetheless, no distinct pattern was evident that indicated an additional or different risk with mometasone treatment as compared with the active comparators (different steroid preparations: beclomethasone, fluticasone, budesonide, triamcinolone and the antihistamine: loratadine). For example, no increased risk for developing liver function test abnormalities, metabolic or endocrine disorders was identified on or after 12 months of treatment with mometasone, compared with 3 months or less of treatment. The sponsor sub-analyzed adverse events by duration of treatment by arbitrarily sub-dividing adverse events by <3 months vs. ≥ 12 months of treatment to better differentiate additional adverse event risk(s) that may be conferred with long-term mometasone use at 200 µg qd. A summary of these results are presented in Table XI. below.

Based on a stratification of adverse events by duration of treatment, (< 3 months or ≥ 12 months), an increase in the adverse events of headache, musculoskeletal pain, dysmenorrhea, viral infection, pharyngitis, sinusitis, and upper respiratory tract infection were noted in subjects treated with mometasone 200 µg qd for 12 months or longer, as compared to those treated for < 3 months. No conclusions can be based on these data because the '12 month and longer'

mometasone treatment group had too few subjects and especially because one would need to correct for the expected increase in adverse events with longer duration of treatment, resulting in no significant proportional increase in adverse event frequency. Hence, the pattern of increased adverse events with prolonged intranasal mometasone use are only minimally suggestive of the known long-term effects of steroid use on immune function, muscle function and possibly adrenal function. While not included in Table XI., a comparison of the other active comparator nasal steroids evaluated in NDA 20-762 to the mometasone treatment, revealed that the active comparator nasal steroids also demonstrated a similar pattern of increased adverse events (again, particularly related to the upper and lower respiratory tract) in subjects treated ≥ 12 months, as compared to < 3 months of treatment [302:53-54].

Table XI. Treatment Emergent Adverse Event (AE) Frequency, AE's ≥ 1%: Mometasone 200 µg qd Treated Subjects vs. Placebo Stratified for a Duration < 3 months and ≥ 12 months for All Controlled Clinical Trials. Pooled Placebo Subjects from all [1]Controlled Trials Included for Comparison.
[302 52-56, 303 391-470, 566-625]

BODY SYSTEM Preferred Term	TREATMENT < 3 Months		TREATMENT ≥ 12 Months
	Mometasone 200 µg qd (n=1639)	Placebo (n=1607)	Mometasone 200 µg qd (n=280)
	n (%)	n (%)	n (%)
All Systems ***Any AE***	***956 (58%)***	***935 (58%)***	***251 (90%)***
Body as a Whole Chest Pain Fatigue Fever ***Headache*** ***Influenza-like Symptoms***	 26 (2%) 19 (1%) 29 (2%) ***374 (23%)*** ***42 (3%)***	 8 (<1%) 32 (2%) 23 (1%) ***350 (22%)*** ***45 (3%)***	 7 (3%) 6 (2%) 15 (5%) ***120 (43%)*** ***28 (10%)***
CNS and PNS Disorders Dizziness	 25 (2%)	 25 (2%)	 4 (1%)
Gastro-intestinal System Disorders Abdominal Pain Diarrhea Dyspepsia Nausea ***Tooth Disorder***	 18 (1%) 18 (1%) 22 (1%) 37 (2%) ***21 (1%)***	 19 (1%) 19 (1%) 23 (1%) 28 (2%) ***12 (1%)***	 9 (3%) 15 (5%) 15 (5%) 12 (4%) ***23 (8%)***
Hearing and Vestibular Disorders Earache	 47 (3%)	 37 (2%)	 19 (7%)
Musculoskeletal System Disorders Arthralgia ***Musculoskeletal Pain*** ***Myalgia***	 23 (1%) ***60 (4%)*** ***36 (2%)***	 20 (1%) ***46 (3%)*** ***28 (2%)***	 13 (5%) ***42 (15%)*** ***28 (10%)***
Reproductive Disorders, Female ***Dysmenorrhea***	 ***21 (3%)***	 ***26 (4%)***	 ***25 (16%)***
Resistance Mechanism Disorders ***Viral Infection***	 ***168 (10%)***	 ***167 (10%)***	 ***76 (27%)***

NOTE: All AE's that increased ≥ 5% in frequency from the 3 month to the 12 month interval are denoted in 'boldface' italic type

[1]Excludes PAR study C94-078, which was submitted after the filing date for NDA 20-762

Table XI. CONTINUED:
Treatment Emergent Adverse Event (AE) Frequency ≥ 1%
Mometasone 200 µg qd Treated Subjects vs. Placebo Stratified for a Duration < 3 months and ≥ 12 months for All Controlled Clinical Trials - Pooled Placebo Subjects from all [1]Controlled Trials Included for Comparison.
[302-52-56, 303-391-470, 566-625]

BODY SYSTEM Preferred Term	TREATMENT < 3 Months		TREATMENT ≥ 12 Months
	Mometasone 200 µg qd (n=1639)	Placebo (n=1607)	Mometasone 200 µg qd (n=280)
	n (%)	n (%)	n (%)
Respiratory System Disorders			
Asthma	***16 (1%)***	***13 (1%)***	***16 (6%)***
Bronchitis	***19 (1%)***	***18 (1%)***	***28 (6%)***
Coughing	***115 (7%)***	***93 (6%)***	***77 (10%)***
Epistaxis	***154 (9%)***	***100 (6%)***	***43 (15%)***
Nasal Burning	45 (3%)	57 (4%)	7 (3%)
Nasal Irritation	34 (2%)	50 (3%)	11 (4%)
Pharyngitis	***168 (10%)***	***153 (10%)***	***52 (19%)***
Rhinitis	***53 (3%)***	***50 (3%)***	***23 (8%)***
Sinusitis	***37 (2%)***	***55 (3%)***	***60 (21%)***
Sneezing	34 (2%)	60 (4%)	3 (1%)
Upper Respiratory Tract Infection	***54 (3%)***	***37 (2%)***	***70 (25%)***
Skin and Appendages Disorders			
Pruritus	22 (1%)	20 (1%)	5 (2%)
Vision Disorders			
Conjunctivitis	***49 (3%)***	***30 (2%)***	***17 (6%)***

NOTE: All AE's that increased ≥ 5% in frequency from the 3 month to the 12 month interval are denoted in 'bold-face' italic type
[1]Excludes PAR study C94-078, which was submitted after the filing date for NDA 20-762

10.3.4. Adverse Event Stratification by Mometasone Dose

For most adverse events, there was no evidence of a dose response among subjects who were treated with mometasone. Importantly, PAR subjects receiving mometasone 200 µg qd and 'variable' dose (100-400 µg qd) mometasone received these treatments for a longer duration of time than the SAR mometasone 50 and 100 µg qd subjects, hence duration of treatment is a potential confounder, in addition to dose of mometasone when assessing adverse event frequency in these 2 subgroups of subjects. Nonetheless, a small dose response was evident for epistaxis, ranging in incidence from 3% in mometasone 50 µg qd subjects to 11% in mometasone 800 µg qd subjects, and perhaps an even smaller dose response was evident for viral and upper respiratory infection. Of the nasal ulcers reported as adverse events (3 cases total), 2 cases were reported for the mometasone 200 µg qd group and 1 case was reported in the 'variable' dose mometasone group [302:223]. Within the 'variable' dose mometasone group, a very small increase in the incidence of earache, pharyngitis, and nasal irritation was evident with increasing doses of mometasone, however the number of subjects in each group was too small to make meaningful conclusions, especially since this trend was not as appreciable for 'non-variable' dose mometasone subjects.

In general, adverse events were less frequent at the mometasone 50 µg qd and 100 µg qd dosage. Although headache and pharyngitis were again more frequent adverse events for all mometasone dose groups, no consistent dose response was seen with higher mometasone doses. A summary of the absolute number of reports of adverse events and the frequency of adverse events for the different doses of mometasone administered during the controlled clinical trials for all SAR, prophylaxis of SAR, and PAR indications are presented in Table XII.

Table XII. Stratification of Adverse Events by Mometasone Dose as Compared with Placebo, Pooled Safety Population
[302 68-69, 303 237-259]

BODY SYSTEM Preferred Term	Mometasone, n (%)								Placebo, n (%) (n=1671)
					*Variable dose (100-400) µg qd				
	50 µg qd (n=96)	100 µg qd (n=221)	200 µg qd (n=2103)	800 µg qd (n=95)	100 µg qd (n=112)	200 µg qd (n=501)	400 µg qd (n=155)	200 µg qd + loratadine 10 mg qd (n=169)	
All Systems Any AE	62 (65%)	115 (52%)	1344 (64%)	65 (68%)	66 (59%)	344 (69%)	103 (66%)	63 (37%)	979 (59%)
Body as a Whole									
Chest Pain	1 (1%)	0 (0%)	38 (2%)	1 (1%)	1 (1%)	3 (1%)	2 (1%)	0 (0%)	10 (1%)
Fatigue	3 (3%)	2 (1%)	32 (2%)	1 (1%)	1 (1%)	10 (2%)	2 (1%)	3 (2%)	32 (2%)
Fever	2 (2%)	1 (<1%)	50 (2%)	3 (3%)	7 (6%)	17 (3%)	4 (3%)	0 (0%)	26 (2%)
Headache	31 (32%)	52 (24%)	551 (26%)	39 (41%)	20 (18%)	145 (29%)	41 (26%)	32 (19%)	366 (22%)
Influenza-like Symptoms	3 (3%)	2 (1%)	91 (4%)	0 (0%)	1 (1%)	12 (2%)	6 (4%)	0 (0%)	51 (3%)
CNS and PNS Disorders									
Dizziness	3 (3%)	6 (3%)	31 (1%)	1 (1%)	2 (2%)	6 (1%)	1 (1%)	1 (1%)	28 (2%)
Gastro-intestinal System Disorders									
Abdominal Pain	0 (0%)	2 (1%)	31 (1%)	0 (0%)	3 (3%)	8 (2%)	4 (3%)	1 (1%)	19 (1%)
Diarrhea	0 (0%)	3 (1%)	36 (2%)	3 (3%)	2 (2%)	5 (1%)	4 (3%)	1 (1%)	19 (1%)
Dyspepsia	1 (1%)	7 (3%)	41 (2%)	0 (0%)	3 (3%)	13 (3%)	2 (1%)	3 (2%)	24 (1%)
Nausea	3 (3%)	3 (1%)	56 (3%)	3 (3%)	1 (1%)	12 (2%)	3 (2%)	0 (0%)	29 (2%)
Tooth Disorder	0 (0%)	1 (<1%)	48 (2%)	0 (0%)	5 (4%)	8 (2%)	7 (5%)	1 (1%)	13 (1%)
Hearing and Vestibular Disorders									
Earache	6 (6%)	4 (2%)	71 (3%)	2 (2%)	***0 (0%)***	***15 (3%)***	***8 (5%)***	1 (1%)	40 (2%)
Musculoskeletal System Disorders									
Arthralgia	3 (3%)	3 (1%)	40 (2%)	1 (1%)	3 (3%)	12 (2%)	3 (2%)	0 (0%)	21 (1%)
Musculoskeletal Pain	4 (4%)	(3%)	112 (5%)	3 (3%)	6 (5%)	28 (6%)	12 (8%)	1 (1%)	***50 (3%)***
Myalgia	1 (1%)	2 (1%)	77 (4%)	2 (2%)	1 (1%)	9 (2%)	5 (3%)	2 (1%)	31 (2%)

NOTE: All AE's that show an increase in frequency with increased mometasone dose are denoted in 'bold-face' italic type

Excludes PAR study C94-078 which was submitted after the filing date for NDA 20-762

*Variable dose mometasone subject number is > 506 in the pooled safety population because AE at each mometasone dose change were counted as new AE's

II. CONTINUED: Stratification of Adverse Events by Mometasone Dose as Compared with Placebo, Pooled Safety Population

[302.68-69, 217, 303:237-259]

STEM Term	Mometasone, n (%)								Placebo, n (%) (n=1671)
	50 µg qd (n=96)	100 µg qd (n=221)	200 µg qd (n=1103)	800 µg qd (n=95)	Variable dose (100-400) µg qd			200 µg qd + loratadine 10 mg qd (n=169)	
					100 µg (N=112)	200 µg (n=501)	400 µg (n=155)		
ive Disorders, Female									
rrhea	1 (4%)	1 (2%)	50 (5%)	1 (3%)	1 (2%)	14 (5%)	3 (4%)	3 (4%)	***26 (3%)***
Mechanism Disorders									
	0 (0%)	0 (0%)	15 (1%)	0 (0%)	0 (0%)	3 (1%)	1 (1%)	0 (0%)	7 (<1%)
nfection	0 (0%)	0 (0%)	16 (1%)	0 (0%)	0 (0%)	7 (1%)	3 (2%)	1 (1%)	2 (<1%)
tion	***4 (4%)***	***4 (2%)***	***292 (14%)***	***1 (1%)***	***14 (13%)***	***93 (19%)***	***28 (18%)***	***2 (1%)***	***181 (11%)***
y System Disorders									
	2 (2%)	1 (<1%)	39 (2%)	0 (0%)	1 (1%)	19 (4%)	3 (2%)	0 (0%)	18 (1%)
	1 (1%)	0 (0%)	41 (2%)	1 (1%)	1 (1%)	22 (4%)	5 (3%)	0 (0%)	20 (1%)
	8 (8%)	9 (4%)	155 (7%)	6 (6%)	8 (7%)	35 (7%)	13 (8%)	4 (2%)	97 (6%)
	3 (3%)	***9 (4%)***	***223 (11%)***	***10 (11%)***	11 (10%)	***44 (9%)***	14 (9%)	***6 (4%)***	***104 (6%)***
g	0 (0%)	10 (5%)	60 (3%)	3 (3%)	4 (4%)	12 (2%)	4 (3%)	3 (2%)	63 (4%)
ation	6 (6%)	6 (3%)	52 (2%)	1 (1%)	***1 (1%)***	***9 (2%)***	***9 (6%)***	0 (0%)	53 (3%)
s	17 (18%)	14 (6%)	246 (12%)	11 (12%)	***7 (6%)***	***52 (10%)***	***19 (12%)***	7 (4%)	162 (10%)
	2 (2%)	9 (4%)	82 (4%)	6 (6%)	3 (3%)	25 (5%)	4 (3%)	0 (0%)	56 (3%)
	2 (2%)	4 (2%)	114 (5%)	1 (1%)	5 (4%)	23 (5%)	7 (5%)	1 (1%)	58 (3%)
	4 (4%)	7 (3%)	38 (2%)	5 (5%)	1 (1%)	11 (2%)	1 (1%)	1 (1%)	64 (4%)
spiratory Tract Infection	***0 (0%)***	***1 (<1%)***	***136 (6%)***	***1 (1%)***	1 (1%)	6 (1%)	1 (1%)	***1 (1%)***	***40 (2%)***
fers									
	1 (<1%)	3 (1%)	31 (1%)	2 (2%)	1 (1%)	12 (2%)	4 (3%)	0 (0%)	22 (1%)
rders									
ns	3 (3%)	3 (1%)	74 (4%)	3 (3%)	2 (2%)	16 (3%)	3 (2%)	0 (0%)	32 (2%)

s that show an increase in frequency with increased mometasone dose are denoted in 'bold-face' italic type

P study C94-078, which was submitted after the filing date for NDA 20-762.

e mometasone subject number is > 506 in the pooled safety population because AE at each mometasone dose change were counted as new AE's.

10.3.5. Adverse Event Stratification by Demographics (Age, Gender, Race)

Stratification of adverse events by age, gender, or race failed to reveal a significant differential response to mometasone treatment as compared to placebo, although the overall incidence of adverse events with both mometasone 200 µg qd and placebo treatment tended to be greater in:

(1) older (i.e. age ≥ 65 years: 147 AE reports (74% incidence)) than younger subjects (18-64 years: 1109 AE reports (65% incidence) and age 12-17 years: 88 AE reports, 46% incidence). No AE's were reported in the one mometasone subject <12 years of age [304:759].

(2) female than male subjects (female subjects: 695 AE reports (70% incidence), male subjects: 649 AE reports (58% incidence).

(3) Caucasian than non-Caucasian subjects (Caucasian subjects: 1214 AE reports (66% incidence), non-Caucasian subjects: 130 AE reports (50% incidence)).

The incidence of AE reports by these demographic groups for all doses of mometasone were similar to those reported for mometasone 200 µg qd [304:759-939, 305:941-1252, 306:1254-1630, 307:1633-1728].

Individual adverse events that appeared to increase with age (a 3-18 percentage point increase in incidence in subjects age 65 years or older as compared with subjects age 12-17) included earache, coughing, epistaxis, pharyngitis, upper respiratory tract infection, arthralgia, myalgia, musculoskeletal pain, and nasal ulcers; the latter, as noted on review of subject nasal examination reports and review of PAR study C94-092 (geriatric study) [302:60-65]. These adverse events were noted to increase with age in both mometasone and placebo treated subjects [302:60-61].

Stratification of individual adverse events by gender revealed that female subjects in both mometasone and placebo treatment groups tended to report most adverse events more frequently (approximately 1-5 percentage points more) than male subjects. The greatest reporting difference between male and female subjects was for headache, with 31% of females and 22% of males treated with mometasone 200 µg qd and 26% of females and 18% of males treated with placebo reporting this adverse event [302:62]. Review of all AE's failed to indicate that either male or female subjects are preferentially at risk for any specific adverse event coincident with administration of mometasone nasal spray. In other words, no gender-specific trend for adverse events was detected with the safety database provided in NDA 20-762.

Review of adverse events by subject racial background revealed that most adverse events were several percentage points (1-3) higher in Caucasian than non-Caucasian subjects, regardless of treatment. The greatest differences were seen for headache, epistaxis, pharyngitis, and sinusitis; with incidences ranging from 2-15 percentage points greater in Caucasian than non-Caucasian subjects [302:64-65]. Because the number of non-Caucasian subjects was small, the overall difference (generally 4-7 percentage points) was small between Caucasians and non-Caucasians and there is no clear biologic rationale to account for such racial

differences, it is unlikely that the differential effect noted in these studies is one which is real.

10.3.6. Subject Discontinuations due to Adverse Events

Incidence of subject discontinuation due to adverse events were low for all mometasone groups (as well as the active comparator nasal steroids and loratadine), and placebo; ranging from 1%-5%. The most common adverse events leading to subject discontinuation in mometasone groups were respiratory disorders, namely epistaxis (13 subject discontinuations (0.4%)), sinusitis (7 subject discontinuations (0.2%), and pharyngitis (5 subjects (0.2%)). Discontinuation rates for these 3 adverse events were likewise similar in placebo group subjects [302:78-85]. As discussed for the individual SAR, prophylaxis of SAR, and PAR studies, the most common reasons for treatment discontinuation were not due to adverse events per se but lack of subject follow-up or non-compliance. Of those discontinuations that were due to adverse events, most of these were unrelated to treatment. A summary table of subject disposition (all reasons for study discontinuation) for all clinical studies in NDA 20-762 was not provided in the NDA submission. Individual subject discontinuations due to adverse events are summarized in Vol 303:78-85 of the NDA submission and are tabulated by organ system in Table XIII. below.

Table XIII. Subject Discontinuation due to Adverse Events by Mometasone Dose as Compared with Placebo, Pool
Safety Population [302:76-77]

BODY SYSTEM Organ Class	Mometasone, n (%)							
	50 µg qd (n=95)	100 µg qd (n=221)	200 µg qd (n=2103)	800 µg qd (n=95)	'Variable dose (100-400) µg qd			200 µg qd + loratadine 10 mg qd (n=169)
					100 µg qd (n=77)	200 µg qd (n=316)	400 µg qd (n=113)	
All Systems-Any AE	3 (3%)	7 (3%)	60 (3%)	3 (3%)	3 (4%)	13 (4%)	6 (5%)	2 (1%)
Autonomic Nervous System	0	0	2 (<1%)	0	0	0	0	0
Body as a Whole-General	0	1 (<1%)	12 (1%)	1 (1%)	0	3 (1%)	1 (1%)	0
Cardiovascular System	0	0	0	0	0	1 (<1%)	0	0
CNS/PNS Disorders	0	1 (<1%)	6 (<1%)	0	0	2 (1%)	0	0
GI System Disorders	0	2 (1%)	2 (<1%)	0	0	1 (<1%)	0	0
Hearing/Vestibular Disorders	0	1 (<1%)	2 (<1%)	0	0	0	0	0
Heart Rate and Rhythm	0	0	1 (<1%)	0	0	1 (<1%)	0	0
Liver and Biliary System	0	0	0	1 (1%)	0	0	0	0
Metabolic and Nutritional	0	0	1 (<1%)	0	0	0	0	0
Musculoskeletal System Disorders	0	0	5 (<1%)	0	0	0	1 (1%)	0
Myo-, Endo-, Pericardial and Valve	0	0	1 (<1%)	0	0	0	0	0
Neoplasm	0	0	1 (<1%)	0	0	0	0	0
Psychiatric	0	0	2 (<1%)	0	0	0	0	0
Reproductive Disorders, Female	0	0	0	0	1*	2*	0	0
Resistance Mechanism (Infection)	1 (1%)	1 (<1%)	4 (<1%)	0	0	1 (<1%)	1 (1%)	1 (1%)
Respiratory System	2 (2%)	1 (<1%)	33 (2%)	1 (1%)	2 (3%)	4 (1%)	3 (3%)	1 (1%)
Skin	0	0	4 (<1%)	0	0	1 (<1%)	1 (1%)	0
Urinary System	0	0	0	0	0	1 (<1%)	0	0
Vision	0	1 (<1%)	1 (<1%)	0	0	0	0	0

Excludes PAR study C94-078 which was submitted after the filing date for NDA 20-762. *No proportion was calculated because the # of female subjects was not identified in 'va

10.3.7. Serious Adverse Events and Death

Among all subjects treated in all treatment groups, 75 subjects (1.1%) were defined by the sponsor as having a 'serious' adverse event, as per the regulatory definition of 'serious'; however on review of the patient capsule summaries [307:1876-1950] many of these subjects never required hospitalization for their problem (e.g. all the subjects with liver function test abnormalities), and had complete reversal of the abnormality on discontinuation of mometasone treatment. 1.2% of all mometasone and 0.8% of placebo treated subjects developed 'serious' adverse events, respectively [302:85]. Of these serious adverse events, many were elective surgeries, and only 6 subjects for all treatment groups combined had serious events that were considered by the principal investigator(s) to be at least 'possibly' related to treatment. For the 4 mometasone treated subjects who developed 'serious' adverse events, these consisted of the following:

(1) One subject (subject C92-011-01, #014) experienced dizziness, wooziness, blurred vision, and disorientation 3.5 hours after the first dose of mometasone 100 µg qd. The subject was evaluated in the emergency room and recovered. Mometasone causality was based on the temporal relationship between mometasone use and onset of symptoms.

(2) One subject (subject I93-221-03, #016) experienced sternal pressure, palpitations, and dyspnea after 10 days of treatment with mometasone 200 µg qd ('variable' dose mometasone group). Two days later the subject stopped using mometasone for 1 day and her symptoms abated. When she resumed mometasone use the following day, the symptoms reappeared, so the subject discontinued mometasone treatment.

(3) One subject (subject C92-011-05, #028) had normal liver function tests at screening consisting of an SGPT=42 IU/L and an SGOT=27 IU/L but developed elevated levels of these 2 parameters (SGPT=79 IU/L, SGOT=159 IU/L) at his final visit after completing a full 4-week course of mometasone 100 µg qd. His LFTs returned to normal range during a repeat evaluation 1-2 weeks later.

(4) The final subject (subject C92-011-05, #015) who had normal liver function tests of an SGPT=17 IU/L and SGOT=14 IU/L at screening, developed elevated levels of these 2 parameters (SGPT=123 IU/L, SGOT=169 IU/L) after 15 days of treatment with mometasone 800 µg qd. The subject discontinued mometasone treatment 3 days later when repeat evaluation showed continued elevation of LFTs (SGPT=175 IU/L, SGOT=80 IU/L). His LFTs returned to normal 5 weeks after the end of treatment.

Other potentially relevant adverse events classified as 'serious' by the sponsor

reported with mometasone use which relate to the known effects of steroids are summarized as follows:

Changes in liver function tests (which consisted of abnormalities of SGOT and SGPT) were reported by the sponsor as 'serious' adverse events in a total of 12 study subjects, 6 of whom were treated with mometasone [302:88-91]. Three of these 6 subjects (a 26 year old male subject treated with mometasone 100 µg qd (subject C92-011-01, # 014) [302:88], a 28 year old male treated with mometasone 200 µg qd (subject C93-215-01, #043) [302:88] and, a 31 year old male treated with mometasone 800 µg qd (subject C92-011-05, #015) [302:89] may have developed LFT abnormalities related to mometasone treatment. None of these subjects were symptomatic and none required hospitalization for their problem (serial laboratory testing in these subjects was performed at the study site(s)). Two subjects (I93-018-02, #008 and I94-079-11, #016) developed viral hepatitis while receiving mometasone treatment which was confirmed by viral serology tests [307:1923, 1948].

One 12 year old male subject treated with mometasone 200 µg qd for 12 weeks (a 'variable' dose mometasone subject) had an abnormally low 8 a.m. plasma cortisol level of 104.0 µg/dL on week 12 of the study that was reported as a serious event, however re-evaluation 3 weeks and 12 weeks later, despite continuation of mometasone treatment, revealed a normal plasma cortisol level (319.8 µg/dL) [292:391, 295:2051, 302:89].

One report of pregnancy and spontaneous abortion occurred in a 33 year old female (subject I93-221-17, # 019) who discontinued mometasone treatment (200 µg qd) 2 weeks earlier, having received a total of 9 weeks of mometasone treatment. The relationship of the spontaneous abortion to mometasone treatment is not clear in that the approximate age of the fetus age at the time of abortion was not known [291:57, 292:391, 302:89].

Three subject deaths (for all treatments) were reported in NDA 20-762; one death due to cerebrovascular accident reported in a 74 year old female who received mometasone 200 µg qd (subject C94-092-02, #02), one death due to renal failure and fatal myocardial infarction reported in a 67 year old male who was discontinued from the 'variable' dose mometasone group 4.5 months earlier (last dose of mometasone received was 200 µg qd, subject I93-221-05, #01), and one death due to an automobile accident reported in a 20 year old male in the placebo group (subject I94-079-21, #07) [302:87].

10.4. Laboratory Test Results

Laboratory tests performed throughout the study duration and which consisted of a complete blood count, blood chemistries, urinalysis, and serum pregnancy test (for all women) did not reveal any unexpected abnormalities in mometasone treated subjects, as compared with placebo. The most notable change in mometasone treated subjects (and also in the active comparator nasal steroids) was a decrease in the peripheral blood eosinophil count (-8.3% median change for mometasone 200 µg qd subjects), with a smaller decrease noted in the total white

blood cell (WBC) count (-4.9% median change for mometasone 200 µg qd subjects) [302:93]. No significant median change or flag shift changes for blood chemistries or urinalysis was noted in mometasone treated subjects, as compared with placebo for the pooled safety population [302:93-94, 96-97, 308:1953-2122]. Stratification by age, gender, and race also failed to reveal any consistent pattern of change in any laboratory tests [302:99-107, 308:2125-2284, 309:2286-2614, 310:2616-2879].

Of the small number of mometasone treated subjects who developed clinically significant laboratory test abnormalities [311:2881-2894], the majority of these involved liver function test or WBC abnormalities and occurred in subjects receiving mometasone 200 µg qd (27/2103 subjects, 1.3% incidence) and 'variable' dose mometasone subjects who received mometasone 200 µg qd (19/506 subjects or 3.8% incidence) [302:107]. These subjects were clinically asymptomatic and did not require hospitalization or further clinical intervention for resolution of their laboratory abnormality with the exception of discontinuation of mometasone treatment. Clinically significant laboratory abnormalities for mometasone treated subjects are summarized in Table XIV, below.

Table XIV. Clinically Meaningful Laboratory Abnormalities in Mometasone Treated Subjects, as compared with Placebo ≥ 1% in Frequency (Pooled Safety Population, Controlled and Uncontrolled Studies), [302:108]

VARIABLE	NUMBER (%) of SUBJECTS	
	All Mometasone Doses (n=3210)	Placebo (n=1671)
↓ WBC	18 (1%)	7 (<1%)
↑ SGPT	13 (<1%)	9 (1%)
↑ SGOT	12 (<1%)	3 (<1%)
↑ Alkaline Phosphatase	6 (<1%)	3 (<1%)
↑ Bilirubin	4 (<1%)	4 (<1%)
↑ Glucose	2 (<1%)	2 (<1%)
↑ Phosphorus	2 (<1%)	2 (<1%)
↓ Hemoglobin	1 (<1%)	2 (<1%)
↑ Albumin	1 (<1%)	0
↑ BUN	1 (<1%)	1 (<1%)
↑ Creatinine	0	1 (<1%)

10.4.1. Special Studies:

10.4.1.a. Hypothalamic-Pituitary-Adrenal (HPA)-Axis Suppression Studies:

Four studies were performed in NDA 20-762 to specifically to assess mometasone's effect on human HPA-axis suppression. These studies and their findings are summarized as follows:

(1) Study C93-196: Multiple-dose Comparative Systemic Bioactivity Study of Mometasone Nasal Spray in Adult Volunteers with Allergic Rhinitis [1.2:19-21].

Study design: This was a randomized, placebo- and positive-controlled (prednisone 10 mg po qd), parallel group, multiple-dose study of mometasone nasal spray administered at 200 µg qd and 400 µg qd vs. placebo and vs. prednisone 10 mg po q a.m. for 36 consecutive days in a total of 64 male volunteers with at least a 2 year history of SAR and documented skin test positivity to a seasonal allergen. Volunteers underwent a.m. plasma cortisol testing and a 6 hour Cortrosyn stimulation test (250 µg of cosyntropin administered intravenously over 6 hours with plasma sampling at 2, 4, and 6 hours during the infusion at both the baseline visit and the final (day 36) visit to assess HPA-axis suppression. An abnormal response in plasma cortisol was defined a priori as an incremental increase in plasma cortisol 6 hours post-ACTH infusion of < 7 µg/dL or a 6 hour post-ACTH infusion plasma cortisol value < 18 µg/dL.

24 hour urinary free cortisol levels were also acquired at the baseline and day 36 visit. Plasma and urine cortisol levels were analyzed via a validated HPLC method. Results from these analyses were statistically analyzed using a 1-way ANOVA to extract treatment effects. Pairwise comparisons for each treatment combination were based on 'Dunnett's multiple comparison procedure.

Results:

Review of HPA-axis suppression data from study C93-196 indicates that overall, no statistically significant decrease in mean plasma cortisol levels or 24 hour urinary free cortisol levels was seen with mometasone nasal spray, given at a dose of either 200 or 400 µg qd. A statistically significant suppression of both mean plasma and 24 hour urinary free cortisols was detected with the positive control, prednisone given at a dose of 10 mg po qd for 36 days. Notable however, was the small decrement on Day 36 in both the plasma and 24 hour urinary free cortisol levels post-ACTH infusion at all time points in mometasone treated volunteers, which was slightly more profound with the 400 µg qd dose. A similar pattern of response was also noted in the placebo volunteers, hence the meaning of this finding is unclear in terms of the mometasone treated volunteers. The plasma cortisol and 24 hour urinary free cortisol data are summarized in Tables XV. and XVI. below.

Importantly however, several outliers in adrenal response were detected in both the mometasone 200 and 400 µg qd groups; namely 2 volunteers (volunteers #28 and 32) in the mometasone 200 µg qd group (2/16 mometasone 200 µg qd volunteers total) and 1 volunteer (volunteer #31) in the mometasone 400 µg qd group (1/16 mometasone 400 µg qd volunteers total) [Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, Study Report for C93-196, p. 14-15]. A total of 11 volunteers (volunteers #5, 13, 21, 27, 36, 47, 48, 49, 56, 57, and 58) in the prednisone 10 mg po qd group had abnormal responses to cosyntropin (ACTH) stimulation. One volunteer (#51) in the placebo group also had an abnormal response to cosyntropin stimulation. Based of these results, one may conclude that most volunteers treated with mometasone at 200 µg qd (or 400 µg qd) would not be expected to have HPA-axis suppression after short-term use (i.e. < 1 month) however, individual adrenal responses may vary, and in rare individual volunteers, mild adrenal suppression could occur at a total daily intranasal dose of 200 µg qd.

Table XV. Mean Plasma Cortisol Levels Pre- and Post-Cosyntropin (ACTH) Simulation Testing. Study C93-196. (Before and After 36 Days of Treatment with Mometasone, Prednisone, or Placebo)
[1.2.20, Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, p. 27]

TREATMENT GROUP	N	TREATMENT PHASE	Hours of ACTH Infusion				'Change in Cosyntropin Stimulated Plasma Cortisol Concentration (µg/dL)
			0	2	4	6	
Mometasone 200 µg qd	16 16	Baseline (Day 1) Final visit (Day 36)	11.0 9.2	19.9 18.8	24.4 20.5	30.0 23.3	19.0 14.1
Mometasone 400 µg qd	16 16	Baseline (Day 1) Final visit (Day 36)	11.5 9.4	21.2 18.5	26.3 20.4	32.5 22.3	21.0 12.9
Placebo	16 16	Baseline (Day 1) Final visit (Day 36)	11.3 8.5	21.6 19.0	25.9 21.1	32.3 22.2	20.4 13.7
Prednisone 10 mg po qd	16 16	Baseline (Day 1) Final visit (Day 36)	11.6 6.0*	20.5 11.8*	24.8 11.7*	29.9 14.8*	18.3 8.8*

'Change denotes change from baseline to Day 36.
*: p<0.01 compared with placebo (Dunnett's test). †:p≤0.05 compared with placebo (Dunnett's test).

Table XVI. Mean 24 Hour Urinary Free Cortisol Levels Pre- and Post-Cosyntropin (ACTH) Simulation Testing. Study C93-196. (Before and After 36 Days of Treatment with Mometasone, Prednisone, or Placebo) [Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, p. 27]

TREATMENT GROUP	N	TREATMENT PHASE	Urinary Free Cortisol (µg/24 hrs) (Pre-ACTH Infusion)	N	Urinary Free Cortisol (µg/24 hrs) (Post-ACTH Infusion)	N	'Change in 24-hours urinary free cortisol (µg/24 hours)
Mometasone 200 µg qd	6 16	Baseline (Day 1) Final visit (Day 36)	16.2 12.1	6 16	477 383	6 16	461 371
Mometasone 400 µg qd	11 15	Baseline (Day 1) Final visit (Day 36)	30.3 13.5	11 15	306 395	11 15	276 382
Placebo	11 15	Baseline (Day 1) Final visit (Day 36)	43.1 14.2	11 15	629 484	11 15	586 470
Prednisone 10 mg po qd	13 15	Baseline (Day 1) Final visit (Day 36)	24 0.7*	13 15	479 329	13 15	455 328

'Change denotes change from baseline to Day 36.
* p<0.01 compared with placebo (Dunnett's test).

(2) Study C92-022: Multiple-dose Safety and Tolerance Study of Mometasone in Healthy Male Volunteers [1.2:16]

Study design: This was a randomized, placebo- and positive-controlled (prednisone 10 mg po qd), parallel group, multiple-dose study of mometasone nasal spray administered at 400 µg qd and 1600 µg qd vs. placebo and vs. prednisone 10 mg po q a.m. for 29 consecutive days in a total of 48 male volunteers.

Volunteers underwent 8 a.m. plasma cortisol testing on Day 1 and serial plasma cortisol testing to determine the plasma cortisol area under the curve (AUC_{0-24}) at 3 a.m., 4 a.m., 5 a.m., 6 a.m. 7 a.m., 8 a.m., 9 a.m., 10 a.m., 11 a.m., 12 noon, 1 p.m., 3 p.m., 5 p.m., 7 p.m., 9 p.m., and 11 p.m. on Days 0, 7, 14, 21, and 28 of the study. An 8 hour Cortrosyn stimulation test (250 µg of cosyntropin administered intravenously over 8 hours with plasma sampling at 2, 4, and 6 hours during the infusion was performed at both the baseline visit and the final (day 29) visit to assess HPA-axis suppression. An abnormal response in plasma cortisol was again defined as an increase in plasma cortisol 6 hours post-ACTH infusion of < 7 µg/dL or a 6 hour post-ACTH infusion plasma cortisol value < 18 µg/dL. Urine was collected as 24-hour block samples for the determination of 24-hour urinary free cortisol and 17-hydroxycorticosteroid levels during both the 24 hour period prior to ACTH stimulation and the 24 hour period following initiation of

the cosyntropin infusion. Plasma and urine samples were analyzed for cortisol using a commercial radioimmunoassay (RIA) method. The area under the plasma cortisol concentration time curve for the 24-hour period following each treatment (AUC_{0-24}) was calculated for each volunteer using the trapezoidal rule. Plasma cortisol levels below 2.0 µg/dL (the lower limit of quantitation) were recorded as zero.

The primary variables of interest in this study were $AUC_{(3-23)}$ (3 a.m. to 11 p.m.), C_{max}, and $C_{(8\ a.m.)}$. For each individual time point, values below assay sensitivity were excluded by the sponsor from statistical analysis. Plasma concentration data were analyzed statistically using ANOVA, extracting the effect due to treatment group.

Results:

In this study, 2 problems were encountered with the methods employed in executing the study which have bearing on interpretation of study results. First, no restrictions were initially placed on volunteers' sleep habits (prior to study Day 7), resulting in plasma cortisol profiles prior to Day 14 of the study that did not have a characteristic diurnal pattern. Hence, the sponsor considered HPA data only to be appropriate for Days 14, 21, and 28. Secondly, use of the RIA to detect plasma cortisol levels exhibited cross-reactivity between cortisol and prednisone in the RIA which precluded interpretation of the prednisone treatment group in this study and limits the conclusions that can be derived from the cosyntropin stimulation test since interpretability of these data are predicated upon a statistically significant difference between the prednisone group and the placebo group.

A summary of the primary variables of interest is presented in Table XVII. below and overall, did not indicate any significant reduction in the plasma cortisol AUC_{3-23}, C_{max}, or $C_{(8\ a.m.)}$ for Days 14, 21, and 28 of the study in mometasone treated volunteers [1 2:18].

Table XVII. Effects of Intranasal Mometasone (400 µg and 1600 µg qd) vs. Placebo on Plasma Cortisol $AUC_{(1-23)}$, C_{max}, and $C_{(8\ a.m.)}$ on Study Day 28. Study C92-022. [1.2:18]

	Plasma Cortisol $AUC_{(1-23)}$ (µg/dL)	[1](%CV)	Plasma Cortisol C_{max} (µg/dL)	(%CV)	8 a.m. Plasma Cortisol Level $C_{(8\ a.m.)}$ (µg/dL)	(%CV)
Placebo	200.0	13	18.4	12	13.7	16
[2]Mometasone 400 µg qd	206.6	11	18.4	12	14.4	21
Mometasone 1600 µg qd	199.7	10	19.5	11	13.5	21

[1]CV=Coefficient of Variation [2]Mometasone administered intranasally
The prednisone group is not included in the analysis because of cortisol cross-reactivity by RIA

Review of the plasma and 24 hour urinary free cortisol levels for individual volunteers by line listings in this study failed to reveal significant HPA-axis suppression in all mometasone treated volunteers with the exception of one volunteer (volunteer #04 in the mometasone 400 µg qd group). Nonetheless, this volunteer had normal HPA function in that his pre-cosyntropin plasma cortisol value was 20 µg/dL (normal range 8 a.m. plasma cortisol: 5-23 µg/dL, *Cecil Textbook of Medicine, 20th Edition, Bennett, JC and Plum F., Eds., 20th Edition, 1996, W.B. Saunders, Co., p.2225*) and his 24 hour urinary free cortisol increased from 3 mg/24 hours to 18 mg/24 hours post-cosyntropin (ACTH) stimulation.

Based on data from this study, which is limited in interpretability because of the study flaws previously discussed, no significant difference in plasma cortisol levels (AUC, C_{max} and 8 a.m. plasma cortisol level) on day 28 was nonetheless noted in either the mometasone 400 µg qd or 1600 µg qd treatment group, as compared with placebo.

(3) Study I90-664: Single-dose Comparative Bioactivity of Mometasone vs. Dexamethasone in Healthy Male Volunteers [1.2:13-15]

Study design: This was a randomized, placebo- and positive-controlled (dexamethasone), parallel group, single-, rising-dose study of mometasone nasal spray suspension administered in rising doses of 1000 µg qd, 2000 µg qd, and 4000 µg qd vs. orally administered mometasone administered in rising doses of 2 mg, 4 mg, and 8 mg po qd, vs. dexamethasone elixir administered in rising doses of 0.2 mg, 0.4 mg, and 0.8 mg po qd, and vs. placebo administered to a total of 24

healthy male volunteers

Volunteers were randomly assigned to the 3 active treatment groups, so that 8 volunteers received intranasal mometasone (1000 µg qd, 2000 µg qd, and 4000 µg qd, and placebo), 8 volunteers received oral mometasone (2 mg, 4 mg, and 8 mg po qd, and placebo), and 8 volunteers received oral dexamethasone (0.2 mg, 0.4 mg, and 0.8 mg po qd, and placebo). Doses were administered at 11 p.m. in a rising progression with the lowest dose administered first. Dose administrations were separated by at least 72 hours.

Plasma cortisol levels were determined at approximately 8 a.m. each day following each 11 p.m. dose; the subsequent 11 p.m. dose in each treatment sequence was not administered until the 8 a.m. plasma cortisol level was not more than 4 µg/dL below the volunteer's designated baseline value and was between 10-25 µg/dL.

In this study cortrosyn (ACTH) stimulation tests were not performed, rather the plasma cortisol area under the curve (AUC_{0-24}) was calculated for the 24-hour period following each treatment based on plasma cortisol levels measured at 11 p.m. prior to treatment administration and at 5 a.m., 6 a.m., 7 a.m., 8 a.m., 9 a.m., 11 a.m., 3 p.m., 6 p.m., and 11 p.m. the following day. Urine for a 24 hour urinary free cortisol assessment was collected as a 24-hour block sample during the 24-hour period prior to the initial treatment administration and during the 48-hour period following each drug administration for subsequent analysis for free cortisol content. Both plasma and urine samples were analyzed for cortisol levels via RIA. Plasma cortisol levels below 2.0 pg/dL were recorded as zero [1.2:15].

Results:

Review of the pooled data and individual volunteer line listings failed to reveal a decrease in the plasma cortisol AUC_{0-24}, 8 a.m. plasma cortisol levels, or 24 hour urinary free cortisol levels in volunteers treated with either intranasal or oral mometasone, as compared with placebo treatment. Conversely, dexamethasone treatment (all doses) resulted in abnormal 8 a.m. cortisol levels (defined as plasma cortisol < 10 µg/dL by the sponsor) and reduced 24 hour plasma AUC values in nearly all volunteers who received dexamethasone treatment, as compared to placebo treatment. Results of the mean AUC_{0-24} for plasma cortisol in all 3 active treatment groups is summarized in Table XVIII. below and confirm a significant adrenal suppression effect only in dexamethasone treated volunteers.

Table XVIII. Mean Plasma Cortisol AUC_{0-24} and Percent Reduction from Placebo for Intranasal Mometasone, Oral Mometasone, and Dexamethasone Treatment Volunteers. Study 190-664. [1.2.15. Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, Study Report 190-664, p. 32]

	Mometasone (Intranasal)			Mometasone (Oral)			Dexamethasone (Oral)		
	1000 µg	2000 µg	4000 µg	2 mg	4 mg	8 mg	0.2 mg	0.4 mg	0.8 mg
Plasma Cortisol AUC_{0-24} (µg hr/dL)	187.3	169.0	174.8	189.1	166.8	166.1	101.1	32.9	13.0
Change from Placebo (%)	-4%	-13%	-10%	+3%	-9%	-9%	-41%	-81%	-92%

(4) Study C94-052: A long-term safety study of Mometasone furoate aqueous nasal spray vs. Triamcinolone acetonide (Nasacort) in PAR [263:472-473, 264:496-497, Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, Study Report C94-052, p. 1-55].

Study design: While discussed in the individual review of study C94-052 and reiterated in this section on HPA-axis studies, analysis of HPA function in study C94-052 was performed using 2 methods in this study: (1) Cortrosyn testing (cosyntropin (ACTH) stimulation: 250 µg of cosyntropin was administered and plasma cortisol levels were measured 45-60 minutes later) after baseline plasma cortisol levels were obtained and (2) 24 hour urinary free cortisol levels pre- and post-treatment with mometasone and triamcinolone on the baseline (pre-treatment visit) and during weeks 12, 24, and 52 during treatment with either intranasal mometasone or triamcinolone. Of note, if a subject's creatinine value at a given visit was not within 35% of the value at screening, then the subject was excluded from the analyses of urinary free cortisol for that visit [262:32].

Results:

Cortrosyn stimulation tests revealed small but inconsistent changes in the plasma cortisol post-stimulation with cosyntropin, as compared to screening values for both treatment groups in pooled data for all subjects tested which are summarized in Table XIX. [263:472]. Furthermore, no statistically significant difference was detected between the 2 steroid treatments. Analysis of the distribution of plasma cortisol levels between the 2 treatment groups showed that similar to screening plasma values post-cosyntropin, the majority (i.e. > 90%) of subjects demonstrated a ≥ 7 µg/100 ml increase in plasma cortisol levels post-cosyntropin administration, indicating that for pooled data, no evidence of HPA-axis suppression was evident at either week 12, 24, or 52 of the study [263:473]. The sponsor states that 1-2 subjects per treatment group had an abnormal response

in Cortrosyn stimulation testing post-initiation of treatment but no subject had more than one abnormal response [262:78]. Review of the subject line listings submitted 07/14/97 per FDA request by the Sponsor indicates that a total of 10 mometasone treatment group subjects failed to have a > 7 µg/dL increase in plasma cortisol post-cosyntropin stimulation after having received at least 12 weeks (or more) of mometasone treatment (13 triamcinolone treated subjects had similar findings) Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, Study Report C94-052, p. 1-55]. Nonetheless, in 9 of the 10 mometasone subjects, all plasma cortisol levels were > 18 µg/dL, indicative of adequate adrenal function. In one subject (subject C94-052-16, #008), plasma cortisol levels pre and post-ACTH stimulation were 15.7 µg/dL and 12.9 µg/dL, respectively, indicative of a blunted adrenal response (of note, one triamcinolone subject (subject C94-052-16, #002) also had a blunted adrenal response).

Overall, however, these data indicate that for the majority of subjects, treatment with mometasone 200 µg qd is unlikely to result in either subclinical or clinically significant adrenal suppression.

Table XIX. Cortrosyn Stimulation Test Results for Study C94-052: Mean Plasma Cortisol Levels, Pre- and Post-Treatment with Mometasone and Triamcinolone and Mean Change (Δ) from Screening (ITT Population) [262:78, 263:472]

	MOMETASONE			TRIAMCINOLONE			
	n	Mean Plasma Cortisol (µg/dL)	Δ from screening (µg/dL)	n	Mean Plasma Cortisol (µg/dL)	Δ from screening (µg/dL)	[1]P-value
Screening	168	Pre: 16.60 Post: 31.93	NA	168	Pre: 16.70 Post: 32.31	NA	0.64
WEEK 12	167	Pre: 17.39 Post: 31.85	-0.88	167	Pre: 17.12 Post: 32.03	-0.71	0.81
WEEK 24	158	Pre: 17.71 Post: 33.16	0.05	162	Pre: 17.44 Post: 33.14	0.15	0.97
WEEK 52	148	Pre: 17.69 Post: 31.66	-1.48	152	Pre: 16.80 Post: 31.12	-1.15	0.33
ENDPOINT	168	Pre: 17.38 Post: 31.42	-1.30	168	Pre: 16.76 Post: 31.39	-0.98	0.51

NA=Not applicable, Study performed at sites -01, -05, -06, and -11.
[1]P-value for mometasone vs. triamcinolone (for treatment difference), α=0.05, 2-way ANOVA.

Evaluation of the 24 hour urinary free cortisol levels at study sites -01, 05, 06, and -011 using pooled data from these sites also failed to reveal an effect or a consistent trend post-treatment in decreasing urinary cortisol levels [264:496], although again pooling of data would be less likely to capture abnormal HPA-axis

function in individual subjects. Also of note, a number of subjects failed to have a creatinine value at the respective study visit during which 24 hour urinary free cortisols were collected that was 35% of the value at screening, hence these subjects were excluded from data analysis of the 24 hour urinary free cortisol levels for that visit. As discussed with Ms. Paula Rinaldi, Regulatory Affairs of Schering Plough, Inc. on 08/29/97, the mean screening value for 24 hour urinary free cortisol values was modified to reflect only those subjects that were used in the data analysis for that study visit, i.e. those subjects with a serum creatinine ≥ 35% of the screening value. Results of these modified 24 hour urinary free cortisol levels are summarized in Table XX.

Table XX. **24 Hour Urinary Free Cortisol Analysis:** Mean and Mean Change from Screening (ITT Population, study C94-052)
[264:496, FAX Schering Plough, Inc., 08/29/97]

	MOMETASONE		TRIAMCINOLONE		
	n	Mean Urinary Cortisol (µg/day)	n	Mean Urinary Cortisol (µg/day)	[1]P-value
Screening (all subjects)	44	25.63	42	24.17	0.53
Screening	31	25.13	23	23.61	
WEEK 12	31	28.52	23	20.61	0.41
Change	31	3.38	23	-3.00	0.43
Screening	28	23.76	27	26.16	
WEEK 24	28	22.90	27	26.22	0.27
Change	28	-0.85	27	0.06	0.52
Screening	24	20.21	24	22.32	
WEEK 52	24	20.07	24	21.49	0.46
Change	24	-0.15	24	-0.83	0.83
Screening	27	20.05	28	21.95	
ENDPOINT	27	20.80	28	22.45	0.45
Change	27	0.75	28	0.49	0.94

Study performed at sites -01, -05, -06, and -11. Only subjects with a creatinine ≥ 35% of the screening value were used to determine the screening mean 24 hour urinary free cortisol level used to calculate the change in 24 hour urinary free cortisol.
[1]P-value for mometasone vs. triamcinolone (for treatment difference), α=0.05, 2-way ANOVA.

10.4.1.b. Mometasone furoate Plasma Concentration:

Plasma concentrations of mometasone furoate were determined in 3 of the phase II/III studies in NDA 20-762 using an HPLC method with a limit of quantitation of 50 pg/mL [302:110-111].

Results of study C920-011 in which subjects at 2 study sites received either mometasone 50, 100, 200, or 800 µg qd, and had blood samples collected on Day 1 (pre-treatment) and Day 28 (1 and 2 hours post-treatment) indicate that out of 128 samples from 56 subjects, only one plasma mometasone value (77.6 pg/ml) was above the lower limit of quantitation in a 1 hour post-dose sample in a subject

receiving mometasone 800 µg qd.

In study C94-052, where plasma samples were collected at screening, and 1 hour post-dose on weeks 12, 24, and 52 at 4 study sites, only 4 values (out of 169 samples from 45 subjects treated with mometasone 200 µg qd) were above the lower limit of quantitation (58.7 pg/mL in one subject on week 12, 66.1 and 57.1 pg/mL for a second subject on weeks 12 and 24, and 1454 pg/mL for a third subject on week 24). This last plasma value was not felt to represent a true (expected) result and was considered a 'pharmacokinetic outlier'.

In study C94-145, in which subjects received mometasone 200 µg qd, plasma samples were collected at screening, day 1 (5 minutes and 1 hour post-dose) and day 15 (pre-dose and 5 minutes and 1 hour post-dose) at 4 study sites. In this study, all plasma mometasone concentrations in 441 samples from 109 subjects were below the lower limit of quantitation, although an appreciable number of samples were either not obtained or had an insignificant volume to perform HPLC analysis [189:1327, 1345-1349].

10.5. Electrocardiograms

Electrocardiograms (ECGs) performed at baseline (all studies except C93-193 and I94-139) and the endpoint visit (all studies except C93-184, C93-193, C93-215, I92-200, I93-133, I93-180, I94-001, and I94-139) revealed that at the endpoint visit, 77-90% of mometasone treated subjects (mean=80% for all mometasone doses) had a normal ECG recording, as compared with 77% of placebo treated subjects, and 76-91% of active comparator treated subjects.

The proportion of subjects with normal baseline ECGs who had abnormal, but not clinically significant ECGs by the endpoint visit were similar all treatment groups (6 reports (6% incidence) for mometasone 50 µg qd subjects, 7 reports (7% incidence) for mometasone 100 µg qd subjects, 56 reports (4% incidence) for mometasone 200 µg qd subjects, 11 reports (2% incidence) for mometasone 'variable group' or 100-400 µg qd subjects, 8 reports (9% incidence) for mometasone 800 µg qd subjects, 0 reports (0% incidence) for mometasone 200 µg qd + loratadine 10 mg po qd (combination treatment) subjects, and 36 reports (4% incidence) for placebo subjects) [302:112].

A comparison of endpoint visit ECGs with baseline for 'clinically significant' ECG changes revealed no significant difference in incidence between mometasone treated subjects and placebo. Only one mometasone 'variable-dose' subject (I93-211-15, #07) had a normal baseline ECG and was found 3 weeks later when she discontinued the study from urticaria and angioedema, to have left anterior hemiblock and an incomplete right bundle branch block on ECG [302:111-112] on her endpoint visit ECG. One active comparator group subject (subject C93-014-04, #21, a 44 year old female who was receiving beclomethasone 336 µg qd) was also found to have a 'clinically significant' abnormality on endpoint visit ECG (new onset anterior wall myocardial infarction) which was not present at baseline. Given the large number of subjects who had ECGs performed in the different treatment groups (n=1246 for mometasone 200

µg qd, n=363 for beclomethasone 336 µg qd, and n=986 placebo subjects) these individual cases (1 for mometasone, 1 for beclomethasone) are too few in number, do not show a dose response, and are thus unlikely to be related to either study drug treatment.

10.6. Vital Signs and Weight

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) were monitored in all clinical studies at screening, baseline, and at each visit, and weight was recorded at the screening and final (endpoint) evaluation.

Review of the vital sign database failed to reveal any clinically relevant change from baseline observed in mean values for the pooled safety population as well as via stratification by age, (<12 , 12-17 , 18-64, ≥ 65 years), gender, or race (Caucasian and non-Caucasian) [302:115-119, 311:2913-2918, 3029-3052]. Flag shift distributions showed that the distribution of subjects by % change from baseline were similar among the different mometasone doses, other active comparators, and placebo [311:2920-2946, 3054-3080]. The proportion of subjects with changes in blood pressure or heart rate ≥ 30% (i.e. outliers) were also similarly distributed among the different treatment groups 311:3082-3259]. As expected, comparison of weight differences at baseline and endpoint between the different demographic groups showed a mean lower weight for subjects age 12-17 years (baseline mean weight=62.4 kg, endpoint mean weight=63.1 kg) than the other age groups, and in female (baseline mean weight=67.4 kg, endpoint mean weight=67.4 kg) vs. male subjects (baseline mean weight=79.7 kg, endpoint mean weight=80.0 kg) [302:118]. In summary, no clinically relevant difference in vital signs or weight was observed for the different treatment groups, the different doses of mometasone, or the different demographic groups [312:3262-3585, 313:3587-3895].

10.7. Physical Examination and Ophthalmic Examination for Glaucoma and Cataracts

Physical examinations performed on mometasone subjects at screening/baseline and at the endpoint visit overall did not reveal any discernable abnormalities, as compared with placebo; with the exception of nasal ulcer formation in a small percentage of mometasone treated subjects which was greater in frequency (1.3%) than in placebo subjects (0.5%, discussed in Section) [302:120]. In addition, a slightly higher frequency of punctate blood was noted the nasal vault in PAR mometasone treatment subjects (5-6%) as compared with SAR mometasone treatment subjects (3%), or placebo subjects (2-4%) [313:3897-3900]. These findings are consistent with the higher incidence of epistaxis in the longer duration PAR studies (12-52 weeks), as compared with SAR studies that were no longer than 4 weeks in duration.

In terms of glaucoma and cataract formation, 2 studies (C92-280 and C93-014) were specifically designed to evaluate subjects for development of these complications via measurement of intraocular pressures and via slit lamp

examination.

While cataract formation was not detected in any mometasone treated subjects, one subject in the mometasone 200 µg qd treatment group developed several scattered punctate cortical opacities in the right eye > left eye by week 12 of treatment [228:6609]. Regarding the incidence of glaucoma in mometasone treated subjects, in study C92-280, mean and median intraocular pressures at screening and week 12 of the study failed to show any significant difference in measurements for all 3 treatment groups, including the mometasone group [220:839]. Evaluation of individual study subject intraocular pressure measurements revealed only 1 subject in the mometasone (200 µg qd) treatment group who at week 12 had a 3 mm Hg increase in intraocular pressure (to a total pressure of 24 mm Hg) in the right eye [228:6597]. This difference was not felt to represent a significant change from baseline (daily fluctuations of up to 4 mm Hg are acceptable variations in intraocular pressure).

In study C93-014, a 1 year follow-up study of C92-280, one mometasone subject (variable dose group, mometasone dose not specified in submission) was noted to have a significant elevation in intraocular pressures in both eyes post-screening [260:2728], although again, mean intraocular pressures for the screening and week 52 visits were similar for all 3 treatment groups (mometasone, active comparator, and placebo) and ranged from 14.8 mm Hg-15.7 mm Hg [254:533].

10.8. Four Month Safety Update

The 4 month safety update for mometasone was submitted 01/31/97 (Vol 7.1-7.5) and comprised safety results for the adult PAR study I94-078 which was individually reviewed in the clinical study section of the medical officer review, along with 3 ongoing phase III and phase IV trials (C96-195, C95-219, P96-017/J96-017) and safety data from 3 completed pediatric trials (C94-140, C95-136, and C95-161). No new or unusual safety findings were evident in these studies.

For study I94-078, again the most frequent adverse events for all treatment groups consisted of headache, viral infection, epistaxis, and pharyngitis [4 Month Safety Update, Schering Plough, Inc., 01/31/97, Vol. 7.1:12-23, 50-117]. There were no reports of nasal perforation, although several subjects in the mometasone and budesonide (the active comparator treatment group) developed nasal ulcerations post-treatment . The only notable ADRs for mometasone treated subjects in this study were the following: (1) one report of a spontaneous abortion in a 32 year female subject (subject I94-078-21, #19, [290:10, A51.1:95. A51.3:636]) in the mometasone treatment group > 30 days after completion of the 13 week study (12 weeks of mometasone treatment) who was using an IUD throughout the study and at the time of conception, (2) one report of an increase in SGPT from 12 IU/L at screening to 92 IU/L by week 12 of mometasone treatment (subject I94-078-07, #01, [A51.1:97, A51.3:640]), and (3) one report of a decrease in the WBC from a screening value of 4.04 to 2.5 x 10^3/mm^3 by week 12 of mometasone treatment (subject I94-078-09, #08, [A51.1:97, A51.3:640, 4

Month Safety Update, Schering Plough, Inc., 01/31/97, Vol. 7.1:44]. These adverse event reports do not add any substantial new information to the pooled safety database discussed in previous sections of the integrated summary of safety (ISS). No significant patterns of laboratory test abnormalities, abnormalities in vital signs, or physical exam were noted in the study.

A review of the sponsor's update on ongoing phase III studies (C96-195-a 52 week sinusitis study in adult subjects, P95-219-a 2 week randomized, double-blind, single center study comparing mometasone to placebo using nasal function, nasal cytology studies, and biochemical markers, and P96-017/J96-017-a 6 week randomized, double-blind, multi-center trial comparing mometasone and placebo for the treatment of subjects with increased asthma symptoms in conjunction with SAR) confirmed the safety findings (e.g. increased incidence of headache in mometasone and placebo treatment groups) of the other SAR and PAR studies in this submission and did not reveal any new, untoward effects of mometasone treatment.

Three studies were likewise completed in pediatric subjects; two of which were phase I studies and one of which was a phase II dose-ranging study. In these studies doses of mometasone ranging from 25 µg qd to 200 µg qd in subjects age 3-12 years were administered to > 500 pediatric subjects for a duration of 7-28 days (all studies combined) and overall showed a similar incidence of adverse events, as compared with frequencies previously discussed in adult subjects. Again, the most common adverse event reported was headache [4 Month Safety Update, Schering Plough, Inc., 01/31/97, p. 30, 34]. Other more frequent adverse events in mometasone treated pediatric subjects, as compared with placebo included epistaxis, pharyngitis, and coughing [4 Month Safety Update, Schering Plough, Inc., 01/31/97, Vol. 7.1:36].

Thirty (30') minute Cortrosyn stimulation tests performed in 36 pediatric subjects (C95-136) before and after treatment with doses of mometasone ranging from 50, 100, to 200 µg qd for 14 days, failed to reveal any significant decrease in plasma cortisol levels on day 14 compared with baseline in any individual subjects and did not significantly change the mean plasma cortisol levels for pooled subjects at each mometasone dose, as compared with placebo treatment [7.1: Study Report for C95-136, p.28-30].

No serious adverse events in pediatric subjects clearly associated with mometasone use were identified in the 4 month safety update, although one 10 year old female subject in study C95-161 (subject C95-161-12, #48) receiving mometasone 200 µg qd for 2-3 weeks developed an upper respiratory infection, and sinusitis, which progressed to pneumonia with nausea and vomiting [4 Month Safety Update, Schering Plough, Inc., 01/31/97, Vol 7.1:47]. The subject was subsequently treated with I.V. antibiotics and the pneumonia resolved. The relationship of this adverse event to mometasone use in this subject is not likely to be related given the short duration of mometasone use.

10.9. CONCLUSIONS:

A review of the integrated summary of safety (ISS) for controlled and all (controlled, uncontrolled, phase I) studies of mometasone for the treatment of SAR, prophylaxis of SAR, and treatment of PAR; along with the 4 month safety update for mometasone, indicates that mometasone furoate nasal spray is safe and well tolerated at the to-be-marketed dose of 200 µg qd in adult subjects.

Adverse events were generally low in frequency, the most common being headache, viral infection, epistaxis, pharyngitis, and upper respiratory infection. With the exception of a small increase in the frequency of epistaxis with increasing doses of mometasone, no significant dose response in adverse events was seen with mometasone treatment. No significant demographic difference in adverse events reporting was appreciated with the exception of a slightly greater number of adverse events reported in older subjects (age ≥ 65 years), in particular, nasal ulcers. Serious adverse events associated with mometasone use were rare and no deaths were reported.

Except for rare reports of a mild increases in liver function tests (SGOT, SGPT, bilirubin, and alkaline phosphatase) and a mild decrease in the total white blood cell count (WBC) for individual subjects, no significant laboratory abnormalities were reported with mometasone administered in a dose of 200 µg qd. No increased risk for glaucoma or cataract formation with intranasal mometasone use was detected in any of the long-term (1 year) safety studies. HPA-axis suppression with long-term (≥ 1 year) mometasone use was not demonstrable, and the number of rare subject outliers of decreased plasma cortisol levels was not significantly different between the mometasone and placebo treatment group. In summary, mometasone furoate nasal spray appears to be safe for the treatment of SAR, prophylaxis of SAR, and for the treatment of PAR at the recommended dose of 200 µg qd.

11.0. CONCLUSION: Executive Summary of Efficacy and Safety

The three pivotal trials, C93-013 (seasonal allergic rhinitis (SAR)), C93-215 (Prophylaxis of SAR), and C92-280 (perennial allergic rhinitis (PAR)) and nine supplementary trials (five supplementary SAR trials, one supplementary prophylaxis of SAR trial, and three PAR trials), evaluated the efficacy of intranasal mometasone furoate spray (NASONEX), 200 µg, given once daily for treatment and prophylaxis of seasonal allergic rhinitis (SAR) and treatment of perennial allergic rhinitis (PAR). The primary efficacy variable in the pivotal trials (with the exception of the prophylaxis trial), was the subject rated mean change in the total nasal symptom score from baseline for the initial 15 day interval of treatment for combined a.m. and p.m. scores. The total nasal symptom score was defined as a 12 point symptom score comprised by the addition of 4 component nasal symptoms: rhinorrhea, nasal congestion, sneezing, and nasal itching which were each individually rated on a 4 point scale (0-3). Symptoms were assessed reflectively over the previous 12 hours in the a.m. and p.m. by study subjects. Instantaneous symptom scores were not recorded.

The three pivotal trials of greater than 1100 adult subjects age 12 and over demonstrated that mometasone nasal spray administered at 200 µg qd produced a decrease in the mean total nasal symptom score for the initial 15 day study interval that was statistically significantly lower than placebo. For the pivotal prophylaxis trial, a statistically significant increase in the proportion of 'minimal' (i.e. total nasal symptom score was ≤ 2) SAR symptom days, which was defined a priori as the primary efficacy variable, was seen in those subjects treated with mometasone nasal spray 200 µg qd, compared with placebo treated subjects. Although subjects were pre-treated with mometasone from 2-4 weeks prior to the anticipated onset of the pollen season in the pivotal (C93-215) and supportive (I93-133) prophylaxis studies, based on the onset of action of mometasone, one (1) week of pre-treatment with intranasal mometasone 200 µg qd appears to be a reasonable prophylaxis period prior to the anticipated onset of a given patient's allergy season.

Mometasone treatment demonstrated an adequate 24 hour duration of activity, supporting once a day dosing of 200 µg via nasal spray. Onset of action (Study C93-184 and C93-013) was shown to be between 2.0-2.5 days, with a statistically significant and consistent decrease in total nasal symptoms demonstrable in mometasone treated subjects at approximately this time point post-initiation of mometasone treatment. The most appropriate dose of mometasone for the treatment of rhinitis in adult subjects was shown to be 200 µg qd (Study C92-011), although lower doses of mometasone (50 µg and 100 µg qd) also demonstrated a statistically significant decrease in rhinitis symptoms, compared with placebo. At the 50 µg qd and 100 µg qd doses of mometasone, the decrease in rhinitis symptoms were not as consistent during the first few days of treatment as with the 200 µg qd dose of mometasone. Conversely, a higher dose of mometasone, given as 800 µg qd intranasally, did not provide a statistically or

consistently numerically greater efficacy response in reducing rhinitis symptoms, than the 200 µg dose. For the majority of clinical studies reviewed in NDA 20-762, mometasone treatment was less efficacious in the treatment of the non-nasal symptoms of rhinitis (eye redness, eye itch, eye tearing, and ear and/or palatal itch), than in the treatment of the nasal symptoms of rhinitis. A number of studies for the three clinical indications in this NDA submission allowed rescue antihistamine use and results of these studies indicate that treatment with mometasone nasal spray decreased rescue medication use, compared with placebo patients.

No significant demographic differences, based on age, gender, or race, were seen in the SAR, prophylaxis of SAR, or PAR studies with mometasone. In summary, mometasone furoate nasal spray administered at 200 µg qd is effective for the treatment of symptoms due to SAR and PAR, and for the prophylaxis of symptoms of SAR.

The adverse event database consisted of over 3000 subjects internationally, the youngest of which (one subject) was < 12 years of age, though this subject's exact age was not specified in the NDA. Of these, 2266 subjects received at least one dose of mometasone furoate nasal spray ≥ 200 µg qd. The exposure ranged from one dose to greater than 1 year (52 weeks).

Adverse events were generally low in frequency, the most common being headache, viral infection, epistaxis, pharyngitis, and upper respiratory infection. With the exception of a small increase in the frequency of epistaxis with increasing doses of mometasone, no significant dose response in adverse events was seen with intranasal mometasone treatment. No significant demographic difference in adverse event reporting was noted with the exception of a slightly greater number of adverse events, (in particular, nasal ulcers), reported in older subjects (age ≥ 65 years). Serious adverse events associated with intranasal mometasone use were rare and no deaths were reported.

Except for rare reports of a mild increase in liver function tests (SGOT, SGPT, bilirubin, and alkaline phosphatase) and a mild decrease in the total white blood cell count (WBC) for individual subjects, no significant laboratory abnormalities were reported with mometasone administered intranasally at a dose of 200 µg qd. No increased risk for glaucoma or cataract formation with intranasal mometasone use was detected in any of long-term (1 year) safety studies (PAR indication) and HPA-axis suppression with long-term (≥ 1 year) mometasone use was not demonstrable. The number of rare subject outliers of decreased plasma cortisol levels was not significantly different between the mometasone and placebo treatment group. In summary, mometasone furoate nasal spray appears to be safe for the treatment of SAR, prophylaxis of SAR, and for the treatment of PAR at the recommended dose of 200 µg qd.

11.1. Reviewer Recommendation

Mometasone furoate nasal spray 200 µg qd is shown to be safe and effective for the treatment of symptoms of seasonal and perennial allergic rhinitis

and for the prophylaxis of symptoms of seasonal allergic rhinitis in adults ≥ 12 years of age. The recommended prophylaxis period for a given patient's seasonal allergies, based on the mometasone onset of action study and the two SAR prophylaxis studies should be ≥ 1 week. The medical reviewer of NDA 20-762 recommends approval of mometasone furoate nasal spray (NASONEX) 200 µg qd for these three clinical indications.

12.0. Division of Scientific Investigation (DSI) Review:

Clinical investigator audits were conducted by the Division of Scientific Investigation (HFD-344, FDA) on 3 individual principal investigators for the pivotal studies for the 3 proposed clinical indications for mometasone furoate nasal spray. For the pivotal SAR study C93-013, Dr. Andrew Pedinoff (site C93-013-07) underwent study audit, for the pivotal prophylaxis of SAR study C93-215, Dr. Donald Aaronson (site C93-215-01) underwent study audit, and for the pivotal PAR study C92-280, Dr. Harold Kaiser (site C92-280-07) underwent study audit.

In addition to checking the protocol used on site, the signed consent forms for each subject, the investigator's brochure, all adverse event source records, case report forms, and correspondence between the study site, the sponsor(s), and the IRB; per request of the medical reviewer, a number of additional clinical parameters were checked for each study site.

For the SAR study C93-013, allergy skin test results (screening visit), total nasal symptom scores (at baseline and on day 15), and concomitant medication use (on day 15) in the source records were checked on select study subjects and compared to the study reports submitted to NDA 20-762. For the prophylaxis study C93-215, the allergy skin test results (screening visit), total nasal symptom scores (at baseline, at day 29, and day 57), and concomitant medication use (on day 57) were checked on select subjects. Finally, for the PAR study C92-280, ophthalmic exam results which included an assessment of intraocular pressures for both eyes and presence/absence of cataract formation (at screening and at week 12), the Water's view X-ray (at screening), total nasal symptom scores at baseline, day 15, and day 29 were checked on select subjects.

Based on these reviews, Drs. Pedinoff and Aaronson were found to have minor problems with their consent forms but otherwise unremarkable audits. No data discrepancies were noted between the source records and the study reports for the clinical parameters listed above. Audit of Dr. Kaiser's study site revealed several data discrepancies (5 out of 22 study subjects) between case report form data and the source data but no trend in reporting (i.e. either favoring or disfavoring mometasone treatment) was detected. Furthermore, exclusion of this study site from data analysis for study C92-280, did not change results of the primary efficacy variable and in general made minimal impact on the overall study results. This investigator was only involved in 3 additional studies in NDA 20-762 (4 out of 21 studies total), and hence would not be anticipated to make a significant impact on overall data findings for the entire NDA. The recommended classification for all 3 investigators was NAI (no action indicated).

Statistical Review and Evaluation

JUL 14 1997

NDA #: 20-762

Applicant: Schering-Plough Corporation

Name of Drug: Nasonex (mometasone furoate monohydrate) Nasal Spray

Indication: Seasonal and Perennial allergic rhinitis

Documents Reviewed: Volumes 1.1, 1.320-1.323, 1.328-1.333, 1.367-377 dated September 30,1996

This review pertains to three placebo and active controlled studies. One was in patients with perennial allergic rhinitis. The other two were in patients with seasonal allergic rhinitis. One of these seasonal allergic trials was a prophylaxis trial while the other was a treatment trial.

The medical officer for this submission was A. Worobec, M.D., HFD-570, with whom this review was discussed.

I. Study C93-013

A. Study Description and Method of Analysis

This was a multi-center, double-blind, active- and placebo-controlled study of mometasone 200 mcg QD, vs BDP (Vancanese AQ) 168 mcg BID vs placebo in patients 12 years or older with seasonal allergic rhinitis. There was a two-day to seven-day period between screening and baseline. The treatment period was 30 days.

The following symptoms were evaluated by the patient in daily diaries:

Nasal Symptoms	Non-nasal Symptoms
Rhinorrhea	Itching/burning eyes
Stuffiness/congestion	Tearing/watering eyes
Nasal itching	Redness of eyes
Sneezing	Itching of ears or palate

The severity of these symptoms were rated using the following scale:

Severity Score	Severity Definition
0=None	No Sign/symptom evident
1=Mild	Sign/symptom clearly present but minimal Awareness; easily tolerated
2=Moderate	Definite awareness of sign/symptom which is bothersome but tolerable
3=Severe	Sign/symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping

The diary symptoms were assessed in the AM and PM. The derived variables of Nasal symptoms, Non-Nasal symptoms and Total symptoms were calculated by summing the 4 nasal symptom scores, the 4 non-nasal symptom scores and all 8 symptom scores, respectively. If a symptom was missing on a day, the corresponding total symptom score and either nasal or non-nasal score were left as missing for that day. The sponsor calculated for each patient an AM symptom score for Days 2-15 by averaging the nonmissing AM symptom scores for that two week period. The sponsor calculated for each patient a PM symptom score for Days 1-15 by averaging the nonmissing symptom scores for that two week period. The sponsor calculated for each patient a Nasal symptom score as the average of the AM and PM Nasal scores for the two week period. This average was calculated even if the AM average or PM average was missing for that patient.

The patients recorded their symptomatology twice daily at the same time of day (each morning and evening) before dosing.

The sponsor had the patient take only the PM dose if the patient came to the clinic after 2 PM at the beginning of treatment. [This slightly favors BDP since it is a twice a day drug (the PM dose of BDP is active, whereas the PM dose of Mometasone is a vehicle).]

Chlorpheniramine was provided for rescue. The patient was to fill out a rescue medication card rating his/her symptoms prior to the use of chlorpheniramine.

Patients were to have at least moderate nasal congestion and one other moderate nasal symptom at baseline. The combined score of nasal symptoms was to be at least 6. The patient's overall condition of rhinitis had to be moderate, i.e. a score of at least 2. The combined scores were to be satisfied at both the screening and baseline visit.

The sponsor did not define in the protocol how baseline would be defined for diary data. In the study report, the sponsor defined the AM baseline as the average score on the day of baseline visit and the AM scores from the 3 consecutive days prior to the day of baseline visit. The baseline PM score was the average of the PM scores of the 3 days prior to the baseline day. The AM & PM combined baseline was the average of the baseline AM and PM scores.

The primary efficacy variable was defined in the protocol as the average change in total nasal symptom score over the initial 15 day study period.

Although the study report states that the evaluable patient population would be primary, this reviewer did not find such a statement in the protocol. This review will focus upon the intent-to-treat analysis. As very few patients were considered unevaluable, the results of the evaluable patient analyses are not much different.

The primary analysis on the changes from baseline for the diary variables is an analysis of variance with factors treatment, investigators and treatment-by-investigator interaction. The sponsor included additional factors, such as gender, in supplementary, exploratory analyses.

B. Results

There were 345 patients randomized into this study at 10 centers. One patient received the first dose of medication and then immediately dropped out with no follow-up efficacy or safety data. This patient was excluded from the intent-to-treat analysis. The intent-to-treat population , therefor, included 344 patients (112 mometasone, 116 BDP and 116 placebo).

The treatment groups were comparable at baseline in demographic variables, except for gender (p=0.03). The placebo group had more females (62%) compared to the other groups (46% and 45%). This difference in gender made the groups nearly significantly different in weight (p=0.07).

Twenty-three patients (10 mometasone, 7 BDP and 6 placebo) did not complete the study.

Table 1 shows the AM and PM averaged nasal symptom score mean changes from baseline for days 1-15, days 16-30 and endpoint. Mometasone is significantly different from placebo for all three analyses. The significant differences between the raw treatment

means shows that baseline definition probably had little effect on the significance of the mometasone vs placebo comparison.

Significant differences of mometasone from placebo in Days 1-15 Averaged AM & PM changes from baseline were seen in all 4 components of the nasal symptom.

Table 2 shows the mean changes for the AM nasal symptom score. Mometasone was significantly different from placebo for Days 1-15 and nearly significantly different for Days 16-30 and endpoint. This comparison is important because it demonstrates that Mometasone has an effect at the end of its dosing interval.

Table 3 provides the mean changes from baseline for the non-nasal AM and PM averages. BDP was significantly better than mometasone for endpoint and nearly significantly better for Days 1-15 and Days 16-30. Mometasone had no effect on the non-nasal symptoms.

The sponsor found a significant (P=.05) treatment-by-investigator interaction for AM and PM average nasal symptom score for Days 1-15, Days 16-30 and endpoint. Significant treatment-by-investigator interaction was found also for other analyses. The sponsor found that 7 centers favored mometasone over placebo, 2 favored placebo over mometasone and 1 was neutral. The ordering of the BDP means compared to mometasone and placebo means also varied. Some of the treatment-by-investigator interaction is caused by BDP. Therefore not much weight should be given to treatment-by-investigator interaction in this analysis. Overall the data favored mometasone over placebo for nasal symptoms.

In an exploratory analysis, the sponsor found a significant treatment-by-gender interaction. Mometasone had more effect in females than males. There was almost no effect over placebo in the males for mometasone.(The two centers above that favored placebo over mometasone had a large number of males in the mometasone group.) This reviewer would attribute this difference to sampling variation as the medical officer indicates that there is no gender differences in nasal mucosa that would account for such a difference (most of the effect of mometasone is topical).

The sponsor did other analyses that could be considered confirmatory. Two worthy of discussion are the use of baseline as a covariate, and the substitution of rescue medication diary card assessments, if the patient used rescue medication. The baseline is highly significant, as is usual in allergic rhinitis symptom assessments. The treatment comparisons were more highly significant for the analysis of covariance of the primary variable, changes in nasal symptom scores. The substitution of

rescue scor[illegible] when patients took rescue medication had negligible effect or [illegible]hanges from baseline and p-values.

II. St[illegible] 80

A. Study Description and Method of Analysis

This was a multi center, double-blind, active- and placebo-controlled, parallel group study of mometasone 200 mcg QD, vs BDP (Vancanese AQ) 168 mcg BID vs placebo in patients 12 years or older with perennial allergic rhinitis. There was a 7 day to 14 day period between screening and baseline. The treatment period was 12 weeks.

The diary variables and analyses were similar to those of study C93-013 above, with the following exceptions. For patients who took rescue medication between visits, the last set of symptom scores recorded in their rescue medication diary prior to using rescue medication were considered as the appropriate evaluation of symptoms for the next 12-hour period. The symptom scores in the diary replaced the corresponding scores in the regular diary for the appropriate 12-hour period in all analyses and summaries of symptom scores (and in their calculation of all composite or total symptom scores). The baseline was calculated from the AM scores at the baseline visit and the 7 days prior, as opposed to 3 days, as in Study C93-013.

Patients had to have congestion and/or rhinorrhea each at least moderate at both Screening and Baseline visit and be at least moderate on the diary entries for 4 of the last seven days (AM, PM or rescue medication diary) of the run-in period, and a total nasal score of at least 5 at both Screening and Baseline visit in order to qualify for entry into the study.

B. Results

There were 491 patients enrolled in the study. One patient on placebo was excluded from all analyses. She took her first dose of medication at the study center and then was an immediate dropout and had no follow up safety or efficacy data. The intent-to-treat population had therefore 490 patients (164 on mometasone, 163 on BDP and 163 on placebo). These patients were in 19 centers.

The treatment groups were comparable at baseline in demographic variables.

Sixty four patients did not complete the study (20 mometasone,

19 BDP and 25 placebo). Treatments were fairly balanced with respect to the reasons for not completing.

Table 4 shows the AM and PM averaged nasal symptom score mean changes from baseline for 15 day averages and endpoint. Mometasone is significantly different from placebo in changes from baseline for all time intervals and endpoint. The significant differences between the raw treatment means suggest that the definition of baseline would have little effect on the significance of the mometasone placebo comparison.

Significant differences were seen in some of the components of the nasal symptom. Significant differences of mometasone from placebo in 15 Day Averaged AM & PM changes from baseline were seen in nasal discharge and sneezing for all but one 15 day period. Nasal stuffiness showed significant differences between mometasone and placebo for only 2 of the 15-day time periods. Nasal itch was not significantly different from placebo for any of the 15 day intervals.

This study demonstrated comparable effects for mometasone in males and females.

Table 5 shows the mean changes for the AM nasal symptom score. Mometasone was significantly different from placebo for all 15 day averages and endpoint. This comparison is important because it demonstrates that Mometasone has an effect at the end of its dosing interval.

Table 6 provides the mean changes from baseline for the non-nasal AM and PM averages. Neither BDP or Mometasone had an effect on the non-nasal symptoms. Some significance was seen in the analyses of raw data but these are effected by differences at baseline (lower mean for BDP) .

III. Study C93-215

A. Study Description and Method of Analysis

This was a multi center, double-blind, active- and placebo-controlled, parallel group study of 8 weeks duration comparing mometasone 200 mcg QD, BDP 168 mcg BID, and placebo in patients with seasonal allergic rhinitis. They received treatment up to four weeks prior to and four weeks after the anticipated onset of the first significant ragweed season in the respective geographical vicinity of each study center. Patients within each center were enrolled as a cohort within a five day-period. If the onset of the pollen period was later than anticipated an

additional visit was scheduled.

Because the mometasone and BDP bottles were not of identical appearance a double-dummy approach was used.

At the end of the study, prior to data analysis, the investigator provided the dates for onset of the appearance of ragweed pollen, the peak dates to include the two weeks of highest counts, and offset of the ragweed season (unless still going).

The prophylactic period was the period from the start of treatment to the day before the start of the ragweed season. The pollen season was the time period from the start of the pollen season through the last day of treatment.

The diary data was handled similarly to that in Study C93-013 with the exception that averages were calculated over the whole prophylactic period and 15 day intervals over the pollen period. Baseline was handled the same as in Study 93-013 (using the AM baseline day values and 3 days of diary before the Baseline visit.) However, the primary efficacy analysis, defined below, was different.

The primary efficacy variable was defined as the proportion of minimal symptom days (days when the total nasal symptom score ≤ 2 based on the average of the AM and PM diary evaluations.) This was analyzed by an analysis of variance with factors treatment, investigators and treatment-by-investigator interaction.

There was an inconsistency in the protocol with respect to the definition of "minimal symptom days". The definition given above was used in the Statistics section. The Synopsis section said it was as above with the additional requirement that all nasal and nonnasal symptoms had to be rated as mild or absent. The sponsor said this latter definition was inadvertently carried over from a early version of the I93-133 study protocol. The sponsor also did an analysis not discussed here using that version of the definition and got similar results.

B. Results

There were 349 patients randomized into the study. Two placebo patients had no follow up visits and were excluded from the intent-to-treat analysis.

The treatment groups were comparable in baseline demographic variables.

Eleven patients (8 placebo, 2 mometasone and 1 BDP) withdrew for treatment failure. In all 37 patients withdrew (19 placebo, 13 BDP and 5 mometasone).

Table 7 contains the results of the analysis of the proportion of minimal symptom days (Total Nasal AM & PM average ≤2) for the ragweed season, the total season and the prophylactic period. Both BDP and mometasone were significantly different from placebo during the ragweed season and the total treatment period. Mometasone was significantly better than placebo during the prophylactic period with Vancanese being nearly significantly different from placebo.

Table 8 shows the AM and PM averaged nasal symptom score mean changes from baseline for the prophylactic period, 15 day averages during the pollen season and endpoint. Mometasone is significantly different from placebo in changes from baseline for endpoint and all time intervals except days 46-61. (The results for days 31-45 were not estimable with the model fit but significant if treatment-by-investigator effect is taken out of the model.) The significant differences between raw treatment means shows that how baseline was defined most probably would have little effect on the significance of the mometasone placebo comparison. Significant differences from placebo were seen in each of the four components of AM & PM average Nasal scores at days 1-15, 16-30 and endpoint.

This study demonstrated comparable effects for mometasone in males and females.

Table 9 shows the mean changes for the AM nasal symptom score. Mometasone was significantly different from placebo for endpoint and all 15 day averages except days 46-61 where sample size is small. This comparison is important because it demonstrates that Mometasone has an effect at the end of its dosing interval.

Table 10 provides the mean changes from baseline for the non-nasal AM and PM averages. Mometasone was significantly different from placebo for endpoint and all 15 day averages except days 31-45 and 46-61. Significant differences of mometasone from placebo were seen in the four components at some of these time points.

IV. Reviewer's Comments

Mometasone has adequately demonstrated efficacy in the three studies reviewed. Significant differences for mometasone from placebo were seen in diary combined AM & PM nasal score in all of the three studies at most of the on-treatment 15-day time

intervals in all three studies. Significant differences favoring mometasone over placebo were also seen in the AM nasal score which indicates that mometasone demonstrates once a day efficacy (significance at end of dosing interval.)

The combined AM & PM non-nasal symptom score was only significant in the prophylactic trial C93-215.

James R. Gebert

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

Concur: Dr. Wilson EW 7/14/97

Dr. Nevius SEN 7-14-97

This review contains 9 pages of text and 9 pages of tables.

cc:
Orig NDA 20-762
HFD-570
HFD-570/Dr. Worobec
HFD-570/Ms. Toyer
HFD-715/Div. File
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson

TABLE 1

C93-013

SAFETY AND EFFICACY OF SCH 32088 VS BECLOMETHASONE DIPROPIONATE, VANCENASE AQ, AND PLACEBO IN SEASONAL ALLERGIC RHINITIS

INTENT-TO-TREAT POPULATION

AM & PM AVERAGED DIARY NASAL SYMPTOM SCORE @ - POOLED DIARY DATA 14-DAY AVERAGE

		A MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES *			PAIRWISE COMPARISONS *		
DAY#		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		112	7.6	2.2	116	7.3	2.2	116	7.6	2.2	2.2	.147	<.001	0.142	0.025		
1-15	RAW	112	5.3	2.2	116	4.5	2.1	116	6.1	2.2	2.2	<.001	<.001	0.111	<.001	<.001	<.001
	CHG	112	-2.3	2.6	116	-2.9	2.1	116	-1.5	2.1	2.4	<.001	0.029	0.155	0.029	<.001	<.001
	%CHG	112	-25	36.2	116	-37	25.6	116	-18	29.2							
16-30	RAW	104	4.4	2.5	110	3.6	2.3	110	5.4	2.6	2.3	<.001	<.001	0.102	<.001	<.001	<.001
	CHG	104	-3.2	3.1	110	-3.7	2.4	110	-1.4	2.5	2.6	<.001	<.001	.1	<.001	<.001	<.001
	%CHG	104	-46	51.4	110	-48	31.3	110	-17	36.7							
ENDPT	RAW	112	4.6	2.7	116	3.7	2.4	116	5.4	2.6	2.5	<.001	<.001	.1	<.001	<.001	<.001
	CHG	112	-3.1	3.1	116	-3.6	2.6	116	-1.6	2.5	2.8	<.001	<.001	.1	<.001	<.001	<.001
	%CHG	112	-45	44.6	116	-47	31.6	116	-21	35.9							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
* P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS. NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL
@ SUM OF 4 NASAL SYMPTOMS FROM AM DIARY -- RUNNY NOSE, STUFFINESS, SNEEZING AND NASAL ITCH
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM AND PM BASELINE VALUE.
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

TABLE 2

C93-013

SAFETY AND EFFICACY OF SCH 32088 VS BECLOMETHASONE DIPROPIONATE, VANCENASE AQ, AND PLACEBO IN SEASONAL ALLERGIC RHINITIS

INTENT-TO-TREAT POPULATION

AM DIARY NASAL SYMPTOM SCORE @ - POOLED DIARY DATA 14-DAY AVERAGE

		A MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES *			PAIRWISE COMPARISONS *		
DAY#		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		112	7.7	2.2	116	7.3	2.2	116	7.7	2.2	2.2	.073	<.001	0.152	0.018	0.094	0.134
1-15	RAW	112	5.4	2.3	116	4.5	2.1	116	6.1	2.3	2.2	<.001	<.001	0.111	<.001	<.001	<.001
	CHG	112	-2.3	2.7	116	-2.8	2.1	116	-1.6	2.3	2.4	<.001	0.048	0.155	0.035	0.001	<.001
	%CHG	112	-29	36.2	116	-36	27.3	116	-19	29.3							
16-30	RAW	104	4.5	2.6	110	3.7	2.4	110	5.4	2.6	2.3	<.001	<.001	0.102	.001	.1	.1
	CHG	104	-3.4	3.1	110	-3.6	2.6	110	-1.5	2.6	2.6	<.001	<.001	0.102	0.029	.1	.1
	%CHG	104	-47	44.6	110	-47	31.6	110	-21	35.9							
ENDPT	RAW	112	4.6	2.7	116	3.7	2.4	116	5.3	2.6	2.4	<.001	<.001	.1	<.001	.1	<.001
	CHG	112	-3.1	3.1	116	-3.6	2.6	116	-1.8	2.5	2.6	<.001	<.001	.1	0.034	.1	<.001
	%CHG	112	-45	45	116	-47	34.6	116	-29	35.6							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
* P-VALUE, ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS. NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL
@ SUM OF 4 NASAL SYMPTOMS FROM AM DIARY -- RUNNY NOSE, STUFFINESS, SNEEZING AND NASAL ITCH
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF THE 4 AM DIARY ENTRIES FROM DAY -BASELINE VISIT DAY AND 1 PRIOR CONSECUTIVE DAY
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

TABLE

SAFETY AND EFFICACY OF SCH 32088 VS BECLOMETHASONE DIPROPIONATE (VANCENASE AQ) AND PLACEBO IN SEASONAL ALLERGIC RHINITIS

INTENT-TO-TREAT POPULATION

AM + PM AVERAGED DIARY NON-NASAL SYMPTOM SCORE # - POOLED DIARY DATA 15-DAY AVERAGE

DAYS	(A) MOMETASONE N	MEAN	SD	(B) VANCENASE AQ N	MEAN	SD	(C) PLACEBO N	MEAN	SD	POOLED SD	ANOVA P-VALUES * TRT	INV	T X I	PAIRWISE COMPARISONS * A-B	A-C	B-C
BASELINE	112	5.5	2.7	116	5.3	2.7	116	5.5	2.6	2.6	0.85	0.01	0.17	0.65	0.95	[illegible]
1-15 RAW	112	4.1	2.5	116	3.4	2.1	116	4.2	2.3	2.3	0.02	0.01	0.93	0.02	0.72	[illegible]
CHG	112	-1.4	2.2	116	-1.9	2.2	116	-1.3	2.0	2.1	0.05	0.64	0.09	[illegible]	[illegible]	[illegible]
%CHG	112	-13	[illegible]	114	-24	[illegible]	114	-19	43.9							
16-31 RAW	104	3.3	2.5	112	[illegible]	2.3	112	3.0	2.5	2.4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CHG	104	-2.1	2.6	112	[illegible]	[illegible]	112	-2.5	2.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
%CHG	[illegible]	[illegible]	95	[illegible]	-46	[illegible]	[illegible]	[illegible]	44							
ENDPT RAW	112	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	114	[illegible]	2.3	[illegible]	[illegible]	[illegible]	93	[illegible]	[illegible]	[illegible]
CHG	[illegible]	[illegible]	[illegible]	115	[illegible]	[illegible]	[illegible]	[illegible]	2.6	[illegible]	[illegible]	[illegible]	14	[illegible]	[illegible]	[illegible]
%CHG	112	-21	91	114	-44	54	114	-35	[illegible]							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
* P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS. NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL
# SUM OF 4 NON-NASAL SYMPTOMS FROM AVERAGED AM AND PM DIARIES -- EYE ITCH, EYE TEAR, EYE REDNESS, AND EAR ITCH
SYMPTOMS ARE SCORED AS: 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM AND PM BASELINEVALUES
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

TABLE 4

092-280

EFFICACY AND SAFETY OF SCH 32088 VS VANCENASE AQ AND PLACEBO IN PERENNIAL RHINITIS

INTENT-TO-TREAT POPULATION

AM & PM AVERAGED DIARY NASAL SYMPTOM SCORE # - DIARY DATA 15-DAY AVERAGE

	(A) MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	163	6.6	2.2	163	6.7	2.0	162	6.9	2.0	2.0	0.34	0.01	0.06	0.69	0.16	0.31
1-15 RAW	163	5.1	2.2	163	5.0	2.3	162	5.9	2.1	2.2	<.01	<.01	0.57	0.75	<.01	<.01
CHG	163	-1.5	2.0	163	-1.7	2.0	162	-1.0	1.6	1.9	0.01	0.07	0.6	0.43	0.22	<.01
%CHG	163	-20	32.2	163	-23	32.9	162	-13	26.1							
16-30 RAW	159	4.4	2.3	157	4.2	2.4	157	5.3	2.2	2.2	<.01	<.01	0.54	0.54	<.01	<.01
CHG	159	-2.2	2.3	157	-2.4	2.5	157	-1.6	2.1	2.2	<.01	<.01	0.37	0.37	<.01	<.01
%CHG	159	-30	34.9	157	-33	40.5	157	-18	59.4							
31-45 RAW	152	4.2	2.5	157	4.0	2.5	153	5.1	2.4	2.4	<.01	<.01	0.34	0.56	<.01	<.01
CHG	152	-2.5	2.7	157	-2.7	2.6	153	-1.8	2.3	2.5	<.01	0.01	0.22	0.21	0.01	<.01
%CHG	152	-33	41.6	157	-37	42.1	153	-19	85.9							
46-60 RAW	147	3.8	2.4	157	3.8	2.5	148	4.9	2.4	2.4	<.01	<.01	0.47	0.95	<.01	<.01
CHG	147	-2.8	2.7	157	-2.9	2.6	148	-2.0	2.4	2.5	0.01	0.02	0.52	0.86	0.01	<.01
%CHG	147	-38	40.5	157	-40	38.5	148	-22	86.9							
61-75 RAW	144	3.7	2.3	150	3.7	2.4	142	4.5	2.4	2.3	<.01	<.01	0.91	0.76	<.01	<.01
CHG	144	-2.9	2.5	151	-3.0	2.5	142	-2.3	2.5	2.4	0.06	<.01	0.5	0.87	0.05	0.23
%CHG	144	-41	35.3	150	-43	35.1	142	-26	90.4							
76-90 RAW	142	3.7	2.3	145	3.6	2.4	139	4.6	2.5	2.3	<.01	<.01	0.88	0.74	<.01	<.01
CHG	142	-2.9	2.5	145	-3.0	2.5	139	-2.3	2.7	2.5	0.04	<.01	0.36	0.75	0.05	0.02
%CHG	142	-42	36.0	145	-43	35.1	139	-25	95.1							
ENDPT RAW	163	3.9	2.5	163	3.9	2.6	162	4.8	2.7	2.5	<.01	<.01	0.96	0.92	<.01	<.01
CHG	163	-2.7	2.7	163	-2.8	2.5	162	-2.1	2.7	2.6	0.03	0.01	0.61	0.83	0.03	0.02
%CHG	163	-38	40.5	163	-41	35.6	162	-24	89.3							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL
@ SUM OF 4 NASAL SYMPTOMS FROM AVERAGED AM AND PM DIARIES -- RUNNY NOSE, STUFFINESS, SNEEZING AND NASAL ITCH
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM AND PM BASELINE VALUES
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT
SYMPTOMS ADJUSTED FOR RESCUE MEDICATION

TABLE 5

C91-28.

EFFICACY AND SAFETY OF SCH 32088 VS VANCENASE AQ AND PLACEBO IN PERENNIAL RHINITIS

INTENT TO TREAT POPULATION

AM DIARY NASAL SYMPTOM SCORE @ - DIARY DATA 15-DAY AVERAGE

	(A MOMETASONE			(B VANCENASE AQ			(C PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	163	6 8	2 2	163	6 8	2 1	162	7 0	2 1	2 1	0 4	0 03	0 07	0 73	< 34	< 29
2-15 RAW	163	5 2	2 3	163	5 0	2 3	161	6 0	2 2	2 2	< 01	< 01	0 56	0 46	< 01	< 01
CHG	163	-1 6	2 0	163	-1 7	2 1	162	-1 0	1 6	1 9	< 01	0 12	0 58	0 64	0 01	< 01
%CHG	163	-21	32 7	163	-23	31 0	162	-13	25 0							
16-30 RAW	159	4 5	2 3	157	4 3	2 5	157	5 4	2 3	2 3	< 01	< 01	0 67	0 36	< 01	< 01
CHG	159	-2 2	2 3	157	-2 4	2 5	157	-1 5	2 4	2 3	< 01	< 01	0 3[illegible]	0 62	< 01	< 01
%CHG	159	-31	34 4	157	-32	36 4	157	-17	51 6							
31-45 RAW	152	4 3	2 5	157	4 1	2 5	153	5 2	2 5	2 4	< 01	< 01	< 45	< 45	< 01	< [illegible]
CHG	152	-2 5	2 7	157	-2 7	2 6	153	-1 4	2 3	2 5	< 01	0 11	0 33	0 79	< 01	< 01
%CHG	152	-34	41 0	157	-36	41 4	153	-19	75 6							
46-60 RAW	147	3 9	2 4	157	3 9	2 6	146	5 [illegible]	2 5	2 4	< 01	< 01	0 45	0 67	< 01	< [illegible]
CHG	147	-2 9	2 7	157	-2 8	2 7	148	-1 0	2 4	2 6	< 01	0 02	< 41	0 [illegible]	< 01	0 01
%CHG	147	-39	39 1	157	-39	40 9	148	-21	88 5							
61-75 RAW	144	3 8	2 3	152	3 7	2 5	142	4 7	2 4	2 3	< 01	< 01	0 90	0 63	< 01	< 01
CHG	144	-3 0	2 4	150	-3 0	2 6	142	-2 3	2 6	2 5	0 04	< 01	0 52	0 81	0 02	0 07
%CHG	144	-41	35 8	152	-42	37 3	142	-24	92 8							
76-90 RAW	142	3 8	2 4	145	3 7	2 4	139	4 7	2 5	2 4	< 01	< 01	0 93	0 57	< 01	< 01
CHG	142	-3 0	2 4	145	-3 0	2 6	139	-2 3	2 7	2 5	0 03	< 01	0 5	0 9[illegible]	0 02	0 02
%CHG	142	-42	36 8	145	-42	37 1	139	-25	83 7							
ENDPT RAW	163	4 0	2 5	163	3 9	2 6	162	4 9	2 7	2 5	< 01	< 01	0 9[illegible]	0 8[illegible]	< 01	< 01
CHG	163	-2 8	2 6	163	-2 8	2 6	162	-2 1	2 7	2 6	0 02	< 01	0 65	0 9	0 01	0 02
%CHG	163	-39	40 4	163	-40	37 1	162	-24	79 3							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL
@ SUM OF 4 NASAL SYMPTOMS FROM AM DIARY -- RUNNY NOSE STUFFINESS SNEEZING AND NASAL ITCH
SYMPTOMS ARE SCORED AS 0=NONE 1=MILD 2=MODERATE 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 8 AM DIARY ENTRIES (DAY -6 THROUGH DAY 1)
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES

ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT
SYMPTOMS ADJUSTED FOR RESCUE MEDICATION

TABLE 4

C93-281

EFFICACY AND SAFETY OF SCH 12086 VS VANCENASE AQ AND PLACEBO IN PERENNIAL RHINITIS

INTENT TO-TREAT POPULATION

AM & PM AVERAGED DIARY NON-NASAL SYMPTOM SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

		A MOMETASONE			B VANCENASE AQ			C PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		163	4.3	2.8	163	3.8	2.5	162	4.2	2.6	2.5	0.16	0.01	0.04	0.08	0.77	0.13
1-15	RAW	163	3.5	2.5	163	3.0	2.3	162	3.5	2.4	2.3	0.03	<.01	0.16	0.04	0.81	.11
	CHG	163	-.9	1.8	163	-0.9	1.7	162	-0.7	1.7	1.7	0.6	0.03	0.08	0.84	0.45	.14
	%CHG	158	-6.1	319	158	-3.8	105	161	-1.9	95.6							
16-30	RAW	159	3.1	2.5	157	2.5	2.3	157	3.1	2.4	2.3	0.03	<.01	.17	0.01	.04	.4
	CHG	159	-1.1	2.2	15	-1.4	2.1	157	-1.1	2.1	2.1	0.62	<.01	0.04	0.55	.44	.11
	%CHG	154	-15	116	152	-16	151	156	-17	78.6							
31-45	RAW	151	2.9	2.5	157	2.4	2.3	15	3.0	2.5	2.5	0.05	<.01	0.14	.01	.04	.4
	CHG	151	-1.4	2.1	157	-1.5	2.3	153	-1.3	2.3	2.2	0.72	0.01	.16	0.8	.11	.4
	%CHG	147	-44	127	152	-39	136	151	-37	125							
46-60	RAW	167	2.7	2.4	157	2.2	2.4	146	2.7	2.5	2.3	.01	<.01	0.09	.17	0.94	0.06
	CHG	147	-1.5	2.4	157	-1.6	2.2	148	-1.5	2.2	2.3	0.72	0.09	0.36	0.97	0.48	2.5
	%CHG	142	-29	92.9	152	-33	89.4	147	-27	112							
61-75	RAW	164	2.6	2.3	152	2.2	2.3	142	2.4	2.3	2.2	0.27	<.01	0.21	0.11	0.54	0.33
	CHG	144	-1.8	2.3	152	-1.6	2.1	142	-1.7	2.4	2.2	0.91	0.02	0.41	0.68	0.89	0.78
	%CHG	139	-38	61.6	145	-34	115	141	-32	94.6							
76-90	RAW	142	2.7	2.4	145	2.2	2.3	139	2.4	2.5	2.3	0.19	<.01	0.61	0.07	0.45	0.3
	CHG	142	-1.7	2.4	145	-1.7	2.2	139	-1.7	2.4	2.3	0.95	0.06	0.37	0.98	0.79	0.77
	%CHG	137	-30	77.6	140	-29	148	138	-31	93.7							
ENDPT	RAW	163	2.7	2.4	161	2.3	2.3	162	2.7	2.6	2.4	0.17	<.01	0.42	0.09	0.85	0.12
	CHG	163	-1.6	2.5	161	-1.6	2.2	162	-1.6	2.5	2.4	0.99	0.05	0.39	0.87	0.91	0.96
	%CHG	158	-5.2	319	156	-27	144	161	-28	91.8							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL
@ SUM OF 4 NON-NASAL SYMPTOMS FROM AVERAGED AM AND PM DIARIES -- EYE ITCH EYE TEAR EYE REDNESS AND EAR ITCH
SYMPTOMS ARE SCORED AS 0=NONE 1=MILD 2=MODERATE 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM AND PM BASELINE VALUES
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT
SYMPTOMS ADJUSTED FOR RESCUE MEDICATION

TABLE

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT TO TREAT POPULATION

PROPORTION OF DAYS WITH AM & PM AVERAGED TOTAL NASAL SYMPTOMSCORE # ** 2

	(A) MOMETASONE			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
RAGWEED	115	0 84	0 25	112	0 79	0 29	109	0 63	0 36	0 29	< 01	< 01	0 02	0 17	< 01	< 01
TOTAL	116	0 89	0 19	116	0 85	0 22	115	0 75	0 26	0 22	< 01	< 01	0 19	0 15	< 01	< 01
PROPHYL	116	0 95	0 16	116	0 93	0 17	115	0 88	0 23	0 19	0 02	< 01	0 9	0 35	0 01	0 06

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION

P VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS NO ADJUSTMENT FOR OVERALL ALPHA LEVEL

SUM OF THE 4 NASAL SYMPTOMS FROM THE AVERAGED AM & PM DIARIES) RUNNY NOSE STUFFINESS SNEEZING AND ITCH

SYMPTOMS ARE SCORED AS 0=NONE 1=MILD 2=MODERATE 3=SEVERE

TABLE [illegible]

[illegible]

[illegible] TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM + PM AVERAGED NASAL SYMPTOM SCORE - POOLED DIARY DATA

DAYS	A [illegible] N	A MEAN	A SD	B VANCENASE N	B MEAN	B SD	C PLACEBO N	C MEAN	C SD	POOLED SD	ANOVA P-VALUES * TRT	INV	T x I	PAIRWISE A-B	A-C	B-C
BASELINE	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
PRE RAW	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
% CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible] RAW	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			
CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			
% CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
[illegible] RAW	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			
% CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			
[illegible] RAW	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			
% CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] RAW	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]
CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			
% CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ENDPT RAW	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]							
CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
% CHG	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

SD = STANDARD DEVIATION   T X I = TREATMENT BY INVESTIGATOR INTERACTION   N E = NON-ESTIMABLE
* P-VALUES ARE FROM [illegible] ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL
PRE = PRE-SEASON TREATMENT INTERVAL - OTHERS ARE DAYS POST-ONSET OF SEASON
# SUM OF THE 4 NASAL SYMPTOMS FROM THE AVERAGED AM & PM DIARIES - RUNNY NOSE, STUFFINESS, SNEEZING AND ITCH
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM & PM DIARY BASELINE VALUES
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETA[illegible] NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM NASAL SYMPTOM SCORE - PHOTO DIARY DATA

DAY	A MTN N	A MTN MEAN	A MTN SD	B VANCENASE N	B VANCENASE MEAN	B VANCENASE SD	PLACEBO N	PLACEBO MEAN	PLACEBO SD	POOLED SD	ANOVA P-VALUES TRT	ANOVA P-VALUES INV	ANOVA P-VALUES T X I	PAIRWISE P-VALUES A-B	PAIRWISE P-VALUES A-C	PAIRWISE P-VALUES B-C
BASELINE	[illegible]	4	5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	49	[illegible]	34	[illegible]	[illegible]	[illegible]
PRE RAW	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
%CH	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
RAW	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] RAW	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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SD = STANDARD DEVIATION   T X I = TREATMENT BY INVESTIGATOR INTERACTION   N.E. = NON-ESTIMABLE
* P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
# SUM OF THE 4 NASAL SYMPTOMS FROM THE AM DIARY - RUNNY NOSE, STUFFINESS, SNEEZING AND ITCH
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 4 AM DIARY ENTRIES - 4 CONSECUTIVE DAYS PRIOR TO AND INCLUDING DAY 1
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

TABLE [illegible]

[illegible]

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE [illegible] NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM + PM AVERAGED NON-NASAL SYMPTOM SCORE - POOLED DIARY DATA

DAY	A MFNS N	MEAN	SD	B VANCENASE N	MEAN	SD	PLACEBO N	MEAN	SD	POOLED SD	ANOVA P-VALUES * TRT	INV	T x I	PAIRWISE COMPARISONS * A-B	A-C	B-C
BASELINE	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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* P-VALUES ARE FROM [illegible]-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS. NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL.
[illegible] SUM OF THE [illegible] NON-NASAL SYMPTOMS FROM THE AVERAGED AM + PM DIARIES [illegible] EYE TEAR, EYE REDNESS, EYE ITCH AND EAR PALATE ITCH
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM + PM DIARY BASELINE VALUES
SYMPTOMS ARE SCORED AS [illegible]=NONE [illegible]=MILD [illegible]=MODERATE [illegible]=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST [illegible] POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO [illegible] BASELINE VALUES
ENDPOINT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

Clinical Pharmacology & Biopharmaceutics Review

NASONEX™ Nasal Spray
(50 µg/Actuation mometasone furoate monohydrate suspension)
NDA 20-762

Type of Submission: New NDA, 1S

Submission Date:
9/30/96

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Reviewer:
Brad Gillespie, PharmD

Synopsis Intended for once daily intranasal administration, each actuation of NASONEX is designed to deliver 50 µg of mometasone furoate. The proposed daily dosage is 2 sprays in each nostril (200 µg) for the prophylaxis and treatment of symptoms associated with seasonal and perennial allergic rhinitis.

In support of this application, the sponsor has submitted the results of eight pivotal clinical trials and 2 human pharmacokinetic studies.

Two pharmacokinetic trials were evaluated and excerpts are included from the Pharmacology/Toxicology (Dr. T. Du) review of *in vitro* metabolism. The *in vitro* metabolism study showed that mometasone is extensively metabolized by rat and mouse S9 liver fraction to 6-hydroxy mometasone (≈40%) and two minor unidentified metabolites (≤2%). The mass balance study demonstrated that when administered as an intranasal suspension, mometasone absorption is minimal (≈2% of administered radioactivity recovered in the urine). When given as intravenous and oral solutions, mometasone is extensively metabolized and excreted mainly in the feces. When given as an intranasal suspension, most of the administered dose is recovered in the feces, probably as unabsorbed drug. Plasma mometasone concentrations after intranasal administration of this product were inadequate to assess its bioavailability. After intravenous administration of mometasone, females were found to have a longer elimination half-life (16.6 versus 7.7 hours in males). After administration of an oral solution, mometasone bioavailability was higher in females then males (C_{max}: +105%; AUC: +51%). Part of these observed differences are probably due to differences in subject volume of distribution (mean subject weights - males: 171.0 lbs; females: 147.8 lbs → male/female = 1.16). The remaining difference is not explained by the data presented. While mometasone bioavailability was inadequate to assess this effect when administered as the intranasal product, the possibility of increased bioavailability in females should be considered when evaluating the safety of this product.

TABLE OF CONTENTS

Page Number

Background Mometasone furoate has been marketed as a topical lotion, ointment and cream since the late 1980s. In this application, the sponsor has submitted the results of eight pivotal clinical trials and 2 human pharmacokinetics studies to support marketing of a metered-dose, manual spray unit containing an aqueous suspension of mometasone furoate monohydrate.

NASONEX's proposed indication is for the prophylaxis and treatment of symptoms associated with seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis in adults and children 12 years of age and older. The proposed recommended dose is two sprays (50 µg of mometasone furoate/spray) in each nostril once daily (total daily dose of 200 µg).

APPEARS THIS WAY
ON ORIGINAL

Summary of Clinical Pharmacology & Biopharmaceutics

I. METABOLISM/MASS BALANCE

In vitro metabolism experiments demonstrated that while mometasone is not metabolized by rat lung S9 fractions, extensive metabolism occurred with liver S9 fractions. In rat liver S9 incubation, SCH 32088 was extensively metabolized. Approximately 40% of SCH 32088 (0.05mM substrate) was converted to 6-hydroxy SCH 32088. Smaller proportions of mometasone and two unknown metabolites were also detected. In mouse liver, 6-hydroxylation, ester hydrolysis and metabolism to an unidentified product were observed.

Drug derived radioactivity was minimally absorbed (~ 2% of administered radioactivity recovered in the urine) when mometasone was administered as a nasal spray. Mometasone was extensively metabolized after administration of intravenous and oral solutions. It appears that the major route of excretion is fecal elimination of metabolized drug. When given as the nasal spray, most of the administered radioactivity is eliminated in the feces, probably as unabsorbed drug.

II. BIOAVAILABILITY

Plasma mometasone concentrations observed after intranasal administration of this product were inadequate to assess its bioavailability.

III. PHARMACOKINETICS

After administration of a 1.0 mg single dose of an intravenous solution, the mean mometasone $AUC_{0-\infty}$ for males and females were: 17557 (CV-30%) pg·hr/mL and 18742 (CV-19%) pg·hr/mL, respectively. The elimination half lives for males and females were 7.73 (CV-48%) and 16.6 (CV-78%) hours, respectively.

IV. SPECIAL POPULATIONS

Gender The effect of gender on mometasone disposition was evaluated by stratifying the volunteers by sex in the Absolute Bioavailability study (C95-050). In the intravenous arm of this study, terminal elimination rates were higher in females versus males (16.6 versus 7.7 hours). After administration of an oral solution, mometasone bioavailability was higher in females then males (C_{max}: +105%; AUC: +51%). Part of these observed difference are probably due to differences in subject volume of distribution (mean subject weights - males: 171.0 lbs; females: 147.8 lbs → male/female = 1.16). The remaining difference is not explained by the data presented. While mometasone bioavailability was inadequate to assess this effect when administered as the intranasal product, the possibility of increased bioavailability in females should be considered when evaluating the safety of this product.

V. FORMULATIONS

The pivotal clinical efficacy and safety trial batches were of full production scale and represent the final, to-be marketed formulation. The batch used for the bioavailability study was of one-half production-scale and used a packaging system different from the to-be-marketed. It is not expected that these differences would have a major effect on bioavailability

COMMENTS (From Study C95-050)

1. Relatively sporadic and transient mometasone plasma concentrations were observed in four female subjects (Subjects 13, 16, 21 and 22) participating in the intranasal arm of this study. The sponsor is requested to provide an explanation for these findings.

2. If the sponsor elects to develop additional mometasone furoate products with bioavailability adequate to permit quantification, a complete human pharmacokinetic program would be necessary for approval. Please contact the Office of Clinical Pharmacology & Biopharmaceutics for further details.

3. Markedly higher bioavailability was observed in female versus male subjects after administration of mometasone furoate as an oral solution. Weight adjustments of C_{max} and AUC were not performed by the sponsor. Based on mean subject weights (males: 171.0 lbs; females: 147.8 lbs → male/female = 1.16) only part of the difference observed is probably derived from differences in volume of distribution. Thus, the possibility of increased mometasone bioavailability in females should be considered when evaluating the safety and efficacy of this product.

Labeling Comments

1. In the *Absorption* portion of the **Pharmacokinetics** section:
   --The last sentence in the first paragraph: "The systemic bioavailability is negligible (≤0.1%)," is not supported by the data and should be removed.
   --The second paragraph should be replaced with: "Studies in normal volunteers have shown that mometasone furoate monohydrate, when administered as the nasal spray is poorly absorbed. A study with radiolabeled drug administered intranasally showed about 2% of the radioactivity excreted in the urine. In the fecal fraction, the 78% of radioactivity recovered probably represented unabsorbed, unchanged drug.
2. The *Distribution* portion of the **Pharmacokinetics** section should be omitted.
3. In the *Metabolism* portion of the **Pharmacokinetics** section:
   --The first sentence should be replaced with: "Mometasone furoate studies have shown that any portion of the mometasone dose which may be swallowed and absorbed undergoes extensive metabolism."
   --The second sentence (The multiple metabolites....) should be omitted.
   --The fourth sentence (After intravenous administration....) should be omitted.
4. The **Special Populations** section should be changed to read: "The effect of special populations on mometasone pharmacokinetics have not been adequately investigated."

Recommendation The Human Pharmacokinetics portion of this submission has been reviewed by the Office of Clinical Pharmacology & Biopharmaceutics and has been found acceptable to support approval of NDA 20-762.

Please forward Comments 1 - 2, Labeling Comments 1 - 4 and the Recommendation, above, to the sponsor.

Bradley K Gillespie 9/11/97
Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

Clin Pharm/Biopharm Briefing: 9/10/97: Drs Conner, ChenM, Worobec and Hunt

RD Dale P. Conner, PharmD, Team Leader

FT 9/11/97 Dale P. Conner, PharmD, Team Leader

cc:
HFD-570 (NDA 20-762, Divisional File, Toyer, Worobec, Himmel)
HFD-870 (ChenME, Conner, Hunt)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

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SCH 32088: Absorption, Metabolism and Excretion of ^{3}H-SCH 32088 Administered by Oral Swallow as a Solution, Oral Inhalation and Nasal Spray as Suspensions (C91-101-01), Intravenous as Solution (C91-103-01), Oral Inhalation by Gentlehaler (C91-102-01) or Oral Swallow (C91-328-01) as Suspensions in Male Volunteers

Investigator

Study Dates C91-101-01: 06/25/91 - 11/12/91
C91-102-01: 11/18/91 - 11/26/91
C91-103-01: 09/09/91 - 09/17/91
C91-328-01: 06/22/91 - 06/30/92

Analytical Facility Schering Plough Research Institute (SPRI)

OBJECTIVE To determine the absorption, metabolism and excretion of ^{3}H-SCH 32088 in healthy male volunteers following single-dose administration by oral swallow as a solution and suspension, by oral metered dose inhaler (MDI) and intranasal inhalation.

BACKGROUND Four separate studies were conducted by the sponsor. The results of these four studies are compiled into a single report, which is the subject of this review.

FORMULATIONS Six subjects were assigned to each of the following six treatment groups:

			Dose		
Study No.	Treatment	Dosage Form	mg/Subject	µCi/Subject	Mode of Administration
C91-101-01	A	Oral Solution	1.03	209	Oral Swallow
C91-101-01	B	MDI	0.86	163	MDI Inhalation
C91-101-01	C	Nasal Spray	0.19	197	Nasal Inhalation
C91-102-01	—	Gentlehaler	0.40	79	MDI w/spacer device
C91-103-01	—	IV Solution	1.03	204	1 minute infusion
C91-328-01	—	Oral Suspension	0.99	195	Oral Swallow

STUDY DESIGN Approximately 12 hours prior to dosing, all volunteers were confined to the study site. Ten hours prior to dosing, a standard light snack was served, and an overnight fast was maintained. On the following morning, subjects were administered the above treatments. After dosing, volunteers remained fasting and ambulatory for an additional 4 hours. After this time, regular meals were served. Subjects were confined at the testing facility from Day 0 until the final urine and fecal samples were collected. Blood samples were obtained just prior to (zero hour), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144 and 168 hours after study drug administration. Urine samples were collected prior to dosing and at the following post-dose intervals: 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Stool samples were collected up to 168 hours after dosing and then pooled into 24 hour blocks for assay. Expired air was collected for

two ten minute periods: immediately after dosing and one hour following drug administration. Gauze pads used to collect any overflow material and filters used to trap exhaled drug after inhalation were extracted with an isopropanol-acetone mixture. All samples were analyzed for radioactivity. Additionally, the sponsor performed profiling of plasma, urine and fecal extracts. Hydrolysis of selected plasma and urine samples were performed using an enzyme preparation containing β-glucuronidase and aryl sulfate. Tritium exchange determinations were conducted by comparing the percent of radioactivity in the urine to a distilled fraction.

ASSAY

DATA ANALYSIS

Plasma (from total radioactivity): - C_{max}, T_{max}, AUC_{tf}[1], AUC_{0-24}, $AUC_{0-\infty}$, k_{el} and $t_{1/2}$
Urine (from total radioactivity): U_{0t} (amount excreted during a collection interval)
Feces: Total radioactivity in pooled fecal samples up to 168 hours after dosing

RESULTS The mean percent of radioactivity administered in the body as tritiated water at 168 hours was estimated to be less than 4%, suggesting only a minor fraction of the tritium label had exchanged with body water. Thus, ^{3}H-SCH 32088 is relatively stable in humans. All subjects completed the study with no dropouts.

Quantifiable plasma radioactivity was detected in subjects after receiving the intravenous, oral solution, MDI and gentlehaler formulations. The mean ng eq TR/mL versus time profiles for the first 36 hours after dosing are presented in Figure 1. Mean plasma TR pharmacokinetic parameters are presented and compared in Table 1. The results of the /radio-flow monitoring analyses demonstrated that following intravenous (IV) and oral (PO) administration of ^{3}H-SCH 32088, plasma radioactivity was primarily associated with metabolites more polar than the available standards. After IV dosing, approximately 39% of the 3-hr post-dose radioactivity was associated with parent drug compared to 1.5% of the 3-hr post-dose plasma radioactivity after oral dosing. Approximately 12% and 33% of the 3-hr plasma radioactivity was associated with parent drug following administration of the MDI and Gentlehaler, respectively. After administration of the nasal and oral suspension formulations, plasma radioactivity was too low to permit profiling. Plasma sample hydrolysis showed modest changes in profiles suggesting some hydrolytic release of conjugated metabolites.

The mass balance of ^{3}H-SCH 32088 in urine and feces is presented in Table 2.

[1] Area under the plasma concentration vs. time profile to the last quantifiable concentration

The metabolite profiles of both urine and fecal samples following intravenous and oral solution administration demonstrated that all of the radioactivity observed was associated with metabolites more polar than the parent drug. As with the plasma samples, enzymatic hydrolysis of the urine showed modest changes in the radioactive profiles. Analysis of fecal extracts from the MDI, Gentlehaler, nasal spray and oral suspension routes, demonstrated the presence of unchanged SCH 32088, probably due to unabsorbed drug.

DISCUSSION Mass balance data obtained after intravenous administration of radiolabel drug suggests that approximately 2/3 of systemic radioactivity is eliminated in the feces and 1/3 of systemic radioactivity is eliminated in the urine. When dosed as an oral or intranasal suspension 73% and 78%, respectively was recovered in the feces. It is not clear to what extent biliary excretion is contributing to this radioactive fraction.

CONCLUSION Drug derived radioactivity was completely absorbed when given orally as a solution but only minimally (~ 2% of administered radioactivity recovered in the urine) when administered as a oral suspension or nasal spray. When administered as an oral inhalation by the MDI and Gentlehaler, moderate absorption was observed (23-30% and 67-69%, respectively). Systemic SCH 32088 was extensively metabolized regardless of the route of administration. Based on observations after administration of intravenous and oral solutions, it appears that the major route of excretion is fecal elimination of metabolized drug. When given as the nasal spray or the oral suspension, most of the administered radioactivity is eliminated in the feces.

Figure 1. Mean Plasma Radioactivity (ng eq/mL) After Administration of ^{3}H-SCH 32088 to Male Volunteers

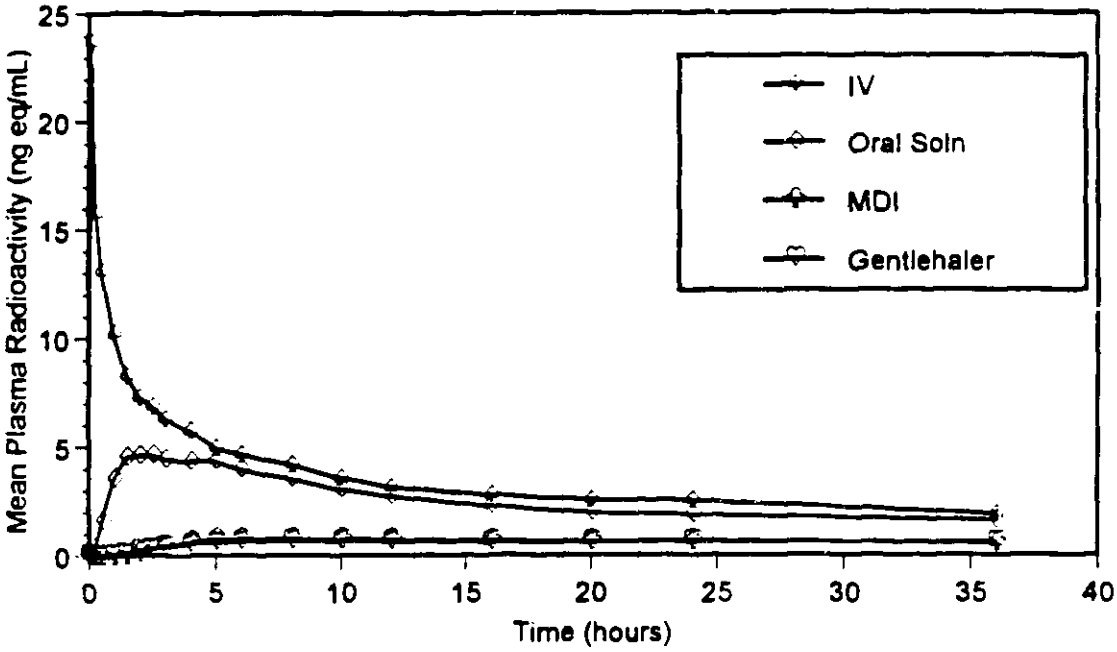

Table 1. Mean (%CV) ^{3}H SCH 32088 Pharmacokinetic Parameters (based on ng eq/mL)

Parameter	(unit)	Intravenous	Oral Solution	MDI	Gentlehaler
C_{max}[2]	(ng eq/mL)	23.7 (26)	4.83 (19)	0.803 (17)	0.685 (18)
T_{max}[3]	(hours)	—	2 (1.5 - 5)	9 (6 - 24)	9 (8 - 48)
AUC_{0-24}	(ng eq•hr/mL)	100.7 (14)	68.7 (13)	14.6 (21)	12.9 (23)
AUC_{∞}[4]	(ng eq•hr/mL)	280.7 (23)	251.7 (26)	45.0 (90)	69.5 (22)
$AUC_{0-\infty}$	(ng eq•hr/mL)	401.1 (41)	488.4 (44)	80.7 (107)	110.2 (41)
$t_{1/2}$	(hours)	100.0 (39)	164.6 (27)	55.4 (96)	90.6 (53)

[2] Maximum Plasma Concentration observed except for IV, which is $C_{5\ min}$

[3] Central tendency described as the *median* and variability as the *range*

[4] Area under the plasma concentration vs. time curve from time zero until last quantifiable timepoint

Table 2. Excretion of Radioactivity Following Administration of ^{3}H-SCH 32088 to Male Volunteers

Parameter	Intravenous	Oral Solution	MDI	Gentlehaler	Nasal Spray	Oral Suspension
Urine[5] (% of Dose)	24	25	7	16	2	2
Feces[6] (% of Dose)	54	62	86	89	78	73
U+F[7] (% of Dose)	78	87	93	105	80	75

[5] Percent of administered radioactivity excreted in the urine through 168 hours
[6] Percent of administered radioactivity excreted in the feces through 168 hours
[7] Total percentage of radioactivity recovered in the urine and feces through 168 hours

SCH 32088: Singe-Dose Absolute Bioavailability Study of Mometasone Furoate Administered as an Intravenous Solution, Oral Solution, Oral Suspension and Nasal Spray- A Four-Way Crossover Design

Study No. C95-050-01 **Volume** 1.155-7 **Pages** 1 - 1113
Investigator

Study Dates 5/10/95 - 6/8/95
Analytical Facility
Analysis Dates 7/19/95 - 10/3/95

OBJECTIVES To determine the absolute bioavailability of mometasone furoate (SCH 32088) administered intranasally as a suspension, orally as a suspension and orally as a solution

FORMULATIONS

Treatment A:	Intravenous (IV) solution - 1.0 mg of mometasone furoate administered as 1.0 mL of a 1.0 mg/mL solution via an IV injection
Treatment B:	Oral (PO) solution - 1 mg of mometasone furoate administered as 33.3 mL of a 0.03 mg/mL solution
Treatment C:	Oral suspension - 1 mg of mometasone furoate administered as 2.0 mL of a 0.5 mg/gm suspension
Treatment D:	Nasal Suspension - 400 µg of mometasone furoate administered as 8 sprays from a nasal pump spray bottle delivering 50 µg/spray

STUDY DESIGN A total of 24 healthy, non-smoking adult subjects (12 male and 12 female) were included in this open-label, randomized, single-dose, 4-treatment, 4-period crossover study. At least twelve hours prior to dosing, all subjects were confined to the study site, and volunteers completed a practice session to ensure proper dosing technique for the nasal sprayer. After an overnight fast, subjects received a single dose of study medication. Volunteers continued fasting and remained ambulatory for 4 hours after study drug administration. At this time, a light lunch was served. Eight hours after dosing, regular meals resumed. A washout interval of seven days separated the dosing periods. Subjects were confined throughout each study phase and abstained from the consumption of grapefruit juice, alcohol and xanthine containing foods and beverages. Blood samples were obtained for plasma SCH 32088 determinations just prior to (zero hour), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36 and 48 hours after study drug administration.

ASSAY

DATA ANALYSIS

Pharmacokinetic: C_{max}, T_{max}, AUC_t[8], $AUC_{0-\infty}$, CL, F, $t_{1/2}$ and $t_{1/2,eff}$[9]

Statistical: Descriptive statistics were provided for all parameters. Analysis of variance (ANOVA) was used to assess the effect of gender on drug disposition.

RESULTS All 24 subjects completed the study in accordance with the protocol. After dosing the oral and intranasal suspension, observed SCH 32088 concentrations were low, and transient. Only when given as an intravenous or oral solution were useful plasma concentration data obtained. The mean plasma concentration versus time profiles for males and females for the first 12 hours after intravenous dosing are presented in Figure 2 Pharmacokinetic parameters following dosing of intravenous and oral solution are presented in Tables 3 and 4, respectively.

COMMENT Mometasone is biotransformed to multiple metabolites. The activity and/or toxicity of these moieties is unknown. Radioalabel mass balance studies demonstrated that when mometasone is administered as a nasal or oral suspension, respectively, only minimal quantities of the drug are systemically absorbed. When given as an oral solution, complete absorption occurs and when mometasone is inhaled, moderate absorption can be expected. Thus, this study, which assessed only the bioavailability of the parent compound, may be inadequate for some of the more bioavailable dosage forms.

DISCUSSION Markedly higher bioavailability was observed in female versus male subjects after administration of mometasone furoate as an oral solution. Weight adjustments of C_{max} and AUC were not performed by the sponsor. Based on mean subject weights (males: 171.0 lbs; females: 147.8 lbs → male/female = 1.16) part of the difference observed is probably derived from differences in volume of distribution. Additionally, high variability observed in both sexes should be considered as a possible source of estimation error.

CONCLUSION This study documented that the absolute bioavailability of the oral mometasone solution is approximately 2%. The source(s) of difference(s) in bioavailability between males and females is/are not clear from the data presented. Thus the possibility of increased mometasone bioavailability in females should be considered when evaluating the safety and efficacy of this product. Plasma mometasone concentrations observed after dosing of the oral suspension and the intranasal suspension were too low to permit a determination of bioavailability.

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[8] Area under the plasma concentration versus time profile to the final quantifiable timepoint

[9] Effective half-life, to estimate potential for accumulation (*J Clin Pharmacol* 1995;35:763-766)

Figure 2. Mean Plasma SCH 32088 Concentrations for the First 12 Hours After Dosing 1.0 mg Intravenous Mometasone Furoate to Males and Females

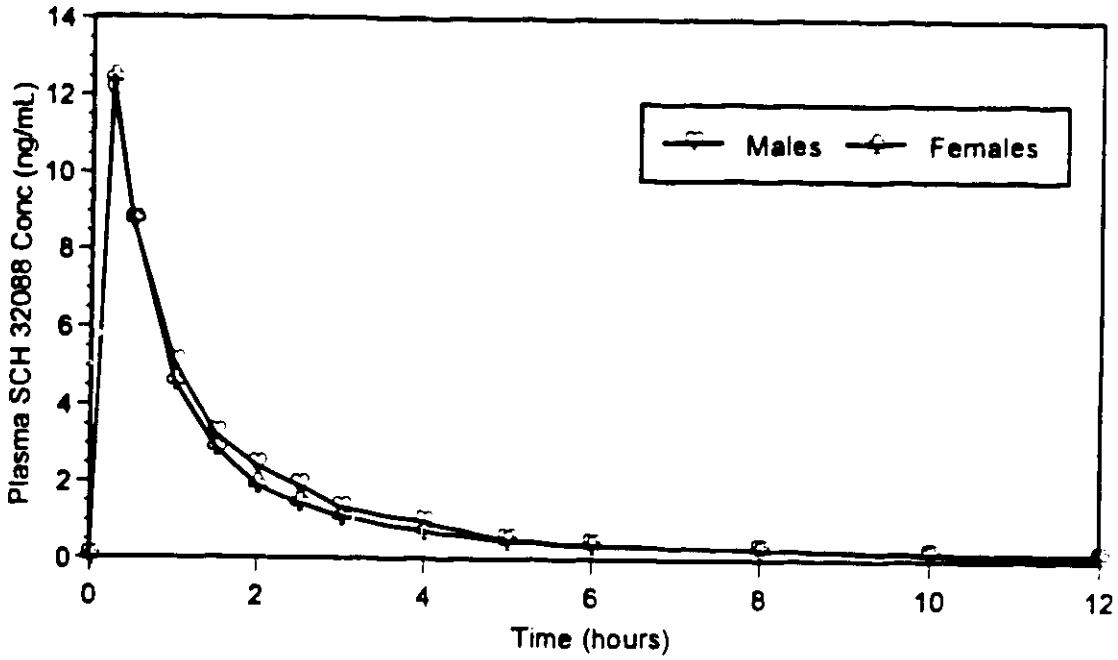


Table 3. Mean (%CV) SCH 32088 Pharmacokinetic Parameters for Male and Female Volunteers After Intravenous Dosing of 1 mg Mometasone Furoate

	AUC_{0-t}[10] (pg·hr/mL)	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hours)	$t_{1/2,eff}$[11] (hours)
Males	17287 (27)	17557 (30)	7.73 (48)	5.04 (10)
Females	16933 (20)	18742 (19)	16.6 (78)	6.93 (46)

Table 4. Mean (%CV) SCH 32088 Pharmacokinetic Parameters for Male and Female Volunteers After Oral Dosing of 1 mg Mometasone Furoate as an Oral Solution

	C_{max} (pg/mL)	T_{max}[12] (hours)	AUC_{0-t}[10] (pg·hr/mL)	F[13] (%)
Males	187 (64)	0.5 (0.25-20)	272 (70)	1.93 (67)
Females	385 (100)	0.5 (0.25-12)	413 (68)	1.99 (74)

[10] Area under the plasma concentration vs. time profile to the last quantifiable timepoint
[11] Effective half-life
[12] Central tendency described as the *median* and variability as the *range*
[13] Mean of individual subject absolute bioavailability

In vitro metabolism in pulmonary and hepatic tissues (P-5642, 8/92; Vol. 152)
(Excerpted from Dr Du's Pharmacology/Toxicology Review)

To determine SCH 32088 metabolisms in rat or mouse pulmonary and hepatic tissues, ^{3}H-SCH 32088 (Batch # 23650-49-7) was incubated in vitro with the supernatant of lung and liver fractions After the culture, the supernatant was analyzed using
Each incubation was divided into three groups Group I represented the live protein, 30 min incubations which were analyzed to identify metabolic products. Groups II (Live protein + 0 min incubation) and III (denatured protein + 30 min incubation) were used as the controls Only peaks presented in Group I (but not in other groups) were identified as the metabolites. If metabolic product appeared in all groups, it was considered as an artifact.

Results showed that no metabolism of ^{3}H-SCH 32088 was found in both rat and mouse lung S9 incubations. Since SCH 32088-9, 11-epoxide was found in all mouse incubation groups, it was considered to be an artifact. (See table below.)

LUNG S9 METABOLIC PROFILE
(Mean (%CV) percent of total peak area)

Incubation	Epoxide*	SCH 32088
Rat Lung		
Ia**	–	99.02 (1.7)
Ib	–	100
IIa	–	100
IIb	–	100
IIIa	–	100
IIIb	–	100
Mouse Lung		
Ia	2.5 (12)	97.5 (0.3)
Ib	1.2 (21)	98.8 (0.3)
IIa	2.9 (76)	97.1 (2)
IIb	1.1 (25)	98.9 (0.3)
IIIa	2.8 (4)	[illegible]
IIIb	1.2 (3)	98.8 (0)

Epoxide*: SCH 32088-9,11-epoxide
a**: 0.05 mM substrate concentration
b: 0.50 mM substrate concentration
I: live protein, 30 min incubation
II: live protein, 0 min incubation
III: denatured protein, 30 min incubation

In rat liver S9 incubation SCH 32088 was extensively metabolized. Approximately 40% of SCH 32088 (0.05mM substrate) was converted to 6-hydroxy SCH 32088. Mometasone and two unknown metabolites (UK1 and UK2) were also detected. In mouse liver, 6-hydroxylation, ester hydrolysis and metabolism to an unidentified product were observed (See table below)

LIVER S9 METABOLIC PROFILE

(Mean (%CV) percent of total peak area)

Incubation	6-OH*	UK1	Mometasone	Epoxide	UK2	SCH 32088
Rat Liver						
Ia**	38.5 (3)	0.8 (24)	0.7 (42)	1.9 (20)	2.1 (16)	56.8 (3)
Ib	5.1 (4)	0.3 (16)	0.3 (9)	0.7 (9)	0.3 (18)	93.8 (0.3)
IIa	–	–	–	0.7 (12)	–	99.3 (0.1)
IIb	–	–	–	0.5 (4)	–	99.5 (0.02)
IIIa	–	–	–	2.2 (8)	–	97.8 (0.2)
IIIb	–	–	–	0.9 (15)	–	99.1 (0.1)
Mouse Liver						
Ia	3.2 (9)	1.0 (31)	0.8 (5)	1.9 (2)	–	93.0 (0.8)
Ib	1.4 (17)	0.3 (25)	0.5 (12)	1.3 (16)	–	96.2 (0.4)
IIa	–	–	–	2.6 (76)	–	97.4 (2)
IIb	–	–	–	1.3 (12)	–	98.7 (0.2)
IIIa	–	–	–	2.7 (23)	–	97.3 (0.8)
IIIb	–	–	–	1.2 (8)	–	98.8 (0.1)

6-OH*: 6β-Hydroxy Mometasone Furoate
UK1: unknown 1
Epoxide: SCH 32088-6,1-epoxide
UK2: unknown 2
a**: 0.05 mM substrate concentration
b: 0.50 mM substrate concentration
I: live protein, 30 min incubation
II: live protein, 0 min incubation
III: denatured protein, 30 min incubation

The above results showed that SCH 32088 in rats or mice was extensively metabolized by liver S9, but no by lung S9 system in vitro. This result can be attributed to low concentrations of metabolic enzymes in the lungs in comparison with the livers.

OCT 17 1996

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-762	**Submission Date:** 9/30/96
Mometasone Furoate Nasal Spray (NASONEX™)	**Submission Type:** New NDA, 1S
	Review Type: Suitability for filing
Schering, Corporation	
2000 Galloping Hill Road	**Reviewer:**
Kenilworth, NJ	**Brad Gillespie, PharmD**

Background NASONEX Nasal Spray is a metered-dose, manual spray unit containing an aqueous suspension of mometasone furorate (MF) monohydrate (equivalent to 0.05% w/w MF anhydrous) in an aqueous medium. Each actuation of the device is designed to deliver the equivalent of 50 µg MF anhydrous.

NASONEX Nasal Spray is a glucocorticosteroid claimed to demonstrate anti-inflammatory properties in the nasal mucosa without systemic activity. In an *in vitro* model, MF was shown to be at least 10 times more potent than other steroids tested, to include, beclomethasone, betamethasone and dexamethasone. In support of this application, the sponsor has conducted 18 clinical safety and efficacy trials. Additionally, the sponsor has submitted 5 clinical pharmacology studies. The first study report is actually a compilation of 4 separate radiolabel mass balance studies. The second study is a four-way crossover study comparing the bioavailability of MF when administered as an intravenous (IV), oral suspension, oral solution or nasal spray. The remaining 3 clinical pharmacology studies were designed to assess the safety of the formulation by measuring suppression of the hypothalamic pituitary adrenocortical (HPA)-axis.

Discussion Originally, the sponsor proposed using an to quantify plasma mometasone concentrations. A second review of the assay validation data determined that this assay was inappropriate. At this time, the sponsor developed a

The lower limit of quantitation for this method is 50 pg/mL. Even at this level of sensitivity, only sporadic plasma mometasone concentrations were observed after the administration of therapeutic doses of MF intranasal. Therefore, the sponsor has submitted an abbreviated Human Pharmacokinetic package in support of this NDA.

Comments

1. The physical and chemical properties of the drug substance/product were adequately described.

2. The proposed package insert was annotated, allowing identification of source studies for data verification.

3. The sponsor proposes marketing a single 0.5 mg/g formulation. The to-be-marketed fomulation was used for all of the pivotal clinical studies.

4. The sponsor has performed radiolabeled mass balance studies to characterize the ADME of this product.

5. As described in the discussion section, above, bioavailability studies are limited by assay sensitivity. In this case of a topical steroid, local bioavailability can be assured by clinical efficacy, while systemic bioactivity can be assessed by evaluating HPA-axis suppression.

6. The sponsor has included an evaluation of gender effect in their proposed package insert. These data will need to be reviewed carefully, in the absence of reliable pharmacokinetic data.

7. Assay validation data for the bioavailability study has been provided by the sponsor.

8. The plasma assay used in the radiolabel mass-balance study was the un-validated method. Therefore, only radioactivity, without plasma concentration data are available in this report.

9. At a July 15, 1995 pre-NDA meeting, the sponsor assured FDA that they were currently conducting *in vitro* studies to characterize the metabolism of mometasone. None of these data are present in this submission. The sponsor is requested to submit these data.

Recommendation This submission has been reviewed in a cursory fashion, and has been found acceptable to permit filing from the Office of Clinical Pharmacology & Biopharmaceutics' (OCPB) perspective.

Please forward Comment 9 to the sponsor in the form of an information request (IR) letter.

10/17/96

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

FT 10/16/96

Dale P. Conner, PharmD, Team Leader

cc:
HFD-570 (NDA 20-762, Divisional File, Toyer)
HFD-870 (Chen, Conner, Hunt, Gillespie)
HFD-870 (Drug, Chron, Reviewer)
HFD-850 (Lesko)
HFD-340 (Viswanthan)

AUG 19 1997

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Supplement Review

NDA Number: 20-762

Supplement Number: N(BB)

Date of Submission: 12/3/1996

Information to be Conveyed to Sponsor: Yes ( ), No (X)

Reviewer: T. Tom Du, Ph.D.

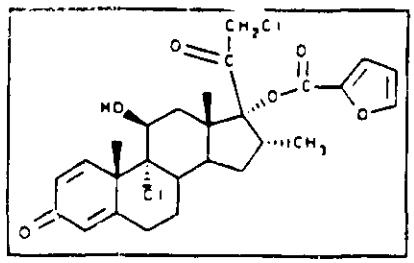
Date Review Completed: 8/19/1997

Sponsor: Schering Corporation
2000 Galloping Hill Road,
Kenilworth, NJ 07033

Drug Name: NASONEX™ Nasal Spray
(SCH 32088; Mometasone furoate monohydrate)

CAS Number: 83919-23-7

Molecular Formula and Structure: $C_{27}H_{30}Cl_2O_6H_2O$



Molecular Weight and Formula: 539.458

Class: Anti-inflammatory steroid

Indication: Prophylaxis and treatment of seasonal allergic rhinitis/Perennial rhinitis

Route of Administration: Intranasal

Study Reviewed in this Amendment:

1 In vitro metabolism of SCH 32088 across species by liver, lung and intestinal tissue preparation (P-6376; 6/93-11/96)

REVIEW OF STUDIES

1. IN VITRO METABOLISM OF SCH 32088 ACROSS SPECIES BY LIVER, LUNG AND INTESTINAL TISSUE PREPARATIONS (P-6376; 6/93-11/96)

Test Lab: Schering-Plough, Kenilworth, NJ
Study Number: 92347 GLP: No
Batch Number of Test Article: 30329-46-10, 36711-94-5, 32613-27-23, 35490-10-3, 50492-059 and 23047-131

This study was to compare the metabolite profiles and metabolites of SCH 32088 in the livers, lungs, and intestines of various species (rat, mouse, dog and human).

Methods: In this study, tissues were harvested from Crl:CD(SD)BR rats, CD-1 mice and beagle dogs, which are the same animal species and strains used in the toxicology and carcinogenicity studies. In vitro incubations of SCH 32088 were performed with the following tissue preparations:

1. Rat, mouse, dog and human liver slices. (Evaluated by LC/MS, LC/MS/MS and 2D-TLC.)
2. Rat, mouse, dog and human liver microsomal preparations. (Evaluated by HPLC, LC/MS, LC/MS/MS.)
3. Human lung slices; rat, mouse, dog and human lung microsomal preparations. (The techniques used for the evaluation were not defined.)

4. Rat, mouse and dog everted intestines.(Evaluated by HPLC.)
5. Rat and mouse freshly isolated hepatocytes and commercially available rat and dog primary cultured hepatocytes. (Evaluated by HPLC.)

After the incubations, drug-derived radioactivity was analyzed using HPLC, HPLC/MS, HPLC/MS/MS, NMR or two dimensional thin layer chromatographic (2D-TLC) techniques.

Results: Following in vitro incubations of SCH 32088 at a concentration of 0.3 µg/g liver, rat, mouse, dog and human liver slices produced highly polar, polar, moderately polar, mometasone-like polarity and non-polar metabolites across all species. (See table below.) Non-polar products were mainly degradation products, including a 9,11-epoxide, a spirodihydrofuranone and a spirodihydrofuranone-9,11-epoxide. The 9,11-epoxide has been tested previously in an in vitro chromosomal aberration study using CHO cells.

In vitro Metabolism of SCH 32088 at 0.3µg/g liver

Sources of Liver Slices	MF Concentration (µg/g tissues)	% Applied Radioactivity					
		Very Polar	Polar	Moderated Polarity[a]	MF*-like Polarity	No-polar Decomposition Compounds	Total
Mouse	0.30	5	7	18	22	47	99
Rat	0.30	5	67	1	28	0	101
Dog	0.30	26	29	4	39	1	99
Human	0.30	21	16	25	26	10	97

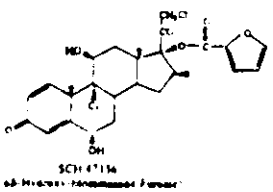
[illegible] was the only in vitro metabolite [illegible] incubations of the [illegible] with liver microsomes of mouse, rat, dog and human. This metabolite was found [illegible] SCH 47156 by [illegible] area, [illegible] retention time, NMR and mass spectra.

[illegible] polar metabolites featuring the 6β-Hydroxy-SCH [illegible] were found to be the dominant metabolite [illegible] from in vitro incubations of high drug concentrations (13.3 µg SCH 32088/g liver tissue) [illegible] with sliced liver of either mouse, rat, dog or human.

[illegible] profiles from liver slice incubations [illegible] similar across species [illegible]

When liver slices were incubated with SCH 32088 at different concentrations, it was noted that in vitro metabolism of SCH 32088 was concentration dependent; hepatic tissues produced large amounts of moderately polar metabolites across all species. The major moderately polar metabolite was 6β-hydroxy-SCH 32088 (SCH 47156; see the structure below). After rat hepatic slices were treated with SCH 32088 at the concentrations of 13.3 and 133 µg/g, liver slices yielded exclusively SCH 47156. (See table below.)

Table 2. Radioactive Profile of Metabolites at High Drug to Liver Tissues Ratio in Rat, Mouse, Dog and Human



Species	µg SCH 32088/g liver	Major Metabolite(s)
Rat	13.3 (Pre-Hydrolysis) 133 (Pre-Hydrolysis)	SCH 47156[a] SCH 47156[a]
Mouse	6.7 (Pre & Post Hydrolysis) 13.3 (Pre & Post Hydrolysis) 40, 80, 120 (Pre & Post Hydrolysis) 133	SCH 47156 including Polar & Moderately Polar metabolites SCH 47156 (Higher Level) including Polar & Moderately Polar metabolites Moderately Polar metabolites[b] Metabolism Inhibited
Dog	26.6, 39.9 & 79.8 (Pre-Hydrolysis)	SCH 47156[c] & Moderately Polar metabolites
Human	6.7 (Pre & Post Hydrolysis) 13.3 (Pre & Post Hydrolysis) 80, 100, 120, 133	SCH 47156[d] & Moderately Polar metabolites SCH 47156[d] & Moderately Polar metabolites Metabolism Inhibited

a In the rat the presence of SCH 47156 was supported by both HPLC (co-elution with reference standard) and by mass spectral analyses. In all other species the presence of SCH 47156 was detected solely by HPLC.

b Scaling up the drug to tissue ratios to 40 µg/g, 80 µg/g and 120 µg/g liver promoted the formation of higher amounts of moderately polar metabolites.

c The presence of a radioactive metabolite, which co-eluted with SCH 47156 reference standard, was detected in all incubations with dog liver slices at high drug to tissue ratios.

d Additional SCH 47156 is released following β-glucuronidase/sulfatase hydrolysis.

Following incubation, rat, mouse, dog and human liver microsomes produced exculsively SCH 47156 across all species. SCH 47156 was the major metabolite following in vitro incubation of SCH 32088 with rat, mouse and dog everted intestines. Extensive in vitro metabolisms of SCH 32088 were also noted in isolated rat, mouse and dog hepatocytes. However, no metabolism was observed when SCH 32088 was incubated with lung microsomes or human lung slices. (See table below.) The lung perfusion study was not provided in this submission.

Table 3. *In Vitro* Metabolism of SCH 32088 - A Consolidated Table

Species	Liver Slices (High Conc.)	Liver Slices (Physiol. Conc.)	Liver Microsomes	Hepatocytes[c]	Intestinal Tract	Lung Perfusion	Lung Microsomes	Lung Slices
Rat	SCH 47165[a]	Extensive metabolism	SCH 47165[a]	Extensive metabolism	SCH 47165	SCH 47165	No Metabolism Observed	Not Tested
Mouse	Moderate polarity & SCH 47165	Extensive metabolism	SCH 47165[a]	Extensive metabolism	SCH 47165	Not Tested	No Metabolism Observed	Not Tested
Dog	Moderate polarity & SCH 47165	Extensive metabolism	SCH 47165[a]	Extensive metabolism	SCH 47165	Not Tested	No Metabolism Observed	Not Tested
Human	Moderate polarity & SCH 47165	Extensive metabolism	SCH 47165[a]	Not Tested	Not Tested[d]	Not Tested	No Metabolism Observed	Tissue Non-Reactive

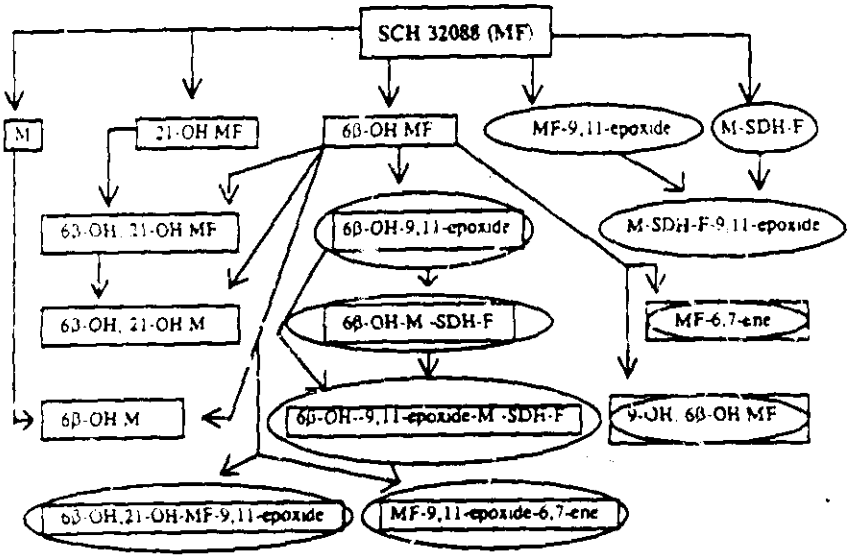
a SCH 47165 is 6β-hydroxy-SCH 32088.

b The chemical structure of this metabolite, including its absolute configuration at C(6), was confirmed by both NMR and mass spectral techniques and by direct LC/NMR analyses.

c *In vitro* drug metabolism studies revealed qualitative differences between freshly isolated hepatocytes (rat and mouse) prepared on-site and the commercially available primary cultured hepatocytes (rat and dog, Cedra Corp.). The overall clearance of SCH 32088 to metabolites was significantly greater in the freshly isolated hepatocytes prepared on-site. The ineffectiveness of Cedra's primary cultured hepatocytes in SCH 32088 metabolism is probably due to a decrease in cytochrome P-450 activity with time.

d No access to human everted intestines.

Since the 2D-TLC may provide a better separation of SCH 32088 metabolites than the HPLC assay, 2D-TLC was used for the analysis. The results showed that polar and non-polar radioactivity images exhibited similar patterns across all species. This suggests that the metabolic profiles of SCH 32088 were qualitatively similar across all species. Based on the results of 2D-TLC, in vitro metabolism and degradation pathway of SCH 32088 in rat hepatocytes is proposed as the follwing:



In conclusion, SCH 32088 was metabolized extensively in the liver and minimally in the lung; metabolic profiles in all species studied were qualitatively similar but quantitatively different. 6β-hydroxy-SCH 32088 (SCH 47156) was one of the major metabolites following the incubations of various tissue conditions. Since the in vitro and in vivo metabolisms of SCH 32088 were not compared in this study, metabolic profile of SCH 47156 in vivo for the humans treated by intranasal administration of SCH 32088 cannot be provided from this study. Lung tissue metabolized the compound only in the pulmonary perfusion study. The study was requested from the sponsor on August 19, 1997 to allow for full evaluation of this data.

Tao Tom Du, Ph.D.
Pharmacologist/Toxicologist

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original, Review No. 1

NDA Number: 20-762

Serial Number: 001

Date of Submission: October 3, 1996

Information to be Conveyed to Sponsor: Yes (x), No ( )

Reviewer: T. Tom Du, Ph.D.

Date Review Completed: August 7, 1997

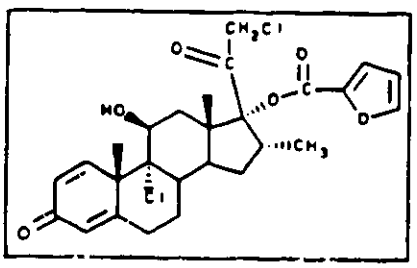
Sponsor: Schering Corporation
2000 Galloping Hill Road,
Kenilworth, NJ 07033

Drug Name: NASONEX™ Nasal Spray
(SCH 32088; Mometasone furoate monohydrate)

Chemical Name: 9,21-Dichloro-11b,17-dihydroxy-16a-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) mometasone

CAS Number: 83919-23-7

Molecular Formula and Structure: $C_{27}H_{30}Cl_2O_6H_2O$



Molecular Weight and Formula: 539.458

Related INDs/NDAs/DMFs (if applicable):

NDA 19-543 Elocon (Mometasone Furoate) Ointment (Schering, approved 04/30/87)*
NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (Schering approved 05/06/87)*
NDA 19-796 Elocon (Mometasone Furoate) Lotion (Schering, approved 03/30/89)*

*Note These products are for dermal topical application

Class: Anti-inflammatory steroid

Indication: Prophylaxis and treatment of seasonal allergic rhinitis/Perennial rhinitis

Clinical Formulation: Mometasone furoate monohydrate is clinically used as a nasal spray. The ingredients in the drug product are listed in the following table. All inactive ingredients are used in various approved nasal or inhalation drug products in similar quantities (Inactive Ingredient Guide, Jan. 1996).

Ingredient	mg/g in drug products
Mometasone Furoate Monohydrate Micronized (Inhalation Grade) Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF 65 cps Glycerin USP Citric Acid USP Monohydrate Sodium Citrate USP Dihydrate Polysorbate 80 NF Benzalkonium Chloride Solution NF (17%, without alcohol) Phenylethyl Alcohol USP Purified Water USP qs ad	a

[a]Equivalent to 0.515 mg g of Mometasone Furoate Anhydrous. A 3% manufacturing overcharge is included for Mometasone Furoate Monohydrate.
[b]Equivalent to 0.204 mg g of Benzalkonium Chloride. A 2% manufacturing overcharge is included for Benzalkonium Chloride.

Route of Administration: Intranasal

Proposed Clinical Protocol: For adults and adolescents 12 years of age or older, the usual

recommended dose for prophylaxis and treatment is 2 sprays (50 µg/per spray) in each nostril once daily (200 µg/day). The daily dose is equivalent to 4 µg/kg on the basis of body weight (50 kg) or 125 µg/m^2 on the basis of body surface area.

Studies Reviewed in this NDA:

PHARMACOLOGY

1. Effects on pulmonary inflammation and cytokines in an allergic mice (D-27191)
2. Effects on pulmonary inflammation in guinea pigs (D-24250)
3. Effects on cytokine production (Vol. 19)
4. Effects on leukotriene production (D-27220)
5. Anti-inflammation activity of oral dosed SCH 32088 (D-23879 and D-26685)
6. Topical anti-inflammatory activity of SCH 32088 (P-4809)
7. Effect of topically used SCH 32088 (P-4809)
8. Progestational and androgenic activities of SCH 32088 (D-17420)
9. Effect on endocrine profiles (D-27252)
10. Effects on electrolyte levels and hepatic glycogen deposition (D24422)
11. Safety pharmacology studies reviewed previously

TOXICOLOGY

1. Acute inhalation toxicology studies (D-22795, D-22742 & P-5948)
2. Acute oral (PO) and subcutaneous (SC) toxicology study (P-4865)
3. Three-day nasal screening study in dogs (D-22324)
4. One-week nasal irritation study in dogs (P-5995)
5. One-month nasal irritation study in dogs (P-5336)
6. One-month nasal irritation study in dogs (P-5474)
7. Six-month intranasal toxicity study in rats (P-6117)
8. Six-month intranasal toxicity study in dogs (P-6118)
9. One-year intranasal toxicity study in dogs (P-6116)
10. A 26-week oral inhalation toxicity study in dogs (P-5991)
11. A 26-week oral inhalation toxicity study in rats (P-5598)
12. Three-month inhalation study in beagle dogs (D-22796)
13. Three-month inhalation study in rats (D-22797)
14. Three-month inhalation study in rats (P-5736)
15. Two week inhalation study in beagle dogs (D-22607)
16. Two week inhalation study in rats (D-22680)
17. Other inhalation studies
18. Subchronic oral toxicity studies

19. One-month nose-only inhalation study in pediatric rats (P-5980)
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1. A pilot oral teratology (Segment II) study in rats (D-26738)
2. Oral teratology (Segment II) study in rabbits (P-5991)
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3. Single oral and intravenous dose studies (P-5941 and P-6368)
4. Disposition studies in rat and dog following a single IV or PO dose (P-5313)

5. One-month nose-only inhalation study in rats (P-6137)
6. One-month nose-only inhalation pharmacokinetic study in mice (P-6122)
7. A 28-day oral inhalation pharmacokinetic study in dogs (P-6096)
8. Three-month nose-only inhalational studies in 2 species (P-5836 & P-5837)
9. Three-month oral studies in 3 species (P-6104, P-6138, P-6007)
10. Tissue distribution studies in rats (D-24338, D-24339 and P-5367)
11. A 21-day tissue distribution and excretion study in rats (P-5976)
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14. Biliary excretion and enterohepatic circulation in rats (P-6009)
15. In vitro protein binding in rat, mouse, rabbit, dog and human plasma (P-6004)
16. In vitro metabolism in pulmonary and hepatic tissues (P-5642)
17. Other studies

CARCINOGENICITY STUDIES

1. Two-year nose-only inhalation carcinogenicity study in rats (P-6005)
2. Two-year nose-only inhalation carcinogenicity study in mice (P-6006)

REVIEW OF STUDIES

PHARMACOLOGY

Inhalation Studies

1. Effects on pulmonary inflammation and cytokine levels in an allergic mouse model (D-27191, Vol. 19)

Ovalbumin (OA) sensitized and challenged male B6D2F1/J mice were used in these studies. Pretreatment with inhaled SCH 32088 at 13 -33 µg/kg significantly decreased eosinophil numbers in bronchoalveolar lavage (BAL) fluid, and also reduced the density of eosinophils in the peribronchial and peribronchiolar regions of the lung tissues. Pretreatment of SCH 32088 also decreased the concentrations of Thy1$^+$ T cells* and T-helper (Th) cells in the BAL fluid.

In comparison to the untreated control mice, SCH 32088 at 33 mg/kg significantly reduced the percentage of Th cells expressing CD44 which is a cell surface molecule on activated/memory cells. For the untreated control mice, OA challenge increased levels of steady-state mRNA for IL-4, IL-5 and IFN-γ in the lung tissues. However, pretreatment with SCH 32088 at 3 - 33 µg/kg reduced mRNA levels of all three cytokines.

In conclusion, SCH 32088 has potent anti-inflammatory activity in allergen-induced pulmonary inflammation in mice.

* Thy 1 is a glycoprotein found on the membrane of T cells as well as other cells

2. Effects on pulmonary inflammation in guinea pigs (D-24250, Vol. 19)

In sensitized and allergen challenged male guinea pigs, pretreatment with aerosolized SCH 32088 (5611 µg/kg/day) or SCH 18020 (beclomethasone dipropionate, 1184 µg/kg/day) reduced eosinophil numbers in BAL fluid. SCH 18020 at 3457 µg/kg/day and SCH 32088 at 5611 µg/kg/day inhibited eosinophil infiltration in the airways and alveoli.

In vitro studies

3. Effects on cytokine production (Vol. 19)

By using anti-CD3 and CD28 antibody stimulated human CD4$^+$ T-cells, effects of SCH 32088 on the cytokine production were compared with betamethasone (BETA), fluticasone propionate

(FP), budesonide (BU), triamcinolone acetonide (TA) and beclomethasone dipropionate (BDP).

SCH 32088 inhibited the production of both IL-4 and IL-5 (IC_{50} = 0.27 ± 0.15 nM). The potency of SCH 32088 on the IL-4 or IL-5 release was much greater than other glucocorticoids used in this study. However, SCH 32088 and other glucocorticoids had similar potency on the inhibition of IFN-γ production. (This study was published in J Allergy Clin Immunol. 97, 288, 1996).

SCH 10745 (betamethasone valerate), SCH 11460 (betamethasone diproprionate), SCH 32088 and BDP were also tested for their effects on IL-5 production in mouse D10.G4.1 cells (D-25067). The results showed that SCH 32088 was the most potent inhibitor for IL-5 production among all 4 steroids. (See table below.)

Inhibition of IL-5 production: IC_{50} (nM)	
SCH 32088	0.12+0.11
Betamethasone Diproprionate	4.2+2.8
Betamethasone Valerate	0.75+0.25
Beclomethasone Diproprionate	1.5+0.87

Inhibitory effects of SCH 32088 on IL-1, IL-6 and TNF-α productions were also compared with BETA, hydrocortisone, dexamethasone, and beclomethasone by using murine WEHI-265.1 cells (P-5559). It was demonstrated that SCH 32088 was the most potent corticosteroid for the inhibition of IL-1 (IC_{50} = 0.1 nM), IL-6 (IC_{50} = 0.15 nM) and TNF-α (IC_{50} = 0.25 nM) production. The potencies of other steroidal drugs for the inhibition of IL-1, IL-6 and T.F.-α production are summarized in the following table.

Inhibition of IL-1, IL-6 and TNF-α productions by other steroidal drugs: IC_{50} (nM)			
Drug Name	IL-1	IL-6	T.F.-α
Betamethasone Alcohol	1.9	–	–
Betamethasone Diproprionate	1.2	7	250
Betamethasone Phosphate	>100	300	2000
Betamethasone Valerate	0.82	2	4
Beclomethasone Diproprionate	–	1.8	2000
Dexamethasone Alcohol	4	40	250
Hydrocortisone	100	290	>10000

4. Effects on leukotriene production (D-27220, Vol. 19)

In this study, peripheral leukocytes from atopic patients were pretreated for 18 hr with either SCH 32088 or beclomethasone dipropionate (BDP). After the cells were stimulated by allergen, anti-IgE, IL-3, calcium ionophore or media, production of total leukotrienes (LTs) was quantified by using an ELISA.

The study displayed that both SCH 32088 and BDP were able to reduce allergen- or calcium ionophore-induced LTs production. However, anti-IgE-induced LTs production was more effectively inhibited by SCH 32088 ($IC_{50} \leq 0.01$ nM) than BDP ($IC_{50} = 6$ nM), suggesting that SCH 32088 may more effectively attenuate leukotriene secretion during the allergic responses.

Other Studies

5. Anti-inflammation activity of oral dosed SCH 32088 (D-23879 and D-26685, Vol. 19)

In the following 2 studies, anti-inflammation activity of orally dosed SCH 32088 was determined by the efficacy of treating Reverse-Passive-Arthus-Reaction (RPAR).

1. In the first study (D-23879), efficacy of SCH 32088 (25 mg/kg) was compared with betamethasone (BM: 0.5 mg/kg), corticosterone (CS: 25 mg/kg) and hydrocortisone (HC: 25 mg/kg). The drugs were given orally at 30 min before RPAR was induced in rat pleural cavities by using bovine serum albumin (BSA) and rabbit anti-BSA. Neutrophil numbers in pleural cavities were counted to determine the activity of the drugs. Results showed that the rank order of therapeutic activity was presented as BM > CS > HC > SCH 32088. Therefore, anti-inflammation activity of orally dosed SCH 32088 was lower than other steroids used in this study.

2. In the second study (D-26685), rats were pretreated orally with SCH 32088 (7.5 to 60 mg/kg), fluticasone propionate (FP: 3.75 to 30 mg/kg), budesonide (BU: 0.5 to 4 mg/kg) and triamcinolone acetonide (TA: 0.125 to 1 mg/kg) at 30 min before RPAR was induced in rat pleural cavities. Inhibition of neutrophil infiltration and edema in pleural cavities were applied to determine the efficacy of the drugs. (See table below). This study demonstrated the oral anti-inflammatory potencies of SCH 32088 and FP was statistically similar, but they were less potent than BU and TA.

Compound	ED_{50}	
	Edema	Neutrophils
TA	0.5 (0.3-0.7)	0.3 (0.2-0.5)
BU	2 (1.4-3.1)	1.4 (0.8-2.8)
FP	33 (24-54)	20 (14-32)
SCH 32088	38 (29-55)	28 (12-31)

In conclusion, systemic anti-inflammatory activity of SCH 32088 was lower than most steroids used in the above studies.

6. Topical anti-inflammatory activity of SCH 32088 (P-4809, Vol. 19)

Therapeutic efficacy of topically used SCH 32088 or betamethasone valerate (BV) was evaluated in several experiments. Results are presented as the following:

1. SCH 32088 and BV had equal potency in the inhibition of croton-oil-produced-acute inflammation on mouse ears (ED_{50} = 0.02μg/ear).

2. For croton oil induced subchronic inflammation on mouse ears, SCH 32088 (ED_{50} = 0.002 μg/ear/day) was 7.7 times as potent as BV (ED_{50} = 0.014 μg/ear/day).

3. For M. Ovalis-induced epidermal acanthosis on the ears of guinea pigs, a 14-day treatment with SCH 32088 had similar potency to BV.

Based on the above studies, efficacy of topically used SCH 32088 was greater than BV for the inhibition of croton oil induced acute and subchronic dermal inflammation. However, SCH 32088 had similar potency to BV for the treatment of M. Ovalis-induced acanthosis.

Safety Pharmacology studies

7. Effect of topically used SCH 32088 (P-4809, Vol. 19)

SCH 32088 and betamethasone valerate (BV) produced side-effects were evaluated in mice by measuring hypothalamic-pituitary-adrenal (HPA) axis suppression, thymolysis and skin atrophy.

1. To evaluate the effect of SCH 32088 on the HPA axis, adrenal response to ether stress was measured by determining plasma corticosterone levels after topical application of SCH 32088 on mouse ears. It was found that a 3-daily application of SCH 32088 (ED_{50} = 5.3 µg/ear/day) was less potent than BV (ED_{50} = 3.1 µg/ear/day) in the suppression of the HPA axis. However, this potency difference was not statistically significant.

2. Thymolysis is a systemic effect of corticosteroids. After mice were treated topically for 5 days, thymus weights were used to determine the potency of SCH 32088 or BV. The results showed that SCH 32088 (ED_{50} = 26.6 µg/ear/day) was 2.2 times as potent as BV (ED_{50} = 51.6 µg/ear/day). However, SCH 32088 (ED_{50} = 11.2 µg/mouse) was 5.6 times more potent than BV (ED_{50} = 59.8 µg/mouse) after both drugs were dosed subcutaneously for 5 days. It is suggested that systemically administered SCH 32088 was more potent than topically used SCH 32088 for the induction of thymolysis.

3. Skin atrophy is a common side-effect caused by chronically used topical corticosteroids. In two individual experiments, mice were treated topically with SCH 32088 and BV, and then sacrificed. Skin tissues were prepared for observation. In the first experiment, SCH 32088 was 8.7 times more potent than BV. In the second experiment, SCH 32088 was approximately 3 times more potent than BV. In conclusion, SCH 32088 was more potent in causing skin atrophy.

Therefore, in comparison with BV, SCH 32088 had less potency for suppressing the HPA axis, but had greater potency for the induction of thymolysis and skin atrophy.

8. Progestational and androgenic activities of SCH 32088 (D-17420, Vol. 19)

Progestational and androgenic activities of SCH 32088 were evaluated in estrogen-primed immature New Zealand white female rabbits and immature male CD rats, respectively.

Progestational activity: After the rabbits were injected subcutaneously with 5 µg of β-estradiol for 5 days, animals were treated subcutaneously for 5 days with various dose levels of progesterone, clobetasol propionate, betamethasone valerate and SCH 32088. Twenty-four hours after the last dose, the uterus was removed and prepared for histological evaluation. The degree of progestational activity was measured by the scoring of endometrial proliferation. The study demonstrated that the progestational potency of SCH 32088 is 20.5 times higher than progesterone. Clobetasol propionate (12 times) and betamethasone valerate (5.3 times) were also more potent than progesterone.

Androgenic activity: Twenty-four hours after immature male rats received 7 daily subcutaneous doses of testosterone (0.05 to 5.0 mg/kg), progesterone (0.2 to 25 mg/kg) and SCH 32088 (0.2 to 25 mg/kg), animals were sacrificed. Seminal vesicles and ventral prostates were removed and

weighed. This study demonstrated SCH 32088 did not increase the weight of the male accessory sexual organs.

In conclusion, SCH 32088 has progestational activity in rabbit, but has no androgenic effects in male rats.

9. Effect on endocrine profiles (D-27252, Vol. 20)

In a group of studies, SCH 32088 was compared with [illegible]icasone Propionate (FP), Triamcinolone Acetonide (TA) and Budesonide (BU) for androgenic, antiandrogenic, estrogenic, antiestrogenic activities in rats. All drugs were also evaluated for their effects on sexual maturation of newborn female rats. All drugs were administered orally at 56 and 280 mg/kg, which were 2-fold and 10-fold their oral anti-inflammatory ED_{50} to the reverse passive Arthus reaction, respectively.

The results are presented in the following:

1) SCH 32088 and other drugs had no androgenic activity.

2) SCH 32088 did not display any antiandrogenic effect on the prostate and seminal vesicles. BU at the highest dose had some effects on the inhibition of prostate growth, but had no effect on the seminal vesicles.

3) Neither SCH 32088 nor other drugs show estrogenic activity.

4) When estradiol benzoate treated immature rats were dosed with different corticoids, SCH 32088 (56 and 280 mg/kg) and FP had some antiuterotrophic activities, but TA and BU had less activity.

5) For immature female rats, the effect of SCH 32088 and other corticosteroids on sexual maturation was determined by the time of vaginal opening. It showed that all steroids significantly delayed vaginal opening and all steroid-treated animals failed to gain weight compared to placebo-treated controls. (Vaginal opening is commonly used to define sexual maturation.)

The results of the above studies suggested that SCH 32088 had significant effects on female sexual maturation, and had some antiuterotrophic activity. However, SCH 32088 had no androgenic, antiandrogenic and estrogenic activity.

10. Effects on electrolyte levels and hepatic glycogen deposition (D24422, Vol. 20)

To compare the effects of SCH 32088, SCH 2509 (Hydrocortisone) and SCH 7302 (Triamcinolone) on electrolyte levels and hepatic glycogen deposition, adrenalectomized male rats were treated with various single subcutaneous or topical doses. (See table below.) Blood samples were collected for electrolyte measurements. Histology and microscopic examination were performed to determine hepatic glycogen deposition.

Test Articles	Subcutaneous Doses (mg/kg)	Topical Doses (gm)
SCH 2509	0.6, 6 and 60	0.1, 0.25 and 0.5 (1% Hytone TH)
SCH 7302	0.06, 0.6 and 6	0.1, 0.25 and 0.5 (0.1% Kenalog TH)
SCH 32088	0.06, 0.6 and 6	0.1, 0.25 and 0.5 (0.1% Elocon TH)

The results showed that serum electrolyte levels were not changed by the treatment of the test articles. After subcutaneous doses, only two SCH 2509-treated rats (at dose levels of 6 and 60 mg/kg, respectively) had minimal glycogen deposition, while minimal or mild hepatic glycogen deposition was found in two SCH 7302-treated rat groups (at dose levels of 6 and 60 mg/kg). At 24 hr after topical treatment with SCH 32088, mild hepatic glycogen deposition was only observed in 1 rat in the 0.5 gm group, but not in other groups.

Based on the above results, SCH 32088 did not have mineralocorticoid activity or any apparent effect on liver glycogen deposition. SCH 2509 and SCH 7302 did not have mineralocorticoid activity, although they had minimal or mild hepatic glycogen deposition activity.

11. Safety pharmacology studies reviewed previously

1. Pharmacological effects on the nervous systems (D-25526, a published article: Yokuoshi, K, et al. J. Yonago medical association 40, 1989)

2. Pharmacological effects on the respiratory and cardiovascular systems (D-25527, a published article: Sakonjo H, et al. J. Yonago medical association 40, 1989)

3. Effect of orally administered mometasone furoate and other steroids on circulating lymphocytes in guinea pigs. (P-5472, Vol. 19)

The above studies are briefly summarized for this submission.

In 2 peer-reviewed articles (D25526 and D-25527), general pharmacological effects of SCH 32088 on the central nervous, cardiovascular, and respiratory systems were reported. In vivo and in vitro measurements were performed using mice, rabbits, guinea pigs, cats, or dogs. Central nervous and autonomic nervous systems were not affected by subcutaneous dose of SCH 32088 at 100, 200, 500 or 1000 mg/kg. SCH 32088 did not affect either biliary secretion or gastric acid and pepsin secretion. After either an intravenous dose at 10 mg/kg or a subcutaneous dose at 200 mg/kg, there were no treatment-related effects on the respiratory and cardiovascular system (blood pressure, EKG and heart rate). However, as shown in the following table, subcutaneous injections of SCH 32088 increased urine volume, creatinine release, accumulation of hepatic glycogen, and decreased levels of ICG (an indicator for hepatic function).

Subcutaneous Dose of SCH 32088 (mg/kg)	Species			
	Rats		Rabbits	Mice
	Urine Volume*	Creatinine*	ICG*	Hepatic Glycogen*
200	40%	11%	58%	54%
500	48%	**	75%	137%

* Percentage changes from the control values

** There was no increase

Results from another study (P-5472) showed that oral administration of SCH 32088 at 13.3 to 150 mg/kg reduced circulating lymphocyte numbers by 13 to 25% in guinea pigs. However, SCH 32088-produced lymphocyte depression was neither statistically significant nor dose-related. In comparison with other drugs, SCH 32088 caused less immunosuppression than beclomethasone dipropionate and betamethasone.

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TOXICOLOGY

Single Dose Toxicity Studies

1. Acute inhalation toxicology studies (D-22795, D-22742 & P-5948; Vol. 23)

Test Lab: 1) D-22795
2) D-22742
3) P-5948:

Acute inhalation toxicities of SCH 32088 were evaluated in mic, rats and dogs. Study designs and mortality of the testing animals are summarized in the following table:

	n/sex	Batch #	Concentration	Exposure time (min)	Observation time	Mortality
Mouse	5	87-MMF-X-2	3.16 mg/L	240	5-week	1♂/1♀
Rat	5	87-MMF-X-2	3.31 mg/L	240	5-week	0
Rat	5	Unknown	5 mg/L	30	3-week	0
Dog	2	93-MMF-DDPX-01	♂: 139.5µg/L ♀:121.5µg/L	60	2-weeks	0

Decreased bodyweight was observed in rodents. Food consumption was only slightly reduced in dogs. After the sacrifice, small spleens were found in rats; discoloration of lungs, livers, kidneys and skins were seen in both rodent species.

2. Acute oral (PO) and subcutaneous (SC) toxicology study (P-4865, 12/82; Vol. 23)

Test Lab: Schering Corporation (GLP: no)

To determine the acute toxicity, rats (10/sex/group) and mice (15/sex/group) were treated orally or subcutaneously with SCH 32088 (Batch #: 14623-034) at 0 (vehicle), 20, 200 or 2000 mg/kg. After treatment, animals were observed for 35 days and then necropsied.

For rats dosed subcutaneously, deaths were found in 3/10 males and 5/10 females in the 2000 mg/kg group. Clinical signs were mainly related to local irritation at the site of injection (hair loss, swelling and scab formation, and/or necrosis). At the end of the study, dose-related reductions in body weight gains appeared in all groups. No abnormal necropsy findings were seen in the 20 and 200 mg/kg groups. However, visceral adhesions were noted in 1/10 female and 2/10 female rats given 2000 mg/kg.

After the mice were injected subcutaneously, deaths were seen in 14 rats/sex of the 2000 mg/kg group. A dose-related decrease in body weight gains appeared in the 20 and 200 mg/kg groups

Major necropsy findings in the 2000 mg/kg groups were intestinal flatulence/distension of the stomach with food (4 ♂ and 2 ♀) and white raised areas on the kidneys (4 ♂ and 1 ♀) or enlarged kidneys (2 ♂ and 1 ♀). Enlarged kidneys were also found in the 200 mg/kg rats (1 ♂ and ♀). There were no abnormal necropsy findings in the 20 mg/kg group.

Following oral administration, death, abnormal clinical signs and necropsy lesions were not observed in either species throughout the observation period. Results from all animal groups are summarized in the following table:

Species	Route	LD50 (mg/kg)	Non-lethal dose (mg/kg)	No-effect dose (mg/kg)
Rats	PO	>2000	>2000	>2000
Mice	PO	>2000	>2000	>2000
Rats	SC	♂>2000 ♀= 2000	200	<20
Mice	SC	♂>200 ♀>200	20	<20

Multiple Dose Intranasal Toxicity Studies:

3. Three-day nasal screening study in dogs (D-22324; 3/88; Vol. 24)

Test Lab: Schering Company, Lafeyette, NJ (GLP: No; Study #: 88025)
Animal: 4 groups of Beagle dogs (2/sex/group; Mean bodyweight: ♂ = 10.7 kg; ♀ = 8.2 kg)
Formulation: SCH 32088 nasal suspension; Concentration = 0.5 mg/ml

Three batches of SCH 32088 nasal suspension were given intranasally to the dogs for 3 days. Each dog was examined daily for the changes during the treatment.

After the treatment, no drug-related changes were observed in a nasal examination. The only reaction in the BA 20709-121 group (1/3 dogs) was mild sneezing on Day 2 and moderate sneezing on Day 3. There were no significant treatment-related changes in the body weight, food consumption, clinical pathology parameters, macroscopic and microscopic findings. (See table below.)

Group	Daily dose (mg/day)*	Daily Dose (♂/♀: mg/kg/day)#	Clinical signs
Saline	0	0/0	none
BA. 20709-116	4.3	0.4/0.52	none
BA. 20709-119	4.3	0.4/0.52	none
BA. 20709-121	4.2	0.39/0.51	mild and moderate sneezing

* one-half this amount per nostril. # calculated by using mean body weights

4. One-week nasal irritation study in dogs (P-5995; 6/94-10/95; Vol. 24)

Test Lab: Schering Company, Lafayette, NJ (GLP: Yes; Study #: 93227)
Animal: 4 groups of Beagle dogs (3/sex/group) with mean bodyweights of 10.7 kg in males and 8.2 kg in females.
Formulation: SCH 32088 nasal suspension; Concentration = 1 mg/ml (Batch # MSMPX05)

Methods: 4 groups were treated once daily for 7 to 10 consecutive days with SCH 32088 at the following dose levels:

Group	Daily dose (mg/day)	Dose volume (ml)	Daily dose (♂/♀: mg/kg/day)*
Vehicle	0	2	0/0
Low-dose	0.5	0.5	0.047/0.061
Mid-dose	1	1	0.093/0.122
High-dose	2	2	0.187/0.244

* Calculated based on the mean bodyweight

Results: Mortality was not seen. There were no dose-related changes in clinical signs, bodyweight, food consumption, clinical pathology parameters and histopathology findings. Nasal irritation was also not noted in the veterinary examinations.

5. One-month nasal irritation study in dogs (P-5336; 7/88-3/89; Vol. 25)

Test Lab: Schering Company, Lafayette, NJ (GLP: Yes; Study #: 88011)
Animal: 3 groups of Beagle dogs (3/sex/group) with mean bodyweight of 11.1 kg in males and 9.1 kg in females.
Formulation: SCH 32088 nasal suspension; Concentration = 0.5 mg/ml (Batch # 22023-061)

Methods: Dogs were dosed intranasally for 28 days with SCH 32088 at the following dose levels:

Group	Daily dose (mg/day)	Dose volume (ml)*	Doses / day	Daily dose (♂/♀: mg/kg/day)#
Vehicle	0	2	4	0/0
Low-dose	2	2	2	0.18/0.22
High-dose	4	2	4	0.36/0.44

* 1 ml nostril
# Calculated based on the mean bodyweight

Results:

Mortality (Daily): No death was noted in any group.

Clinical signs (Daily): No treatment-related clinical signs were noted in any group.

Nasal examination (twice daily): Daily nasal examinations did not reveal any nasal irritation.

Bodyweight (Weekly): No remarkable changes were observed.

Food consumption (Daily): No remarkable changes were observed.

Necropsy (Week 5): No gross lesions were observed.

Histopathology (Week 5): Focal polymorphonuclear leukocyte infiltrations were seen in the respiratory mucosa and submucosa of the control (♂: 1/3) and high-dose groups (♂: 2/3; ♀: 1/3). However, this morphological alteration was not observed in the low-dose group.

Based on the results of this study, the NOEL dose is 0.18 mg/kg/day for male dogs and 0.22 mg/kg/day for female dogs.

6. One-month nasal irritation study in dogs (P-5474; 2/90-9/90; Vol. 25)

Test Lab: Schering Company, Lafayette, NJ (GLP: Yes; Study #: 89085)
Animal: 3 groups of Beagle dogs (3/sex/group) with mean bodyweights of 9.4 kg in males and 7.9 kg in females.
Formulation: SCH 32088 nasal suspension; Concentration = 0.5 mg/ml (Batch # 23605-152)

Methods: 3 groups were treated for one month with SCH 32088 at the following dose levels:

Group	Daily dose (mg/day)	Dose volume (ml)	Daily dose (♂/♀: mg/kg/day)*
Vehicle	0	2	0/0
Low-dose	2	2	0.21/0.25
High-dose	4	2	0.43/0.51

* Calculated based on the mean bodyweight

Results:

Mortality (Daily): No death was noted in any group.

Clinical signs (Daily): No dose-related clinical signs were noted. Red-colored saliva was seen in all of high-dose females, but not in other groups.

Bodyweight (Weekly): No remarkable changes were observed.

Food consumption (Daily): No remarkable changes were seen.

Necropsy (Week 5): No gross lesions were reported.

Histopathology (Week 5): Focal neutrophilic inflammation was observed in the nasal cavity of the 1/3 control, 1/6 of the low-dose and 1/2 of the high-dose animals. In the lungs, chronic interstitial inflammation was seen in 1/3 of the control, 1/3 of the low-dose and all of the high-dose dogs. No other dose-related pathological alterations were observed.

Since the incidences of pathological change in the low-dose group were similar to the controls, the NOAEL dose was defined at 0.21 mg/kg/day for the males and at 0.25 mg/kg/day for the females.

7. Six-month intranasal toxicity in rats (P-6117; 9/94-2/96; Vol. 95)

Test Lab:
Animal: 6 groups of Sprague Dawley rats (25/sex/group; Mean bodyweight: ♂= 162g; ♀=153g)
Formulation: SCH 32088 nasal suspension; Concentration = 0.5 mg/ml (Batch # 33208-013)

Methods: Six rat groups were dosed intranasally for 6 mouths with SCH 32088 at 0 (non-dosed), 0 (vehicle), 0.017, 0.05, 0.15 and 0.6 mg/kg/day.

Results:

Mortality (Daily): One male in the vehicle group and one male in the 0.17 mg/kg group died on days 37 and 49, respectively. The causes of death were attributed to the dosing procedure. On Day 156, one 0.15mg/kg male died due to a metastatic yolk sac carcinoma. SCH 32088-related mortality was not found.

Clinical signs (Weekly): Dorsal alopecia was found in one 0.05 mg/kg male, one 0.15 mg/kg female, 5 males and 17 females in the 0.6 mg/kg groups. No other dose-related clinical signs were found.

Bodyweight (Weekly): Significant reductions in the bodyweight gain were found in the 0.15 mg/kg females between 21 to 25 weeks postdosing (11 to 14%). However, except in the 0.6

mg/kg group, no constant bodyweight reductions were noted in other groups. At the end of the study, both bodyweights (♂: 13%↓; ♀: 12%↓) and bodyweight gains (♂: 13%↓; ♀:26%↓) were statistically lower in the 0.6 mg/kg group when compared with the vehicle treated controls.

Food consumption (Daily) There was no significant decrease in food consumption.

Ophthalmoscopy (Before dosing and at week 26): No treatment-related effects were noted.

Hematology (Weeks 13 and 27): No treatment-related effect were noted.

Biochemistry (Weeks 13 and 27): Compared with the vehicle treated controls, serum cholesterol was statistically increased in the 0.15 (24-53%) and 0.6 mg/kg (16-31%) males, but not in the females. The values of triglyceride were slightly decreased in the 0.017 (15%), 0.15 (15%) and 0.6 mg/kg (20%) females, but not in the males. Serum corticosterone levels were highly variable, but were not changed with dose increases. No drug-related significant changes were seen in other parameters.

Urinalysis (Weeks 13 and 27): There was no treatment-related change in urine.

Pharmacokinetics (Day 1, 30 and 183) Blood samples were collected from 4 rats/sex/timepoint at 0.25, 0.5, 1, 2, 4, 8 and 24 hr on Days 1 and 30, and then collected from 5 rats/sex/timepoint at 0.25, 1 and 4 hr on Day 183. Plasma was analyzed by using HPLC-APCI-MS/MS (level of quantifiable value: LOQ = 50 ng/ml). There were no apparent gender-related differences in pharmacokinetic parameters. Except at a few sporadic time points, plasma SCH 32088 levels of 0.017 mg/kg group were generally below the LOQ of the assay. (See table below.)

Parameter	Day	Dose (mg/kg)			
		0.017	0.050	0.150	0.600
Cmax (pg/ml)	1	--[a]	59.5	127	413
	30	--[a]	115	236	645
	183	--[a]	34[c]	198[c]	460[c]
Tmax (hr)	1	--[a]	1.0	2.0	4.0
	30	--[a]	4.0	2.0	1.0
	183	--[a]	0.25	1.0	1.0
AUC(tf)[b] (pg/hr/ml)	1	--[a]	137	487	2471
	30	--[a]	322	772	2585
	183	--[a]	--[a]	--[a]	--[a]

a: Could not be determined due to insufficient data points.
b: tf was 4 hr for the 0.05 mg/kg dose group and 8 hr for the 0.15 and 0.60 mg/kg dose groups, respectively. AUC(0-24 hr) and AUC(I) could not be determined due to insufficient data points in the terminal phase.
c: Apparent Cmax based on 3 sample time-points.

Organ weights (Week 27): There were no drug-related changes.

Necropsy (Week 27): Except for alopecia, there were no other drug-related macroscopic changes.

Histopathology (Week 27): Skin hypotrichosis was observed in the 0.6 mg/kg group (♂: 6/25; ♀: 11/25). Dose-related morphological alterations were not seen in the nasal cavities. No dose-related morphological changes were reported in the liver, nasal cavity and other organs. Since only 1/25 high-dose males died due to a metastatic yolk sac carcinoma, this tumor finding may be not important.

Based on the results of this study, the NOAEL dose was 0.05 mg/kg/day for the rats. Since no major pathological alteration was found in the rats treated at 0.15 mg/kg/day, except alopecia, this dose can be considered a tolerated dose with mild glucocorticoid effects. A target organ of systemic toxicity was not identified in this study.

8. Six-month intranasal toxicity in dogs (P-6118; 10/94-4/96; Vol. 101)

Test Lab:
Animal: 6 groups of Beagle dogs (5/sex/group; Mean bodyweight: ♂=8.4kg; ♀=8.4kg)
Formulation: SCH 32088 nasal suspension; Concentration = 0.5 mg/ml (Batch # 33208-013)

Methods: Six groups were dosed intranasally for 6 months with SCH 32088 at 0 (untreated), 0 (vehicle), 0.0075, 0.015, 0.045 and 0.15 mg/kg/day.

Results:

Mortality (2 times/day): Mortality was not found in any group.

Clinical signs (2 times/day): Dose-related clinical signs were not noted.

Nasal irritation examination (Before dosing and at weeks 1, 9, 17 and 25): SCH 32088 did not cause any nasal irritation.

Bodyweight (Weekly) and *Food consumption (4 days/week)*: The mean values of bodyweight and food intake were comparable between the control and treated groups.

Ophthalmoscopy (Before dosing and at Months 3 and 6): There were no dose-related changes.

Hematology (Before dosing and at weeks 4, 13 and 26): After the treatment, eosinophil counts in the 0.15 mg/kg group were lower (at Week 26, ♂: 55%; ♀: 68%) than the vehicle-treated

controls. However, the total leukocyte and lymphocyte counts were comparable among the groups.

Biochemistry (Before dosing and at weeks 4, 13 and 26): Increased serum cholesterol levels were seen in the 0.15 mg/kg females (31 to 33%↑) at Week 13, but not at Week 26. Plasma cortisol levels in the 0.15 mg/day group were generally lower than the vehicle-treated controls. After animals were treated for 26 weeks, serum cortisol concentration in the 0.045 mg/kg group was also decreased. However, post-ACTH cortisol response value in the 0.045 mg/day group was similar to the control group. (See table below.) No drug-related significant changes were seen in other parameters.

Sex	Treatment (mg/day)	Serum Cortisol (µg/dL)					
		Week 4		Week 13 (µg/dL)		Week 26 (µg/dL)	
		Pre-ACTH	Post-ACTH	Pre-ACTH	Post-ACTH	Pre-ACTH	Post-ACTH
Males	0 (Undosed)	1.09	15.75	0.[illegible]	13.97	0.44	13.44
	0 (Vehicle)	0.92	16.02	0.86	13.12	0.37	13.1
	0.0075	3.04	14.13	1.38	12.77	0.93	13.18
	0.015	1.69	13.34	0.59	6.25	0.55	12.42
	0.045	2.01	13.9	1.44	11.64	0.7	11.41
	0.15	1.03	10.91	0.46	8.86	0.73	9.03
Females	0 (Undosed)	2.09	17.25	1.09	14.28	0.62	11.54
	0 (Vehicle)	2.68	16.85	1.98	14.91	1.6	11.97
	0.0075	2.1	15.56	1.22	17.35	1.16	11.83
	0.015	1.83	14.49	1.88	14.74	1.42	10.84
	0.045	2.82	13.46	1.2	11.69	0.57	10.75
	0.15	1.97	7.68	0.71	7.18	0.12	0.92

Heart rates, blood pressure and EKG (Before dosing and at weeks 9, 17 and 25): There were no significant dose-related effects on the heart rate, blood pressure and EKG results.

Urinalysis (Before dosing and at weeks 3, 13 and 26): There were no treatment-related changes noted in the urialysis.

Pharmacokinetics: On Days 1, 30 and 180, plasma samples were collected at 1, 2, 6 and 24 hr postdosing. By using a HPLC-APCI-MS/MS technique (LOQ = 50 ng/ml), plasma SCH 32088 level was only quantifiable in the 0.15 mg/kg group. Serum drug concentrations in the 0.0075, 0.015 and 0.045 mg/kg groups were below the LOQ of the assay. Based on the available data, gender differences in pharmacokinetic parameters were not found in the 0.15 mg/kg dogs.

Mean (%CV) Pharmacokinetic Parameters in Male and Female Beagle Dogs (Combined)				
Dose (mg/kg/day)	Exposure Day	Cmax (pg/ml)	Tmax (hr)	AUC(tf) (pg · hr/ml)
0.15	1	80.4 (85)	1.00	84 (125)
0.15	30	151 (45)	1.20	444 (112)
0.15	180	114 (60)	1.13	246 (98)
(%CV) = Coefficient of variation expressed as a percent (n = 10, 5 males and 5 females)				

Organ weights (Week 27): Adrenal weights were decreased in the SCH 32088 treated groups (17% - 27%). Liver and lung weights were only slightly reduced. (See table below.)

Percentage change from the vehicle-treated controls

Treatment (mg/kg)	Males		Females	
	Adrenal	Lungs	Adrenal	Liver
0.0075	17%↓	–*	–	–
0.015	16%↓	–	–	9 %↓
0.045	12 %↓	%	22%↓	–
0.15	27%↓	9.5%↓	23%↓	7 %↓

* – indicates that the change from the control value was either < 10 %, or none

Necropsy (Week 27): There were no dose-related macroscopic findings.

Histopathology (Week 27): Morphological findings occurred sporadically and were distributed in all groups, including the controls. No dose-related pathologic alterations were observed in any organ.

Based on the results of this study, the NOEL dose was 0.015 mg/kg/day for the dog. Since post-ACTH cortisol response in the 0.045 mg/day group was similar to the control group, it can be considered a tolerated dose with mild glucocorticoid effects. Target dose toxicity was not clearly defined by this study.

9. One-year intranasal toxicity in dogs (P-6116; 7/94-7/96; Vol. 104)

Test Lab: Schering-Plough Research Institute, Lafayette, NJ (GLP: Yes; Study #: 93196)
Animal: 6 groups of Beagle dogs (5/sex/group; mean body weight: ♂ =10 kg; ♀ =8.4 kg)
Formulation: SCH 32088 nasal suspension; Concentration = 0.5 mg/ml (Batch # 33208-013)

Methods: Beagle dogs in each group were treated daily for 12 mouths by intranasal administration of SCH 32088 at the following dose levels:

Treatment of SCH 32088 (mg/day)	Estimated dose (mg/kg/day)* ♂ / ♀
0 (untreated)	0 / 0
0 (vehicle)	0 / 0
0.1	0.0075 / 0.0089
0.2	0.015 / 0.018
0.6	0.045 / 0.054
2.0	0.15 / 0.179

* Based on the mean body weight and 75% absorption

Results:

Mortality (Daily) Mortality was not found in any group.

Clinical signs (Daily): During treatment, alopecia was mainly seen in the 2 mg/day group, but was also found incidentally in other groups. At the end of the study, occurrences of alopecia from the control to the high-dose (2 mg/day) groups were 0/5, 0/5, 1/5, 0/5, 1/5 and 3/5 in the males, and 0/5, 1/5, 0/5, 0/5, 0/5 and 3/5 in the females. No nasal irritation or other dose-related clinical signs were observed.

Bodyweight (Weekly): There were no dose-related bodyweight changes.

Food consumption (Daily): There were no significant decreases in food consumption.

Ophthalmoscopy (Before dosing and at Weeks 12, 24, 36 and 48): No treatment-related effects were noted.

Physical Examination(Before dosing and at weeks 7, 16, 23, 31, 40 and 47): SCH 32088 did not significantly affect the body temperature, respiratory rate, heart rate, blood pressure and EKG results.

Hematology (Before dosing and at Weeks 4, 14, 27 and 52): At the end of the study, total leukocyte counts in all treated males were lower than the vehicle-treated controls. Percentages of lymphocytes (Lym%) and eosinophils (Eos%) were generally decreased after the treatment of SCH 32088. (See table below.) No other dose-related effects were noted.

Percentage change from the vehicle-treated controls

Treatment (mg/day)	Males			Females		
	WBC	Lym%	Eos%	WBC	Lym%	Eos%
0.01	-*	17 %↓	22%↓	-	-	51 %↓
0.02	20 %↓	-	22%↓	-	14 %↓	36 %↓
0.06	15 %↓	12 %↓	31%↓	-	15 %↓	49 %↓
2.0	28 %↓	39 %↓	75 %↓	7 %↓	22 %↓	92 %↓

* – indicates that the change from the control value was either < 10 %↓ or none

Biochemistry (Before dosing and at Weeks 4, 14, 27 and 52): The treatment of SCH 32088 severely affected the serum cortisol levels of the 2 mg/day group. For this group, baseline cortisol was significantly decreased in Week 4, and was undetectable from Week 14 to 52. The post-ACTH cortisol response was also lower in the 2 mg/day group when compared with the vehicle-treated controls. At the end of the study, post-ACTH cortisol response values in the 2 mg/day group were below the quantifiable limits. Two 0.6 mg/day males had undetectable pre-ACTH values and normal post-ACTH cortisol responses. Adrenal cortex atrophy was noted in one of the dogs. Except for the 2 mg/day group, the mean values of plasma cortisol in the 0.1, 0.2 and 0.6 mg/day groups were comparable to control groups. (See table below.) Dose-related effects were not seen in other parameters.

Sex	Treatment (mg/day)	Serum Cortisol (µg/dL)					
		Week 4		Week 27 (µg/dL)		Week 52 (µg/dL)	
		Pre-ACTH	Post-ACTH	Pre-ACTH	Post-ACTH	Pre-ACTH	Post-ACTH
Males	0 (Untreated)	2.98	13.46	1.54	11.42	2.03	11.18
	0 (Vehicle)	1.04	12.18	1.14	10.94	0.96	9.74
	0.1	1.9	10.1	1.38	11.93	1.56	10.9
	0.2	1.44	10.4	0.98	9.74	0.93	9.96
	0.6	1.46	10.74	1.3	8.36	1.15	8.98
	2	0.75	4.3	0	2.35	0	0
Females	0 (Untreated)	2	12.5	1.08	10.66	0.86	11.38
	0 (Vehicle)	2.54	11.76	1.92	10.54	1.24	11.34
	0.1	2.44	12.24	2.46	12.16	1.7	11.76
	0.2	2.86	10.68	2	10.84	1.5	11.04
	0.6	1.9	9.88	1.76	9.82	1.46	9.08
	2	0.8	2.23	0	1.8	0	0

Urinalysis (Before dosing and at Weeks 4, 14, 27 and 52): There were no treatment-related findings in urine.

Pharmacokinetics (Days 1, 30 and 363). Plasma samples were collected at 1, 3, 6 and 24 hr postdosing. By using an HPLC-MS/MS (LOQ = 50 ng/ml) technique, SCH 32088 concentration was only quantifiable in the 2 mg/day group, but not in other groups. Gender differences were not found. When the AUC and Cmax levels obtained on Day 30 and 363 were compared, no drug accumulation was found in the 2 mg/kg group. Plasma SCH 32088 concentrations in the 2 mg/day group are presented in the following table:

Dose (mg/day)	Study Day	Mean (%CV)		
		Cmax (pg/ml)	Tmax (hr)	AUC(tf) (pg•hr/ml)
2.0	1	NC[a]	NC	NC
	30	447 (61)	4.29[b] (203)	3836 (85)
	363	278 (20)	1.4 (60)	2756 (29)

a: Not calculated; data not amenable to rigorous pharmacokinetic analysis.
b: Tmax observed at 1 hr for 6/7 animals. 7th value of 24 hr skewed mean value.

Organ weights (Week 53/54): Organ weight changes were mainly observed in the 2 mg/day group. Thyroid and thymus weights were also altered in other treated groups.

Percentage change from the vehicle-treated controls

Treatment (mg/day)	Males				Females				
	Thyroid	Thymus	Adrenal	Testes	Thyroid	Thymus	Spleen	Adrenal	Ovary
0.1	25 %.	36%↑	--#	--	--	16%↓	--	--	--
0.2	22 %.	33%↑	--	--	16%↓	--	-	-	-
0.6	16 %↓	21%↑	--	--	--	--	--	--	15%↑
2	33 %.	50%↑	42 %↓	25 %↓	17%.	39%↓	20%↑	63%↓	19%↑

– indicates that the change from the control value was either < 10 %. or none

Necropsy (Week 53/54). Small adrenal glands were observed in 4/5 males and 5/5 females of the 2 mg/kg group. Except skin alopecia, there were no other drug-related macroscopic changes.

Histopathology (Week 53/54): A few small lymphoid aggregates (1-6) were observed in the nasal turbinates of untreated control dogs. After treatment with vehicle or 0.1 mg/kg, lymphoid aggregates in the nasal turbinates were smaller or fewer than the untreated controls. Absence of lymphoid aggregates was mainly seen in the 0.6 and 2 mg/kg dogs. No nasal irritation or inflammation was seen in all dosed groups. Therefore, the changes of the lymphoid aggregates can be attributed to a local response to corticosteroids, but not a toxic effect.

Dose-related thymus atrophy was observed in all groups, however, it was mainly present in the 0.6 and 2 mg/kg groups. Lung granuloma was found in all groups, including the control group. Although the occurrences of lung granuloma were increased with the doses administered, lung granuloma was also seen in the untreated- and vehicle-treated controls. Therefore, lung granuloma was not considered a drug-related change. Adrenal cortex atrophy and epidermal atrophy were only found in the 0.6 and 2 mg/day groups. Dose-related histological alterations were not reported on other organs. (See table below.)

Pathological Alterations	SCH 32088 Treatment (mg/day) to Males						SCH 32088 Treatment (mg/day) to Females					
	0	V*	0.1	0.2	0.6	2	0	V*	0.1	0.2	0.6	2
Absence of lymphoid aggregates #	0/5	0/5	0/5	1/5	3/5	5/5	0/5	1/5	0/5	0/5	2/5	4/5
Thymus atrophy	0/5	1/5	2/5	2/5	1/5	4/5	2/5	1/5	3/5	2/5	4/5	4/5
Lung granuloma	0/5	1/5	1/5	1/5	3/5	3/5	1/5	1/5	0/5	0/5	1/5	2/5
Adrenal cortex atrophy	0/5	0/5	0/5	0/5	1/5	5/5	0/5	0/5	0/5	0/5	0/5	5/5
Epidermal atrophy	0/5	0/5	0/5	0/5	0/5	3/5	0/5	0/5	0/5	0/5	0/5	3/5

* Vehicle treated-group # At the level 4 location (3rd premolar tooth)

In summary, intranasal administration of SCH 32088 did not produce nasal irritation in beagle dogs. The changes in the nasal lymphoid aggregates were considered an effect of corticosteroids. Systemic effects were seen mainly in the adrenal gland, thyroid, thymus and skin. These changes can be attributed to a longtime corticosteroid administration. The NOAEL dose is 0.1 mg/day. Intranasal administration at 0.2 mg/day can be considered a tolerated dose with mild glucocorticoid effects. Since plasma drug concentration was only measurable in the 2 mg/day group, systemic exposure of the SCH 32088 was not clearly determined in the animals treated at 0.1 or 0.2 mg/day. Although adrenal cortex atrophy and undetectable pre-ACTH values were found in one 0.6 mg/day male, average cortisol levels were comparable between the 0.6 mg/day and control groups. Based on the pathological findings, target organs of systemic toxicity were thymus, skin and adrenal gland.

Subchronic Toxicity Studies in Adult Animals:

10. A 26-week oral inhalation toxicity study in dogs (P-5991; 10/88-6/91; Vol. 100)

Test Lab:
Animal: 4 groups of Beagle dogs (4/sex/group)
Formulation: SCH 32088 inhaler (Batch # 22023-074)

Study Design: Four groups were treated for 26 weeks by oral inhalation at the following doses:

Group	Target dose (µg/kg/day)	Achieved dose (µg/kg/day)*
Control	0 (Vehicle)	0
Low-dose	20	21
Mid-dose	40	37
High-dose	80	74

* Calculation was based on total deposition

Results:

Mortality (2 times/day): Mortality was not found in any group.

Clinical signs (2 times/day): Vomiting, loose feces, ocular discharge and estrous were seen in many groups. However, these clinical signs were not dose-related. Redness of skin and a pinna mass were also observed incidentally.

Bodyweight (Weekly): Body weights of most test groups were similar to the controls. At the end of the study, the mean bodyweight of high-dose females was slightly, but not statistically lower than the controls (14%.);

Food consumption (Weekly): Food consumption in the high-dose males was statistically decreased (16% - 22%.; $p<0.05$) at Weeks 16, 23, 24 and 26. Food consumption was not significantly changed in other test groups.

Ophthalmoscopy (During the treatment period and 13th and 26th treatment week): No treatment-related effects were noted.

EKG and blood pressure (Before and at Weeks 13 and 26): No treatment-related effects were noted.

Hematology (Before and at Weeks 13 and 26): In this study, total leukocyte counts were comparable among the groups. However, leukocyte differential counts were not performed in this study. Therefore, the suppression of lymphocytes or other leukocytes could not be evaluated. No other dose-related changes were found during treatment.

Biochemistry (Before and at Weeks 13 and 26): During Week 13, serum sodium and potassium levels, particularly in the males, were increased from the control values. At the end of the study, blood concentrations of sodium and potassium were not much higher than the controls. Serum

GTP levels were generally increased in the males and decreased in the females. However, the changes of GTP did not reach statistically significant levels. Therefore, the changes in the serum sodium, potassium and GTP levels may not be biologically significant.

Circulating cortisol levels were variable among the animals. However, the mean concentrations of blood cortisol in the high-dose group were much lower than the controls. This finding appeared to be a SCH 32088-related change. (See table below.) Drug-related changes were not seen in other parameters.

Percentage change from the control values

Sex	Group	Week 13				Week 26 (Terminal)			
		Na	K	Cortisol	GPT	Na	K	Cortisol	GPT
Males	Low-dose	1.0%↑*	13%↑*	17%↓	1.5%↑	0.7%↑	9.3%↑	12%↓	0%↑
	Mid-dose	1.1%↑*	15%↑*	42%↓	16%↑	1.1%↑	7.1%↑	0%↓	15%↑
	High-dose	1.0%↑*	15%↑*	83%↓*	11%↑	1.0%↑	13%↑	82%↓	21%↑
Females	Low-dose	0.2%↑	10%↑	33%↓	13%↓	0.7%↑	6.8%↑	54%↓	5%↑
	Mid-dose	2.6%↑*	6%↑	4.8%↑	16%↓	0.8%↑	6.8%↑	60%↓	27%↓
	High-dose	2.2%↑	8%↑	76%↓	23%↓	2.3%↑*	13%↑	77%↓	28%↓

* Statistically different from the control values ($p < 0.05$)

Urinalysis (Before a. 1 at Weeks 13 and 26): There were no treatment-related changes in urinalysis.

Organ weights (Week 27): Adrenal weights in the high-dose males were statistically reduced (48%.) from the control values. However, significant adrenal weight reduction was not observed in the drug-treated females. Drug-related changes were not noted in other organs.

Necropsy (Week 27): There were no drug-related macroscopic changes.

Histopathology (Week 27): Cortical atrophy of the adrenals was observed in 2/4 males of the mid-dose group, and 3/4 males and 4/4 females of high-dose groups. No other dose-related changes were seen.

Based on the results of this study, the inhalation dose of 21 µg/kg/day is a tolerated dose with mild glucocorticoid effects. Target organ toxicity was noted in the adrenal glands in this study.

11. A 26-week nose-only inhalation study in rats (P-5598; 10/88-3/91; Vol. 93)

Test Lab

Animal: 4 groups of Sprague Dawley rats (20/sex/group; Mean bodyweights: ♂ = 325g, ♀ = 222g)

Formulation: SCH 32088 oral inhaler (Batch # 22023-074; MDI)

In this study, rats were exposed to SCH 32088 for 26 weeks by nose-only inhalation at the following doses.

Group	Target dose (µg/kg/day)	Achieved dose (µg/kg/day) for ♂/♀*
Control	0 (Vehicle)	0/0
Low-dose	40	50/55
Mid-dose	80	93/102
High-dose	160	214/234

* Calculation based on oral deposition

Mortality and Clinical signs (2 times/day): After the treatment, the animals had dose-related alopecia (5%, 74%, 89% and 93% of male rats in the control to high-dose group; 10%, 76%, 78% and 100% of female rats in the control to high-dose group) and scabbing of muzzle, neck and other skin regions (5%, 37%, 67% and 60% of male rats in the control to high-dose group; 5%, 65%, 56% and 53% of female rats in the control to high-dose group). Between Weeks 12 and 26, 16 animals were sacrificed due to progressive respiratory abnormalities (wheezing, gasping and labored breathing) and the number of animals increased with dose level (1, 4 and 11 rats in the low-, mid- and high-dose group, respectively). Histopathological results characterized the findings as focal acute necrotizing tracheitis caused by a fungal infection.

Labored breathing was also observed in 1 control male. This rat was sacrificed in Week 14. Histopathological examination showed glomerulonephritis and liver necrosis, but no remarkable findings were seen in the lung tissues.

Additionally, 1 low-dose male and 1 high-dose female rats were found dead during the study. These animals were also necropsied. Reduced sizes of thymus, spleen and lymph nodes were observed in these rats.

Bodyweight (Weekly): In comparison with the controls, dose-related statistically significant body weight decreases were present in all treated groups throughout the study. (See table below.)

Sex	Time	Treatment		
		Low-dose	Mid-dose	High dose
Males	Week 1	7 %↓*	9 %↓*	11 %↓*
	Week 26	28 %↓*	34 %↓*	46 %↓*
Females	Week 1	5 %↓*	10 %↓*	9 %↓*
	Week 26	15 %↓*	27 %↓*	36 %↓*

*P< 0.01

Food consumption (Weekly): Reduced food consumption was also seen in all dosed groups. (See table below.)

Sex	Time	Treatment		
		Low-dose	Mid-dose	High-dose
Males	Week 1	11 %↓*	10 %↓*	17 %↓*
	Week 25	12 %↓*	14 %↓*	22 %↓*
Females	Week 1	34 %↓	38 %↓*	40 %↓*
	Week 25	28 %↓	34 %↓	32 %↓

*P< 0.01

Ophthalmoscopy (Before the treatment and at Week 25): No treatment-related effects were noted.

Hematology (Before and at Week 14 and 26): Hematological examination revealed dose-related increases in neutrophils and decreases in lymphocytes and total leukocyte counts at Weeks 14 and 26.

Biochemistry (Before and at Week 14 and 26): Blood biochemical analysis revealed treatment-related changes primarily in the males at all dose levels and included increases in total protein and/or albumin, increases in cholesterol (also seen in females); and decreases in LDH, (also see in high dose females), alkaline phosphatase, GOT, phosphate and corticosterone levels at Week 14 and/or 26.

Urinalysis (Before and at Weeks 13 and 26): There were no obvious treatment-related changes in urinalysis, although potassium levels were decreased in the high dose females at Week 26.

Necropsy and Organ weights (Week 27): Small organs were observed in all treated groups. In comparison with the control values, the mean weights of these organs were decreased.

particularly in the spleen, thymus, uterus and adrenal glands. (See table below.) This changes were also seen in the relative organ weights.

Sex	Dose group	Percentage decreases in organ weight (%)								
		Liver	Spleen	Heart	Lungs	Thyroid	Adrenal	kidney	Prostate/Uterus	Thymus
Male	Low-dose	13%↓	28%↓	15%↓	20%↓	12%↓	16%↓	8.4%↓	8.1%↓	46%↓
	Mid-dose	11%↓	39%↓	15%↓	23%↓	8%↓	20%↓	7.8%↓	6.7%↓	56%↓
	High-dose	17%↓	45%↓	21%↓	22%↓	16%↓	50%↓	14%↓	18%↓	62%↓
Females	Low-dose	–*	10%↓	1.5%↓	14%↓	22%↓	17%↓	–*	25%↓	47%↓
	Mid-dose	–*	18%↓	6.4%↓	15%↓	17%↓	22%↓	1.7%↓	36%↓	65%↓
	High-dose	–*	32%↓	11%↓	14%↓	11%↓	37%↓	2.4%↓	46%↓	71%↓

* indicating that organ weights were slightly increased or not changed

Histopathology (Week 27): Generally, adrenal, spleen, thymus and lymph nodes were atrophied at all dose levels. A secondary lesion in several animals of all treated groups consisted of focal acute necrotizing tracheitis caused by a fungal infection (2/40, 4/40 and 10/40 in the low- to high-dose groups). This infection was considered to be a reflection of SCH 32088-induced immunosuppression. (See table below.)

	Treatment (µg/kg) for males				Treatment (µg/kg) for females			
	0	50	93	214	0	55	102	234
Adrenal Atrophy	0/20	0/20	0/20	7/20	0/20	0/20	0/20	3/20
Spleen Atrophy	1/20	2/20	7/20	18/20	1/20	1/20	3/20	13/20
Thymus Atrophy	3/20	16/20	19/19	17/18	7/20	14/18	16/16	17/17

Finally, testes, prostate gland, epididymides and mammary gland in the control and high-dose males; and ovaries, uterus, vagina and mammary gland of all females were re-examined by a reproductive endocrinologist. He reported that SCH 32088 caused a subtle perturbation of the estrous cycle and enhanced mammary gland lobuloalveolar development in all dose groups.

Based on the above results, a tolerated dose with mild glucocorticoid effects was not established in this study. Major target organ toxicity were seen in the liver, spleen, lungs, thymus, heart, kidney, thyroid, adrenal and mammary glands.

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The following toxicity studies were reviewed previously These studies are re-evaluated and summarized for this submission

12. Three-month inhalation study in beagle dogs (D-22796, 1988, Vol. 60)

This study was conducted by . In the study, beagle dogs (4/sex/group) were treated inhalationally for 13 weeks with SCH 32088 (Batch #: 21108-059, oral inhaler) at 0 (placebo), 44 (low-dose), 79 (mid-dose) and 158 (high-dose) µg/kg/day. Plasma SCH 32088 concentration was not measured in this study.

After treatment, 1 low-dose female died due to bronchopneumonia, it was considered to be unrelated to the treatment. SCH 32088 did not induce dose-related clinical signs, ophthalmic alterations or EKG changes. Drug related reductions in body weight and food consumption were not significant. In Weeks 4 and 13, significant reductions in the leukocyte counts were found in the mid- and high dose females, but not in the males.

Decreased levels of BUN were noted at mid- and high-dose males. At the end of this study, cortisol levels in all treated groups were lower than controls, particularly in the mid- and high-dose groups.

Adrenal and thymus weights were reduced after treatment. Liver weights were increased in a dose related manner. The histopathology evaluation showed that liver glycogen accumulation was found in all high-dose dogs and about 50% mid-dose and low-dose dogs. Dose related changes in the zona glomerulose of adrenal glands was also observed.

Based on the results of this study, a no effect dose was not established. Target organs of systemic toxicity were liver, thymus and adrenal glands.

13. Three-month inhalation study in rats (D-22797, 10/88; Vol. 57)

This study was conducted by In the study, rats (15/sex/group) were treated inhalationally with SCH 32088 (Batch #: 21108-052 & 21108-058; oral inhaler) at 0 (placebo), 30 (low-dose), 160 (mid-dose) and 320 (high-dose) µg/kg/day for 13 weeks. Estimated achieved doses for the rat groups were 0, 48, 102 and 273 µg/kg/day, respectively. Pharmacokinetic parameters were not evaluated.

After the treatment, no mortality was noted. Alopecia was observed in all treated groups in a dose-dependent manner. Dose-related reductions in body weights and food consumption were observed that were significant in the mid- and high-dose groups. Leukocyte and lymphocyte counts were significantly decreased in the mid- and high-dose groups. Increases in plasma cholesterol, glucose and reduction in cortisol were observed in the mid-dose and high-dose groups, but not in

the low-dose group.

Reduced spleen, adrenal and thymus weights were associated with morphological alterations in the mid- and high-dose groups.

In conclusion, inhalation dose at 80 µg/kg targeted dose (48 µg/kg achieved dose) was considered as the NOAEL in rats. Target organs of systemic toxicity were defined as the thymus, spleen and adrenal gland.

14. Three-month nose-only inhalation study in rats. (P-5736, 2/94; Vol. 54)

This study was conducted by
In this study, SD rats were treated with SCH 32088 (Batch #: 26951-133; MDI) by nose-only inhalation at 0 (vehicle), 0.25, 0.5, 1, 2 and 4 µg/L. The target doses were 8, 17, 34, 67 and 134 µg/kg/day for the males, and were 8, 18, 37, 73 and 146 µg/kg/day for the females.

There was no death in any group. Dose-related clinical signs were not observed. When compared with the vehicle group, terminal body weights were statistically lower in the 1, 2, and 4 µg/L males (13%↓, 19%↓ and 31%↓, respectively), and the 2 and 4 µg/L females (12%↓ and 22%↓, respectively). Body weights in the 0.25 and 0.5 µg/L were slightly, but not significantly decreased from the controls. Lung weight was significantly reduced in the 4 µg/L group. Significant reductions in spleen weights were found in the 2 and 4 µg/L groups. Histologically, there were treatment-related decreases in tracheal globule cells. Reduced uterine granulocytic leukocytes was present in a dose-related fashion, but was also observed in the control group. No dose-related pathological changes were reported in the liver, spleen and lungs.

Pathological Alterations	SCH 32088 Treatment (µg/L) to the Males						SCH 32088 Treatment (µg/L) to the Females					
	0	25	0.5	1	2	4	0	25	0.5	1	2	4
Decreased tracheal globule cells	0/10	10/10	10/10	10/10	10/10	10/10	0/10	10/10	10/10	10/10	10/10	[illegible]
Decreased uterine granulocytic leukocytes	--	--	--	--	--	--	1/10	2/10	2/10	3/10	6/10	[illegible]

Systemic toxicity was not obviously found in the 1 µg/L rats (or ♂: 34 µg/kg; ♀: 37 µg/kg). Decreased tracheal globule cells was found in all treated animals, but not in any of the controls which suggests that SCH 32088 may cause degranulation of tracheal globule cells (Breeze RG and Wheeldon EB (1977) Am Rev Respir Dis. 116: 705). Therefore, a NOEL dose was not established in this study.

15. Two-week inhalation study in beagle dogs (D-22607, 5/88; Vol. 59)

This study was conducted by In this study, dogs (3/sex/group) were exposed to SCH 32088 aerosols for 2 weeks at 0, 80 (low-dose), 240 (mid-dose) and 800 (high-dose) µg/kg/day. The achieved doses were 0, 80, 240 and 810 µg/kg/day, respectively.

During exposure, no mortality or dose-related clinical signs were observed. Treatment did not affect body weight change, food consumption, hematological parameters and blood chemistry. Plasma cortisol levels were not measured in this study. Liver weight was increased in the high-dose group. Adrenal weights were reduced in the mid- and high-dose groups, but not in the low-dose group. Histopathological changes in liver, adrenal cortex, lymph nodes, mammary gland and thymus were mainly observed in the mid- and high-dose group. Adrenal gland atrophy was also seen in the 80 µg/kg group (♂: 1/3; ♀: 1/3).

Since no other obvious abnormalities were seen in the low-dose group, except adrenal atrophy, the inhalation dose of 80 µg/kg/day was considered a tolerated dose with mild glucocorticoid effects in dogs.

16. Two-week inhalation study in rats (D-22680, 5/88; Vol. 52)

This study was conducted by Rats (10/sex/group) were treated inhalationally with SCH 32088 (Batch #: 20431-040 & 20211-151; oral inhaler) at 0, 80 (low-dose), 240 (mid-dose) and 800 (high-dose) µg/kg/day. Achieved doses were 0, 68, 239 and 676 µg/kg/day for males and 0, 76, 268 and 710 µg/kg/day for the females.

For the mid- and high-dose groups, there were reductions in body weight, food consumption, WBC and lymphocyte count and GPT, GOT and alkaline phosphatase levels. Increased RBC counts and hemoglobin concentrations were found in all dosed groups.

Decreased weights of spleen, thymus, adrenal glands were found in the mid- and high-dose groups. Adrenal and thymus atrophy were mainly seen in the mid- and high-dose group. Adrenal gland atrophy was also found in the 80 µg/kg group (♂: 0/10; ♀: 1/10).

In conclusion, inhalation dose at 80 µg/kg for 2 weeks is considered as a tolerated dose with mild glucocorticoid effects in rats, although changes of adrenal cortical atrophy were seen.

17. Other Inhalation Studies

In addition to the above inhalation studies, SCH 32088 was also administered inhalationally to rats, dogs and mice at various dose levels and in different formulations. As listed in the following

table, major target organs of toxicity in these studies were generally defined in the adrenal, thymus, lymph tissue, liver, spleen, skin, bone marrow and mammary gland regardless of the species. No effect doses were not clearly determined in the listed inhalation studies. It is presumably due to relatively higher serum drug concentrations, although valid pharmacokinetic data were not provided in these studies. In comparison to the toxicology studies reviewed in this submission, the target organs of toxicity were generally similar in all studies.

Study	Report No. (#/sex/group; Batch #)	SCH32088 Daily Dose (µg/kg)	Target Organs of Toxicity
Rat: 2-wk nose-only inhalation (powder)	P-5834 (16; 92-MMF-DDPX-01)	♂: 12, 27, 48 ♀: 19, 38, 89	adrenal, thymus, lung, spleen, trachea, bone marrow, reproductive tracts (♀)
Rat: 2-wk nose-only inhalation (dry powder/ lactose)	P-6121 (16; 25887-023)	♂: 6.9, 23.4, 67.9; ♀: 4.5, 16.1, 57.5	thymus, lymph organ, trachea, bone marrow, mammary gland (♀)
Rat: 3-mon nose-only inhalation (powder)	P-5836 (25; 92-MMF-DDPX-01)	♂:3.4, 13, 56 ♀:4.5, 17, 70	adrenal, thymus, liver, lymph organ, lung, kidney, trachea, mammary gland
Dog: 2-wk nose-only inhalation (powder)	P-5835 (3; 92-MMF-DDPX-01)	♂:95, 141, 636 ♀:39, 144, 557	adrenal, thymus, liver, lymph node, lung, spleen, trachea, bone marrow
Dog: 2-wk oral inhalation (MDI)	D-22607 (3; 0431-040)	80, 240, 800	adrenal, lymph nodes, liver, thymus, mammary gland
Dog: 4-wk oral inhalation (DI)	D-24448 (4, 20432-040)	80	adrenal, thymus, spleen
Dog: 3-mon nose-only inhalation (powder)	P-5837 5(92-MMF-DDPX-01)	♂:35, 93, 192; ♀:57, 161, 250	adrenal, lymph organ, liver trachea, bone marrow, reproductive systems (♂ & ♀)
Mouse: 1-mon nose-only inhalation (MDI)	P-5739 (10; 26951-110)	♂: 102, 407 ♀: 80, 320	thymus, spleen, bodyweight gain↓ (LD: 50%; HD 100%)
Mouse: 3-mon nose-only inhalation (MDI)	P-5737 (10; 26951-133)	♂:27,82,159,313.648 ♀:26.64.152.235.601	Liver, lymph organ, adrenal, skin

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18. Subchronic Oral Toxicity Studies

Oral doses of SCH 32088 were also given to rats, dogs and mice. After oral administration, major target organs of toxicity in the animals were the adrenal, thymus, lymph tissue, liver, spleen, skin, bone marrow and mammary gland. Based on the results of the 3-month studies, the NOAEL doses in rat, dog and mouse were 1.25, 10 and 50 µg/kg, respectively.

Oral Toxicity Study	Report No. (#/sex/group; Batch #)	Daily dose (µg/kg)	Observation
Rat: 2-week study	P-5424 (10; 8-MMF-X-6003)	200, 600, 2000	NOAEL = 200 µg/kg Target organ: adrenal, thymus, lymph tissues
Rat: 3-month study	P-5946 (15 or 25; 92-MMF-DDPX-01)	1.25, 50, 150, 450, 600	NOAEL = 1.25 Target organ: adrenal, lymph tissue, stomach, cecum, mammary gland (♀), thymus, spleen, reproductive tract (♀)
Rat: 3-month study	P-6138 (15 or 25; (92-MMF-DDPX-01)	50, 150, 450, 600	NOAEL = 50 µg/kg Target organ: lymph tissue, spleen, adrenal, mammary gland (♀), reproductive tract (♀)
Dog: 2-week study	P-5416 (3; 8-MMF-X-6003)	200, 600, 2000	NOAEL was not established. Target organ: adrenal, lymph tissue, liver, thymus
Dog: 3-month study	P-5917 (6; 92-MMF-DDPX-01)	50, 150, 600	NOAEL was not established. Target organ: adrenal, lymph tissue, liver, skin, skeletal muscle
Dog: 3-month study	P-6007 (6; 92-MMF-DDPX-01)	10, 150, 600	NOAEL = 10 µg/kg Target organ: adrenal, lymph tissue, liver, skin
Mouse: 3-month study	P-5947 (15 or 25; 92-MMF-DDPX-01)	2.5, 50, 150, 450, 600	NOAEL =50 ug/kg Target organ: adrenal, thymus, spleen, lymph tissues
Mouse: 3-month study	P-6139 (15 or 17; 92-MMF-DDPX-01)	50, 150, 450, 600	NOAEL = 150 µg/kg Target organ: adrenal, thymus, spleen

Subchronic Toxicity Studies in Pediatric Animals:

19. One-month nose-only inhalation study in pediatric rats (P-5980; 1/94-2/95; Vol. 82)

Test Lab:
Animal: 2 weeks old Sprague-Dawley rats
Formulation: Micronized SCH 32088 powder (Batch # 92-MMF-DDPX-01)

Study Design: The rats were exposed to micronized SCH 32088 powder by nose-only inhalation

at 0 (filtered air), 0.01, 0.05, 0.25 or 1 µg/L for 1 month. The study design consisted of a main study group, a single-dose pharmacokinetic study group and a 1-month pharmacokinetic study group. (See table below.) Toxic effects of SCH 32088 were observed in the main study group.

Group Name	SCH 32088 concentration (µg/L)	Estimated dose (µg/kg/day)* ♂/♀	Rats (No./sex/group)			
			Main Study	Single-dose PK study	1-month PK study	Total
Control	0 (air)	0 / 0	24	12	8	44
Group 1	0.01	0.2 / 0.2	24	48	24	96
Group 2	0.05	1.1 / 1.1	24	48	24	96
Group 3	0.25	4.9 / 4.5	24	48	24	96
Group 4	1	17.7 / 21.7	24	48	24	96

* During Week 5

Results:

Mortality (2 times/day): In the main study, no treatment-related deaths were observed. One control male and 1 control female died accidentally. Two males were mis-sexed and were excluded from this study.

Clinical signs (Weekly): No drug-related clinical signs were reported.

Bodyweight (Weekly): After a 1-month treatment, statistically reduced body weight gain was only seen in the 1 µg/L group. (See table below.)

SCH 32088 concentration (µg/L)	Percentage difference in mean bodyweights (MBW)@ ♂ / ♀	Percentage difference in mean bodyweight gains (MBWG)* ♂ / ♀
0 (air)	-/-	-/-
0.01	8.5% / 3%	6.1% / -0.3%
0.05	7.1% / 5.8%	-0.6% / -3.3%
0.25	5.6 % / 5.6%	-1.8 % / -3.8%
1	-[illegible] / -1.8%	-14.8 % * / -19.2 %*

* $p < 0.01$. @Percentage difference in MBW = (MBW of test groups - MBW of control group) x 100 / MBW of control group

*Percentage difference in MBWG = (MBWG of test groups - MBWG of control group) x 100 / MBWG of control group

Food consumption: This parameter was not reported.

Ophthalmoscopy (During Week 4): No treatment-related effects were noted.

Pulmonary Functions (During Week 4): There were no dose-related changes in the respiration rate and minute volume.

Hematology (Prior to necropsy): In the 1 µg/L group, compared with the control values, statistically significant changes were observed in erythrocytes (♂: 15%↑; ♀: 9.6%↑), hemoglobin (♂: 11%↑; ♀: 7%↑), and the counts of leukocytes (♀: 24%↓), lymphocytes (♀: 33%↓) and monocytes (♀: 58%↓). However, dose-related hematological changes were not seen in other treated groups.

Biochemistry (Prior to necropsy): The serum potassium (14%↑), albumin (6%↑), globulin (14%↑) and total protein levels (9.3%↑) in the 1 µg/L males were statistically greater than the control males. However, these changes were not significantly present in other treated groups. In comparison with the controls, serum corticosterone levels were statistically higher in the treated males, but not in the treated females. (See table below.)

One-Month Nose-Only Inhalation Study of SCH 32088 Powder in Pediatric Rats– Serum Corticosterone at Terminal Sacrifice (Mean ± SD; N=12)

SCH 32088 Target Exposure Concentration (µg/L)	Serum Corticosterone (ng/mL)	
	Males	Females
0[a]	112 ± 102[b]	220 ± 225
0.01[a]	269 ± 136[†]	105 ± 77
0.05	203 ± 166	106 ± 120[b]
0.25	236 ± 121*	324 ± 244
1.0	440 ± 101*	240 ± 248

[a]Filtered Air Control
[b]N = 11
[†]p≤0.05
*p≤0.01

Urinalysis (During Week 4): There were no treatment-related changes in urinalysis.

Pharmacokinetics (During Weeks 1 and 5): Plasma samples were initially analyzed by the sponsor using EIA technique by Schering Co. The samples collected in Weeks 1 and 5 were then pooled together and reanalyzed using HPLC. Proportions of the plasma collected from 2 sampling days were not defined. Based on the report from DSI, PK data from this study were invalid.

Organ weights (At the end of the study): Liver weights were statistically increased in drug-treated males and females. In comparison with the controls, testis or epididymides weights in the males and adrenal weights in the females were much higher. Lung and thymus weights were statistically lower in the high-dose group when compared with the control values. (See table below.) Since these organ weight changes were generally not dose-dependent and since pathological alterations were not found in these organs, the organ weight changes may be minimal corticosteroid effects.

Percentage change in the organ weights from the controls

Treatment (µg/L)	Males					Females			
	Liver	Lung	Testes	Epididymides	Thymus	Liver	Lung	Adrenal	Thymus
0.01	13 %↑*	–#	–	9 %↑	–	9 %↑*	–	13 %↑	–
0.05	14 %↑	–	20 %↑*	20 %↑*	–	11%↑*	–	23 %↑*	–
0.25	12 %↑*	–	20 %↑*	19 %↑*	–	11%↑*	–	9.7 %↑	–
1	11 %↑*	9 %↓*	26 %↑*	15 %↑*	32 %↓*	6.4 %↑	10 %↓*	19 %↑*	30.1 %↓*

* Statistically significant ($p<0.05$)

\# -- indicates that the change from the control value was either < 10 %, or none

Necropsy (At the end of the study): Dose-related gross lesions were not found.

Histopathology (At the end of the study): Major target organs affected by SCH 32088 were the trachea, nasal cavity, bone marrow and mammary gland. Dose-related decreases in the tracheal globule cells and the appearance of nasal goblet cell hyperplasia were observed in the treated rats. Bone marrow adipose cells appeared in all groups in a dose-related fashion. Enhanced mammary gland secretion and lobuloalveolar development were found in all test group, but not in the control females. (See table below.)

Pulmonary alveolar histiocytic infiltration was found in all SCH 32088-treated males, but not in the control males. For the females, histological features of reproductive organs were within normal limits. No dose-related abnormalities were observed in the liver, thymus, testes,

epididymides and adrenal gland.

Pathological Alterations	SCH 32088 Treatment (µg/L) to the Males					SCH 32088 Treatment (µg/L) to the Females				
	0	0.01	0.05	0.25	1	0	0.01	0.05	0.25	1
Decreased tracheal globule cells	0/23	0/24	0/24	9/24	24/24	1/24	0/23	3/23	24/24	24/24
Nasal goblet cell hyperplasia	0/24	0/24	0/24	1/24	8/24	0/24	0/23	0/23	1/24	8/24
Increased bone marrow adipose cells	6/23	7/24	9/24	11/24	21/24	6/24	9/23	14/23	9/24	23/24
Mammary gland lobuloalveolar development	13/22	10/24	12/22	14/20	19/24	0/24	1/23	2/23	5/24	19/24
Mammary gland secretory activity	11/22	7/24	10/22	12/20	19/24	0/24	1/23	4/23	6/24	20/24
Lung: alveolar histiocytic infiltration	0/23	1/24	1/24	1/24	5/24	0/24	0/23	0/23	0/24	0/24

Based on the results of this study, an inhalation dose of 0.2 µg/kg/day (0.01 µg/L) can be considered a tolerated dose with mild glucocorticoid effects for male rats. However, the NOEL dose for progestational-like activity was not established in the female rats because of the appearance of enhanced mammary gland development in one 0.2 µg/kg female (0.01 µg/L). In this study, the major target organs of toxicity were defined as the trachea, nasal cavity, bone marrow, mammary glands and lungs based on the pathological alterations.

20. A 7-week oral inhalation study in pediatric dogs (P-5981; 12/93-12/94; Vol. 91)

Test Dog:
Animal: 4 groups of 6 weeks old Beagle dogs (5 or 10 /sex/group)
Formulation: Micronized SCH 32088 powder (Batch # 92-MMF-DDPX-01)

Study Design: This study was initially designed as a 3-month inhalation study. Aerosol exposure in this study was performed using a modified mask, which provided mouth-only inhalation and prevented nasal breathing. Four dog groups were exposed to either filtered air (control) or aerosolized SCH 32088 dry powder for 1 hour per day. After 7 weeks of inhalation, 5 dogs/sex/group were sacrificed because the dogs were struggling with their exposure masks and the study was not continued. Five dogs/sex/group in the control and high-dose groups remained on study for an additional 9-week recovery period and then sacrificed. The study design is presented in the following table:

Group	Dogs (No./sex/group)		Aerosol concentration (µg/L)	Estimated dose levels (µg/kg/day)* ♂/♀
	7-week treatment	9-week recovery		
Control	5	5	0 (air)	0
Low-dose	5	0	0.04	1.1
Mid-dose	5	0	0.2	7.3/7.1
High-dose	5	5	1	29.6/24.5

* During Week 5

Results:

Mortality (2 times/day): One mid-dose male died on Day 35 with obvious abdominal distension. One control male suffered from pulmonary hemorrhage and was sacrificed humanely on Day 47. Both dogs were necropsied.

Clinical signs (Weekly): In this experiment, certain animals in all groups struggled with the exposure masks. During inhalation exposure, 23 dogs experienced syncope or a syncope-like syndrome; some dogs exhibited grey pallor of the tongue and mucus membranes indicative of anoxia; some dogs had distended abdomens and tympany. However, these findings appeared in all groups and were neither dose-related nor duration-related. These abnormalities were attributed to the effects of the exposure masks, and not to SCH 32088. The most frequent clinical signs reported were listless and thin animals. However, the signs did not increase with dose and were also present in the controls. No other dose-related clinical signs were reported.

Bodyweight (Weekly): At the end of Week 7, there were dose-related decreases in the mean body weight gains of the treated groups, particularly in the high-dose females. After the recovery period, the mean body weight gain in the high-dose g oup was greater than the controls. (See

Time	Group	Percentage difference in mean bodyweight gains (MBWG)* ♂ / ♀
Week 7	Control	-/-
	Low-dose	10.9% / 0%
	Mid-dose	-2.7% / -1.2%
	High-dose	- 3.9 % / -21%
Week 16	Control	-/-
	High-dose	6.2 % / 23.7

*

Food consumption (Daily): There were no drug-related changes in the food consumption.

Ophthalmoscopy (Before and during the treatment): No treatment-related effects were noted.

EKG, heart rate and blood pressure (Before and at Weeks 1, 4, 7 and 9): No treatment-related effects were noted.

Pulmonary Functions (During Weeks 5): There were no treatment-related changes in the respiration rate, tidal and minute volumes

Hematology (At Weeks 5 and 7, and after Week 9): At Week 7, compared with the control values, mean values of erythrocytes (12%↑) and hemoglobin (13%↑) were slightly increased in the high-dose females; total leukocytes numbers (12%↓) were slightly decreased in the high-dose males. There were no lymphocyte depressions or other dose-related changes. After the recovery period, hematology parameters in the high-dose group were similar to controls.

Biochemistry (At Weeks 5 and 7, and after Week 9): At Week 7, the serum concentrations of potassium (♀:15%), GGT(♀:9.7%), ALT (♀:26%) and ALP (♂:16%; ♀:31%) were obviously increased in the high-dose animals, but not in other treated groups. After the recovery period, these parameters in the high-dose group were similar to the control values.

ACTH response (During Weeks 5 and Week 17): During either Weeks 5 or Week 17, baseline serum cortisol levels in the high-dose group were generally lower than the air-treated group. However, these dogs had normal post-ACTH cortisol values. (See table below.)

SCH 32088 Target Exposure (µg/L)	Serum Cortisol				
	Exposure Week 5 (µg/dL)		Exposure Week 7 (µg/dL)	Study Week 17 (µg/dL)	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0[a,b]	1.82 ± 1.05	13.24 ± 2.83	1.76 ± 0.85[c]	8.41 ± 4.01[d]	18.13 ± 2.05[c]
0.04[d]	1.47 ± 0.30	13.48 ± 1.72	1.94 ± 1.26		
0.2[d]	2.82 ± 1.82	12.72 ± 2.89	1.85 ± 1.09[c]		
1.0[d]	0.89 ± 0.67	10.82 ± 2.11	0.78 ± 0.85	5.80 ± 4.80[d]	17.06 ± 1.85[c]
Females					
0[a,b]	1.14 ± 1.07	14.18 ± 1.44	2.82 ± 2.89	8.86 ± 4.06[d]	17.63 ± 2.79[d]
0.04[d]	2.03 ± 1.36	13.82 ± 2.56	2.45 ± 0.86		
0.2[d]	2.56 ± 0.84	13.71 ± 0.76	2.03 ± 0.84		
1.0[d]	1.71 ± 1.23	11.42 ± 2.65	0.94 ± 0.80	6.12 ± 5.68[d]	18.81 ± 3.98[d]

[a] N = 10
[b] Filtered air control
[c] N = 9
[d] N = 4

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Urinalysis (At Weeks 5 and 7, and after Week 9): There were no treatment-related changes in the urinalysis.

Pharmacokinetics (During Weeks 1 and 5): Plasma samples were collected at 0, 0.25, 1, 3 and 6 hr postdosing on Day 6, and at 0, 0.25, 1, 3, 6, 12 and 22 hr postdosing on Day 35. The samples were analyzed by using a LC-API-MS/MS procedure (LOQ = 50 pg/ml) at Taylor Technology Inc., NJ. The results showed that the plasma concentrations of SCH 32088 were gender-independent. Serum SCH 32088 was not detectable in the low-dose group during Weeks 1 and 5. For the high-dose males and females, Cmax and AUC levels in Week 5 were higher than the parameters obtained in Week 1. (See table below.) It suggests a possible drug accumulation.

Hour[a]	Target (Actual) Exposure Dose (µg/l)											
	0 (0)			0.04 (0.04 ± 0.01)			0.2 (0.20 ± 0.01)			1.0 (1.0 ± 0.1)		
	Plasma SCH 32088 (pg/ml)											
	Mean	%CV	n	Mean	%CV	n	Mean	%CV	n	Mean	%CV	n
Week 1												
0.25	0	–	20	0	–	10	0	–	10	187	34	20
1	0	–	20	0	–	10	0	–	10	72.2	69	19
3	0	–	20	0	–	10	0	–	10	14.4	198	18
6	0	–	20	0	–	10	0	–	10	0	–	17
Cmax (pg/ml)	NC	NC		NC	NC		NC	NC		189	33	20
AUC(tf) (pg·hr/ml)	NC	NC		NC	NC		NC	NC		227	57	20
Week 5												
0.25	0	–	20	0	–	10	48.3	73	10	420	51	20
1	0	–	20	0	–	10	0	–	10	184	42	19
3	0	–	20	0	–	10	9.33	316	10	65.2	91	20
	0	–	20	0	–	10	0	–	10	9.06	247	20
	0	–	20	0	–	10	0	–	10	0	–	19
22	0	–	20	0	–	10	0	–	10	6.22	3.5	20
Cmax (pg/ml)	NC	NC		NC	NC		74.1	21	7	420	51	20
AUC(tf) (pg·hr/ml)	NC	NC		NC	NC		59.4	68	7	787	82	20

[a] Time after termination of 1 hr exposure
NC Not calculated

Organ weights (After Week 7 and recovery period): Decreased lung and adrenal weight and increased thyroid weight were generally found in all drug-treated dogs. Reduced epididymides and spleen weights were seen in the drug-treated males and females, respectively. Thymus weights were also decreased in the high-dose females.

Lungs (males) and thymus weights (females) in the low-dose group were

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controls. After a 9-week recovery period, organ weights in the high-dose group were similar to the control group except for decreased epididymides weights. (See table below.)

Percentage differences in the organ weights from the controls

Time	Group	Males				Females				
		Lung	Adrenal	Epididymides	Thyroid	Lung	Spleen	Adrenal	Thymus	Thyroid
After Week 7	Low-dose	19%↑	--*	--*	24%↑	--*	16%↓	--*	13%↑	--*
	Mid-dose	16%↓	--*	21%↓	39%↑	--*	--*	--*	--*	26%↑
	High-dose	17%↓	10%↓	18%↓	49%↑	2[illegible]%↓	28%↓	16%↓	32%↓	19%↑
After recovery										
	High-dose	--*	--*	18%↓	--*	--*	--*	--*	--*	--*

* The change was less than 10%.

Necropsy (After Week 7 and recovery period): After 7 weeks of exposure, hemorrhage was observed in the lung tissues in 15 out of 38 dogs, including the controls. After the recovery period, no abnormal necropsy finding was reported.

Histopathology (After Week 7 and recovery period): After the treatment, no dose-related pathological changes were found in any organ. From the control to high-dose dogs, acute pulmonary hemorrhage was seen in 0/4, 5/5, 2/4 and 0/5 males and 3/5, 3/5, 3/5 and 0/5 females. Perivascular hemorrhage, alveolar edema as well as acute cellular infiltrations were also observed in all groups. These pulmonary abnormalities were also reported in 1 mid-dose and 1 control males that died during the study. After a 9-week recovery period, most pulmonary alterations in the control and high-dose groups were recovered. Following the recovery period, no additional dose-related pathological findings were observed.

This study was designed as an oral inhalation study. Since a dog normally breathes through its nose, it is difficult for a young dog to breathe without proper acclimation to an exposure mask. Clinical signs found in this study were mainly caused by struggling with the face masks. The struggling may be due to the following 3 major possibilities: 1) The face mask was not fitted during the growth period of a young dog. 2) The young dogs were not adapted to the conditions of the face mask and inhalation experiment; or 3) The dogs were hurt by the face masks during the experiment. Based on the pharmacokinetic data, systemic drug exposures were achieved in the experimental animals although this inhalation study was not properly conducted due to the problems with the face masks. Based on the results of this study, orally inhaled doses at 7.1 - 7.3 µg/kg/day can be considered as a tolerated dose with mild glucocorticoid effects for pediatric dogs. Target organs of toxicity were present in the adrenal, lungs, epididymides and thyroid.

21. Other Studies using pediatric animals

In addition to the above two inhalation pediatric studies, SCH 32088 were also given to pediatric rats and dogs by oral and intravenous routes of administration. After a 2-week intravenous administration of SCH 32088, the NOEL dose was not established in either rats or dogs. Target organs of toxicity were thymus, lymph tissue and adrenal gland in the rats, and liver, thymus, kidney and adrenal glands in the dogs.

When rats were treated orally at 0.5 to 125 µg/kg, the NOEL dose was determined at 5 µg/kg. However, oral NOEL was not defined in dogs treated with SCH 32088 at 50 to 2500 µg/kg. Target organs of toxicity for these animals were thymus, lymph tissues, liver, adrenal gland and skin.

Study (Animals/sex/group; Report #; Conducting laboratory)	Daily dose: µg/kg (Batch #)	Observation
Young rat: 2-wk IV study (10; P-5440, Schering)	60, 120, 240 (23459-066)	NOEL was not established Target organs: thymus, lymph tissue, adrenal
Young dog: 2-wk IV study (3; D-24315; BioResearch)	100, 300, 1000 (23459-066)	NOEL was not established. Target organs: Liver, adrenal, thymus, kidney
Young rat: 1-mon oral study (16; P-6045; Schering)	0.5, 5, 125 (93-MMF-DDPX-01)	NOEL = 5 µg/kg Target organs: thymus, lymph tissue
Young dog: 1-mon oral study (5; P-6008; Schering)	50, 150, 600,2500 (92-MMF-DDPX-01)	NOEL was not established Target organs: adrenal, liver, thymus, lymph tissue, skin.

REPRODUCTIVE TOXICOLOGY

1. A pilot oral teratology (Segment II) study in rats (D-26738, 1/95; Vol. 108)

Test Lab: Schering Company, Lafayette, NJ (GLP: No)
Animal: 5 groups of Sprague Dawley female rats (n = 25 /group)
Formulation: SCH 32088 (Batch # 92-MMF-DDPX-01) in 0.4% aqueous methylcellulose at the concentrations of 0.004 mg/ml to 0.12 mg/ml

Study Design: The rats were treated orally with SCH 32088 from Day 6 through 15 after mating. (See table below.) After treatment, all rats were sacrificed on Day 21 after mating.

Daily dose (µg/kg)	Dose volume (ml/kg)	Number of Females
0 (Vehicle)	5	8
0.02	5	8
0.1	5	8
0.2	5	8
0.6	5	8

Results: No obvious drug-related clinical signs were observed in any group. Body weights in all rat groups were comparable. No treatment-related differences were found in pregnancy or offspring parameters. There were no gross malformations or variations seen in this study.

Based on this non-GLP study, 0.6 mg/kg/day for pregnant rats can be accepted as a tolerated dose with mild glucocorticoid.

2. Oral teratology (Segment II) study in rabbit (P-5991, 6/95; Vol. 109)

Test Lab: Schering Company, Lafayette, NJ (GLP: Yes)
Animal: 4 groups of mated New Zealand White females (n = 18 + 4 /group)
Formulation: SCH 32088 (Batch # 93-MMF-DDPX-01) in 0.4% aqueous methylcellulose at the concentrations of 0.5 µg/ml to 100 mg/ml.

Study Design: From Days 6 through 19 after mating, the rabbits were dosed orally with SCH

32088. Four additional rabbits in each group were used to determine plasma drug concentrations at 0.5, 1, 3, 6 and 24 hr postdosing on Day 19. The study design is presented in the following table:

Group	Daily dose (mg/kg)	Females for teratology study	Females for PK study
Control	0 (Vehicle)	18	4
Low-dose	0.14	18	4
Mid-dose	0.7	18	4
High-dose	2.8	18	4

The animals in the teratology study were killed on Day 30 after mating. After sacrifice, all offspring were examined for developmental variations and malformations. Rabbits used for the PK study were killed after the last blood collection on Day 19. The plasma samples were assayed by using a HPLC-MS technique (LOQ = 50 pg/ml).

Results:

Maternal Effects:

Mortalities and Pregnancy (Daily): No death was found in any group. The number of pregnant rabbits were 15/18, 13/18, 16/18 and 14/18 in the control to high-dose group. One mid-dose and 5 high-dose rabbits aborted. Seven high-dose rabbits resorbed all their conceptus. Only 2 high-dose rabbits remained pregnant to Day 30.

Clinical Signs (Daily): No dose-related clinical signs were observed in the rabbits.

Bodyweight (At Days 0, 7, 13, 19, 30 of gestation): During the dosing period (Days 7-19), mean body weight gains were reduced in a dose-related manner (0.09, 0.01, -0.03, -0.09 in the control, low-, mid- and high-dose groups, respectively). The bodyweight gains in the mid- and high-dose groups were statistically lower than the controls. The reduction of body weight gain remained in the high-dose until the end of the study.

Food consumption (Daily): Food intake in each group was not significantly different from the controls.

Necropsy (Day 30): There were no treatment-related macroscopic findings.

Pharmacokinetics (Day 19): Plasma SCH 32088 concentrations were only measurable in the

high-dose group. In the high-dose group, Tmax was observed at 3 hr postdosing. Cmax and AUC are present in the following table:

Dose (mg/kg/day)	Mean pg SCH 32088/ml plasma[a]					AUC(0.5-24 hr)
	0.5 hr	1 hr	3 hr	6 hr	24 hr	(pg-hr/ml)
0	0.0	0.0	0.0[b] (3)	0.0 (3)	0.0	0.0 (2)
0.14	0.0	0.0	0.0	0.0	0.0	0.0
0.7	0.0	0.0	0.0	0.0	0.0	0.0
2.8	136	109	222	128	24.0	2282

a. Each value is the mean of the data from 4 female rabbits, unless indicated otherwise in parentheses.
b. SCH 32088 was detected in the plasma of one control rabbit at 3 hr post-dose; the concentration was low and inconsistent with pharmacokinetic parameters and was not used in the calculation of the mean plasma concentration.

Litter Findings

Corpora lutea, implantation and resorption: The mean number of corpora lutea and implantation in all groups were comparable. However, the percentage of resorptions was significantly increased in the high-dose group. (See table below.)

Mean±SE	Animal groups			
	Control	Low-dose	Mid-dose	High-dose
Corpora lutea	9.93±0.45	9.38±0.65	10.07±0.56	9.22±0.81
Implantation	8.87±0.46	8.62±0.59	9.67±0.56	9±0.97
Resorption	0.27±0.12	0.62±0.4	1±0.35	8.44±1.16*

*p<0.01

Litter analyses: Litter size, sex distribution, distribution of fetuses in the left or right horn of the uterus, pup body weights and 24-hour offspring survival were comparable to control in the low- and mid-dose groups. However, two surviving high-dose dams produced only 4 live pups and 1 dead pup.

Malformations: Malformations were seen in all groups. The types of malformation varied in the control and low-dose groups. In the control group, 3/129 fetuses (2.3%) had malformations. One control fetus had a shortened body, absence of gonads, umbilical hernia and agenesis of tail. Another control fetus had hemivertebra. Missing or fused ribs were observed in all 3 control fetuses.

Malformations were found in 5/104 low-dose fetuses (4.8%). One was a conjoined twin. Extra sternebra (2 fetuses) and fused ribs (2 fetuses) were seen in other fetuses.

In the mid-dose group, 9 of 130 fetuses (6.9%) had malformations. In 8 of these, the primary findings were cleft palate and/or head malformations that consisted of hydrocephaly or a domed head. These findings were reported in rabbits treated with corticosteroids during pregnancy(Schardein J., Drugs as Teratogens, 1976, p. 218; Lanhoff L., et al., Anat Rec 193/3:598, 1979; Walker B., Proc Soc Exp Biol Med 125:1281, 1967). In the high-dose group, one of four fetuses (25%) had a cleft palate. However, only 4 fetuses are insufficient for a meaningful evaluation of prenatal development.

Based on the above results, oral administration of SCH 32088 at ≥ 0.7 mg/kg or above caused maternal and fetal toxicities to rabbits. The malformation rate in the 0.14 mg/kg group was considered to be comparable to the control value (2.3%). Since the oral dose at 0.14 mg/kg did not produce significant toxic or teratogenic effects to either the dams or their offspring, it was accepted as a NOAEL.

3. Subcutaneous teratology study in rats (P-5543, 3/91; Vol. 108)

Test Lab: Schering Company, Lafayette, NJ (GLP: Yes)
Animal: 4 groups of Sprague Dawley female rats (n = 25 /group)
Formulation: SCH 32088 (Batch # 9-MMF-X-6002) in 0.4% aqueous methylcellulose at the concentrations of 5 µg/ml to 60 mg/ml.

Study Design: The rats were treated subcutaneously with SCH 32088 from Day 6 through 15 after mating. After treatment, all rats were sacrificed on Day 21. The study design is presented in the following table:

Group	Dose (µg/kg/day)	Dose volume (ml/kg)	Number of Females
Control	0 (Vehicle)	0.5	25
Low-dose	2.5	0.5	25
Mid-dose	15	0.5	25
High-dose	30	0.5	25

Results:

Maternal Effects:

Mortalities and Pregnancy (Daily): All rats survived after the treatment. Pregnancy rates were 24/25, 24/25, 25/25 and 22/25 from the control to high-dose group.

Clinical Signs (Daily): No dose-related clinical sign was seen in the study.

Bodyweight (At Days 0, 6, 9, 12, 15, 18 and 21 after mating): During the dosing period (Days 6-15), mean bodyweights were comparable between the control and low-dose groups. However, bodyweights of the mid- (25%↓) and high-dose (40%↓) groups were statistically lower than the control values.

Food consumption (Days 0-6, 6-10, 10-15 and 15-21 after mating): Food consumption was not significantly different from the controls.

Necropsy (Day 21): Bilateral hydronephrosis was observed in one control rat. However, no treatment-related macroscopic abnormality was found in the study.

Litter Findings

Corpora lutea and implantation: There were no significant differences in the mean numbers of corpora lutea, implantation and resorption in all groups. (See table below.)

Mean±SE	Animal groups			
	Control	Low-dose	Mid-dose	High-dose
Corpora lutea	15.96±0.43	17.17±0.35	17±0.44	16.55±0.47
Implantation	15.38±0.63	16.71±0.32	16.32±0.54	16.09±0.57
Resorption	0.96±0.19	0.71±0.2	0.88±0.19	1.59±0.37

Litter and fetuses: Litter size, sex distribution, offspring delivered as well as 24-hour offspring survival were comparable among all groups. In comparison with the controls, mean fetal body weights were slightly lower in the mid-dose group. However, this low mean body weight was primarily produced by 1 fetus in the mid-dose group. When this fetus was excluded from the litter mean calculation, the mean fetal bodyweights were comparable between the mid-dose and control groups.

Malformations: No drug-related malformations were observed in this study. Incidental malformations were seen in 3/1435 fetuses and were equally distributed in the control, mid- and high dose groups (1 fetus/group). No malformations were observed in the low-dose group. The incidences of skeletal variations, predominantly delayed ossification of the phalanges and sternebrae were slightly increased in the mid- and high-dose groups.

Based on the results of this study, the subcutaneous dose of 2.5 µg/kg/day was the NOEL dose to both dams and fetuses.

4. Single dose pharmacokinetic studies in pregnant female rats (P-6084, 7/95; Vol. 138)

The objective of this study was to determine pharmacokinetic parameters in pregnant rats. Pregnant SD rats (18-day pregnancy; n=3/interval) were treated either subcutaneously (SC) or orally (PO) with a single dose of SCH 32088 suspension (Batch #: 93-MMF-DDPX-01). Blood samples were collected at 0, 1, 2, 3, 4, 8, 12, 24 and 48 hr postdosing and then analyzed using LC-APCI-MS/MS method (LOQ = 50 pg/ml).

As demonstrated in the following table, Tmax was 4 hr in pregnant female rats regardless of administration routes.

Mean Parameters	Subcutaneous Dose (0.03 mg/kg)	Oral Dose (0.6 mg/kg)
Cmax (pg/ml)	517	3381
Tmax (hr)	4	4
$AUC_{0\text{-}24\ hr}$(pg.hr/ml)	6601	16797
$AUC_{0\text{-}48\ hr}$(pg.hr/ml)	8250	17595

Relative bioavailability of PO vs. SC administration was determined using the following formula and the result was approximately 11%

$$(AUC_{0\text{-}48\ hr}\ PO/AUC_{0\text{-}48\ hr}\ SC)\ X\ (SC\ Dose/PO\ Dose) = 11\%$$

Therefore, the drug exposure after SC administration was much higher than that after PO administration.

5. Multiple dose pharmacokinetic study in female rats (P-6105, 7/95; 146)

To determine pharmacokinetic parameters, female SD rats (n=4 rats/interval) were treated PO or SC with SCH 32088 suspensions for 10 consecutive days at 2.5, 15 or 30 µg/kg/day. On Days 1 and 10, blood samples were collected at different intervals for up to 24 hr postdosing. Pharmacokinetic parameters in the plasma determined by a HPLC-APCI-MS/MS assay (LOQ = 50 pg/ml). The data are displayed in the following table:

Parameters	2.5 µg/kg/day				15 µg/kg/day				30 µg/kg/day			
	PO*		SC**		PO		SC		PO		SC	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
Cmax(pg/ml)	BQL*	BQL	211	234	120	85	661	794	185	225	903	1360
Tmax (hr)	BQL	BQL	3.0	3.0	2.5	1.5	2.0	2.0	2.0	2.0	3.0	4.0
$AUC_{0\text{-}24\ hr}$ (pg.hr/ml)	BQL	BQL	1248	1457	202	328	7282	9090	613	596	10667	15827
tf	N/A**	N/A	20	14	6	12	24	24	6	12	24	24

* BQL - Below quantifiable limits. ** not applicable

* Blood samples were collected at pre-dose and then at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hr after oral administration

** Blood samples were collected at pre-dose, and then at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 20, and 24 hr after subcutaneous administration.

Based on the above table, Cmax and AUC levels in both groups were increased with the dose administered. Cmax and AUC values in SC group were higher than those in PO group.

Plasma drug concentrations were similar following single and multiple oral dose administrations, suggesting that there was no drug accumulation or enzyme induction after oral administrations. Following subcutaneous administration, plasma SCH 32088 levels on Day 10 were normally higher than those on Day 1. It suggests the possibility of a slight drug accumulation.

The above study indicated that subcutaneous administration produced a high systemic exposure in the female rats.

The following 5 reproductive toxicology studies were reviewed previously. These studies have been reevaluated and briefly summarized for this NDA submission.

6. Subcutaneous teratology (Segment II) study in mice (P-5578, 10/91; Vol. 107)

In this study, SCH 32088 (Batch #: 9-MMF-X-6002) was administered subcutaneously to CD-1 mice during days 6-15 of gestation at 20, 60 or 180 µg/kg/day. Loss of body weight (maternal

and offspring) and cleft palate at 60 µg/kg/day (2.9%) and 180 µg/kg/day (42%) were observed. The NOEL was 20 µg/kg/day for both the dams and offspring. Subcutaneous dose at 60 µg/kg/day was the maternally toxic and teratogenic dose in mice.

7. Dermal teratogenicity study (Segment II) in rats (P-5054, 5/85, Vol. 108)

CD (SD) BR rats were treated topically with 0.1% ointment (Batch # 15784-130) at 0 (vehicle), 0.3, 0.6 and 1.2 mg/kg of SCH 32088 from gestation days 6 through 15.

The study showed that the body weight gain of the treated dams was significantly reduced during the treatment. However, after withdrawal of the treatment, the weight gain among treated and untreated rats were comparable. No treatment-related mortality was reported. Pregnancy rate, litter size, distribution of fetuses in the uterus, sex distribution at birth, and body weights of pups at birth were lower than control at all doses. At 0.6 and 1.2 mg/kg, body weights were significantly lower than control.

No treatment related changes were observed in the number of corpora lutea, implantations and resorptions in the treated rats compared with the vehicle treated rats.

Results of the malformation and variation are presented as the following:

1. At 0.3 mg/kg: Dilated renal pelvis, delayed ossification, unossification of cervical vertebra.

2. At 0. 6 mg/kg: Cleft palate, umbilical hernia, delayed ossification.

3. At 1.2 mg/kg: Umbilical hernia, delayed ossification and unossification of cervical vertebra [illegible] thoracic [illegible]

8. Dermal teratogenicity study (Segment II) in rabbits (P-5066, 5/85, Vol. 109)

NZ rabbits were treated topically with 0.1% of ointment (Batch # 15784-130) at 0 (vehicle), 150 and 300 mg/kg of SCH 32088 from Days 7 through 19 after mating.

The study showed that dermal application of mometasone produced skin erythema at both dose levels. During treatment at both doses, rabbits lost bodyweight gain significantly. Pregnancy rates among these rabbits were not affected by treatment. Mean offspring weights were reduced significantly at low and high doses.

Incidences of malformations in the dosed groups were significantly higher than the control group. These abnormalities were gallbladder agenesis (absence of the organ) and flexed front paws. The high dose group showed umbilical hernia and cleft palate. The low dose group displayed omphalocele and hydrocephaly. In conclusion, dermal application of mometasone at either 150 or 300 µg/kg was maternal and fetal toxic to rabbits.

9. Subcutaneous fertility and general reproduction study (Segment I) in rats (P 5174, 1/87; Vol. 107)

Sprague Dawley rats were dosed subcutaneously with SCH 32088 (Batch #: 16524-033) at 0 (vehicle), 2.5, 7.5 and 15 µg/kg/day. Male rats were dosed for 63 days before mating and throughout the mating period. Female rats were treated from 14 days before mating until they were sacrificed at either Day 14 after mating or Day 21 after parturition.

The results showed that SCH 32088 did not impair estrous cycles, mating performance and fertility. The pregnancy rate was 96%, 88%, 80% and 92% in the control to high-dose groups. For the F_0 generation males, bodyweight reductions were seen in the 7.5 (15%↓) and 15 µg/kg males (26%↓), but not in the 2.5 µg/kg males. Food intake was only reduced in the 15 µg/kg males.

For the F_0 generation females, bodyweight gains were statistically decreased in the 7.5 and 15 µg/kg females during the premating and gestation period. (See table below.) Food consumption was only reduced in the 15 µg/kg group. Dystocia was also found in the 15 µg/kg groups.

Body weight gains (g) of F_0 generation females

Period	Treatment with SCH 32088			
	0 (Vehicle)	2.5 µg/kg	7.5 µg/kg	15 µg/kg
Pre-mating period (Week 8 - 10)	12.4+2.17	7.8+1.08	0.36+1.24*	-6.24+1.46*
Gestation period (Day 0 -21)	157.57+3.69	153+38+4.06	137.17+5.18*	117.14+7.22*

* P< 0.05

Reproduction parameters were comparable among the control, 0.25 and 7.5 µg/kg groups.

Significant reductions in the offspring delivered, litter size and survival rate were noted only after the treatment of 15 µg/kg. Increased resorptions were also seen in the 15 µg/kg group. (See table below.)

Mean±SE	Animal groups (Dose: µg/kg)			
	Control (0)	Low-dose (2.5)	Mid-dose (7.5)	High-dose (15)
Offspring delivered	14.29±0.42	13.85±0.46	12.75±0.99	7.00±2.05*
% of alive offspring on Day 4	57.4	58.8	61.3	30.2
Resorption	0.78±0.17	1.05±0.28	0.67±0.23	0.2±0.2

*p<0.05

In conclusion, SCH 32088 at 2.5 µg/kg was the NOEL for the rats. Impairment of fertility in the rat was not produced by subcutaneous dose up to 15 µg/kg/day. Since the subcutaneous dose at 7.5 µg/kg only causes bodyweight reductions and no other effects, 7.5 µg/kg is considered a tolerated dose with mild glucocorticoid effects in the Segment I study based on the effects on the offspring.

10. Subcutaneous perinatal and postnatal reproduction study (Segment III) in rats (5164, 11/86; Vol. 109)

Sprague Dawley rats were treated subcutaneously with SCH 32088 (Batch #. 16824-(3) at 0 (vehicle), 2.5, 7.5 and 15 µg/kg from Day 14 of gestation through Day 21 after parturitions. The results showed that SCH 32088 at 15 µg/kg caused bodyweight gain reduction, dystocia, difficulty in labor, reduction in the litter size, and decreased live births. In the 7.5 µg/kg group, prolongation of gestation was also observed when compared to the controls (22.25 days vs. 21.96 days), however, this change was not statistically significant. In conclusion, a subcutaneous dose of 15 µg/kg was maternally toxic in rats. Subcutaneous doses at 2.5 and 7.5 µg/kg were well-tolerated by rats.

GENETIC TOXICOLOGY

All genetic toxicology studies were conducted under GLP.

Background: Ten genetic toxicology studies are submitted in this NDA. However, 8 out of 10 studies were reviewed previously. SCH 32088 induced chromosomal aberration in CHO cells in one study (D-20741). However, negative results were found in other studies, including the Ames test, mouse lymphoma assay, mouse bone marrow micronucleus assay, UDS assay, and chromosomal aberration assays in CHL cells and rat bone marrow cells. In the following section, all genetic toxicology and chromosomal aberration assays are summarized.

Summary of genetic toxicology studies reviewed previously:

1. Ames Test: Two Ames tests were conducted using the test stains of TA1535, TA1538, TA97, TA 97a, TA98, TA100, TA102 and WP2uvrA. In the range finding studies, precipitate was observed at the concentration of about 500 µg/plate and cytotoxicity was not induced until 5000 µg/plate of SCH 32088. Therefore, the maximum doses used for these 2 studies were selected at 500 and 2500 µg/plate, respectively. The studies showed that SCH 32088 did not induce an increase in revertant colony counts in any test strain.

2. In vitro mouse lymphoma assay: the L5178Y TK$^{+/-}$ 3.7.2C mouse lymphoma cell line was used in this test. Cytotoxicity and solubility limits of SCH 32088 were approximately 10 and 100 µg/ml, respectively. SCH 32088 was used at the concentrations of 3.125 to 100 µg/ml. With or without S9, mutant frequencies in SCH 32088 treated cells were similar to the negative controls.

3. In vivo mouse bone marrow micronucleus assay: In a pilot study, the LD_{50} in CD-1 mice was determined at 1500 mg/kg after a 2-day intraperitoneal administration. Therefore, the CD-1 mice in the micronucleus assay were treated intraperitoneally at 0 (vehicle), 600, 900 or 1200 mg/kg [illegible]. Bone marrow cells were then taken at 24 and 48 hr after the final dose and slides were prepared for evaluation. Results of this study showed that SCH 32088 did not have significant micronucleus-inducing activity in bone marrow erythrocytes.

4. In vivo hepatocyte UDS assay: Male and female F-344 rats in the range-finding study were dosed orally with a single dose of SCH 32088 at 0 (vehicle), 312.5, 625, 1250, 2500 or 5000 mg/kg. The dose used at 5000 mg/kg reached the maximum viscosity possible of dose suspensions. After the livers were removed at 7 days postdosing, hepatocytes were prepared for cultures. The results suggested that SCH 32088 was not genotoxic to F-344 rat hepatocytes.

For all of the above studies, the results from the positive or negative controls were acceptable.

Summary of chromosomal aberration assays reviewed previously:

Since SCH 32088-induced chromosomal aberration in CHO cells was observed in one study (D-20741), all chromosomal aberration studies are summarized as the following.

5. The first chromosomal aberration assay in CHO cells (D-20741) was conducted by and reported in January 1987. In this study, chromosomal aberrations were observed when CHO cells were cultured with SCH 32088 (Batch #: 15994-109) at the concentration of 12.5 µg/ml without S9. This finding was attributed by the sponsor to a spontaneous decomposition product of SCH 32088 (9-11-epoxide). Therefore, it was suggested that the sponsor repeat a chromosomal aberration assay in CHO cells using a batch containing 9-11-epoxide, and the sponsor should also conduct 2 in vivo chromosomal aberration assays using rat bone morrow cells and mouse spermatogonia.

6. The in vivo chromosomal aberration assay in rat bone marrow cells was examined by After male and female rats were treated with SCH 32088 suspension (in 0.4% methylcellulose) at 500, 1000 and 2000 mg/kg, they were sacrificed at 6, 24 and 48 hr postdosing. Bone marrow cells were collected and prepared for examination. The study indicated that SCH 32088 did not induce chromosomal aberrations in rat bone marrow somatic cells in vivo.

7. In another study (D-23296), Chinese hamster lung (CHL) cells were treated with SCH 32088. Dose levels under metabolic activation and non-metabolic activation were 13.2 and 6.6 µg/ml, respectively. The study showed that the incidences of chromosomal aberration in SCH 32088-treated cultures were similar to those in negative control cultures.

Detection of chromosome aberration in CHO cells using 2 batches of SCH 32088 and SCH 32088 degradation product (D-23579, 11/89; Vol. 119)

The results of the repeated chromosomal aberration study in CHO cells and the in vivo chromosomal aberration assay in mouse spermatogonia are reviewed below.

This study was performed by using the following test articles:

a) SCH 32088 (Batch #: 15994-109): This batch has been previously used in another chromosomal aberration study (D-20741). It was called "SCH 32088 Original" in this study by the sponsor.

b) SCH 32088 (Batch #: 8-MMF-X-600): This batch has not been tested in any chromosomal aberration study. It was named "SCH 32088 New" by the sponsor.

c) SCH 32088 Degradation Product (SCH 32088-DP; Batch 1936-047-02) is known to be the 9,11-epoxide of SCH 32088.

The objective of this study was to determine the ability of SCH 32088 Original, SCH 32088 New, and SCH 32088-DP to induce chromosomal aberrations in CHO cells with or without S9 activation. This study was a repeat of a previous chromosomal aberration study (D-20741).

Methods: CHO cells were prepared and incubated with different test articles. Untreated and dimethyl sulfoxide (DMSO)-treated CHO cells were used as negative and solvent controls, respectively. For the positive controls, cyclophosphamide (CP; 25 and 50 µg/ml) was used with rat S9; mitomycin C (MMC; 0.5 and 1 µg/ml) was used without S9 activation.

Dose ranges for SCH 32088 were determined previously in study D-20741. A range-finding assay for SCH 32088-DP was conducted in this study. Based on the results of those studies, the dose levels of SCH 32088 Original, SCH 32088 New and SCH 32088-DP were decided as the following table:

Test article	S9 conditions	Incubation time	Dose range (µg/ml)
SCH 32088 Original	with	10 hr	25 to100
	without	10 hr	1 to 20
SCH 32088 New	with	10 hr	25 to [illegible]0
	without	10 hr	1 to 20
SCH 32088-DP	with	10 hr	100 to 601
	without	10 hr	1 to 6.01
	without	20 hr	6 to 20

After an initial chromosomal aberration study, a repeated study was conducted at the following dose ranges:

Test article	S9 conditions	Incubation time	Dose levels (µg/ml)
SCH 32088 Original	with/without	10 hr	15, 17.5, 20, 22.5, 25, 27.5 and 30
SCH 32088 Original	with/without	10 hr	
SCH 32088-DP	with/without	10 hr	15, 20, 25, 30, 40, 50, 60, 100 and 200
	without	20 hr	204, 306 and 408

Results: According to the range-finding study, toxicity of SCH 32088-DP was observed at 667 and 2000 µg/ml without S9 activation. With S9 activation, SCH 32088 at 20 to 200 µg/ml only produced slight toxicity and delayed cell cycles. Complete toxicity was observed at 100 µg/ml with S9 activation and at 10 µg/ml without S9 activation. (See table below.)

Compound: SCH-32088 Assay Number: 9106

Trial No.: 1 Lab Code: CY 5016

Activation	Treatment	% Cells[a] M1	% Cells[a] M1+	% Cells[a] >M2	Confluence[c] % Control
Without	Negative Control	0	2	98	100
	Solvent Control DMSO 10 µl/ml	1	35	64	100
	Positive Control MMC 250 ng/ml	100	0	0	100
	300 ng/ml	4	37	59	100
	1.0 µg/ml	6	48	46	100
	3.0 µg/ml	1	27	72	71
	10.0 µg/ml[b]				

Trial No.: 1 Lab Code: CY 5016

Activation	Treatment	% Cells[a] M1	% Cells[a] M1+	% Cells[a] >M2	Confluence[c] % Control
With	Negative Control	0	15	85	100
	Solvent Control DMSO 10 µl/ml	1	9	90	100
	Positive Control CP 20 µg/ml	5	95	0	100
	3.0 µg/ml	1	15	84	100
	10.0 µg/ml	3	15	82	100
	30.0 µg/ml	2	34	64	71
	100.0 µg/ml[b]				

[a] % cells that have completed one (M1), two (M2), or between one and two (M1+) cycles in BrdUrd.

[b] Toxic dose level.

[c] This endpoint is based upon visual observations which are made prior to the harvest of the metaphase cells. Actual cell counts are not taken and any hypertrophy of the attached cells cannot be evaluated. At the time of the confluence observation the flasks are also evaluated for the appearance of floating mitotic cells and dead cells.

In the initial study, chromosomal aberration assays were repeated twice. In the initial experiment, a positive result was found when CHO cells were cultured with SCH 32048 Original at 20 µg/ml without S9 activity. The percentage of cells with aberrations at the concentration of 15 µg/ml was about 2 times higher than the controls. (See table below.) However, negative results were

observed after CHO cells were cultured with SCH 32088 New and SCH 32088-DP.

Initial study using SCH 32088 Original: Chromosomal aberration in CHO cells under non-S9 activation				
	Scored	[illegible] per cell	% of cells with aberrations	% of cells with >1 aberration
Negative & Solvent	200	0.03	2	0.5
Positive control	25	0.36	32*	4
SCH 32088: 0.996 µg/ml	200	0.03	2.5	0
SCH 32088: 4.99 µg/ml	200	0.05	2	0.5
SCH 32088: 9.89 µg/ml	200	0.02	2	0
SCH 32088: 15 µg/ml#	200	0.06	4.5	1
SCH 32088: 20 µg ml#	178	0.13	6.2**	2.2

* Significantly greater than the pooled negative and solvent controls, $p < 0.01$
** Significantly greater than the pooled negative and solvent controls, $p < 0.05$
# Nearly toxic dose level 100 cells not available from one of replicated culture

In a repeated study using high concentrations of the test articles, no chromosomal aberrations were observed in the culture treated with SCH 32088-DP. Significant increases of simple chromatid and chromosome gaps and breaks were observed with SCH 32088 Original and SCH-32088 New. (See the 2 table below.) However, the percentage of cells with chromosomal aberrations did not increase with dose.

[illegible] Original: Chromosomal aberration in CHO cells under non-S9 activation				
	Cell	No of aberration	% of cells with aberrations	% of cells with >1 aberration
Negative & Solvent	200	0.02	0.5	0.5
Positive control	50	0.28	28*	0
SCH 32088: 15 µg/ml	200	0.11	6.5*	2.5
SCH 32088: 15 µg/ml@	100	0.05	5*	0
SCH 32088: 17.5 µg/ml	200	0.35	14.5*	9*
SCH 32088: 17.5 µg/ml@	100	0.34	17*	11*
SCH 32088: 20 µg/ml	200	0.24	10*	3.5
[illegible]				

* Significantly greater than the pooled negative and solvent controls, $p < 0.01$
@ closed flask
# Toxic dose level

Repeated study using SCH 32088 New: Chromosomal aberration in CHO cells under non-S9 activation				
-	Cell Scored	No of aberrations per cell	% of cells with aberrations	% of cells with >1 aberration
Negative & Solvent	200	0.02	0.5	0.5
Positive control	50	0.28	28*	0
SCH 32088: 15 µg/ml	200	0.05	3	1
SCH 32088: 17.5 µg/ml@	150	0.26	13.3*	7.3*
SCH 32088: 20 µg/ml@	150	0.07	5.3*	2
SCH 32088: 22.5 µg/ml#				

* Significantly greater than the pooled negative and solvent controls, p< 0.01
@ Nearly toxic dose level. 100 cells not available from one of the replication culture
# Toxic dose level

In summary, SCH 32088 was positive in the induction of chromosomal aberrations in CHO cells only under non-S9 condition, but not under S9 condition. However, SCH 32088-produced chromosomal aberrations were found only under toxic dose levels, and the percentages of the cells with chromosomal aberrations were displayed in a non-dose-related fashion. With or without S9 activity, SCH 32088-DP was negative for inducing chromosomal aberrations.

9. In vivo Chromosomal Aberration Assay **in Spermatogonial Cells (D-23580, 11/89; Vol. 1)**

This study was to determine if SCH 32088 can induce chromosomal aberrations in spermatogonia obtained from male mice. Based on the results of a range-finding study, male mice (5 males/group) were injected intraperitoneally with SCH 32088 (Lot: 8MMF-X-6003, in 0.4% methylcellulose) at 0 (vehicle), 378, 796 and 1626 mg/kg and then killed at 6, 24 and 48 hr postdosing. Positive control mice were treated with cyclophosphamide (CPA) at 40 or 80 mg/kg and killed at 24 hours postdosing.

The results of this study showed that the frequency of chromosomal aberrations was significantly increased in CPA-treated mice. However, the incidences of chromosomal aberration in the SCH 32088 treated mice were similar to the vehicle-treated control mice. In conclusion, SCH 32088 did not induce structural chromosomal aberrations in mouse spermatogonial cells.

10. [illegible] metabolism and excretion in male mice following a single intraperitoneal dose [illegible]/92; Vol. 139)

This study was conducted in support of micronucleus and spermatogonial studies in mice. Male CD-1 mice (n= 80 group) were injected intraperitoneally with an ^{3}H-SCH 32088 suspension (Batch 32650-49-7) at 500 or 100 mg/kg. Plasma, urine, feces and bone marrow were collected at 6, 24, 48 or 168 hr postdosing. All samples were analyzed by a scintillation spectrometer. Selected plasma samples were analyzed using a LC/MS analysis (LOQ = 50 pg/ml).

By scintillation counting, peak concentrations of ^{3}H-SCH 32088 were observed in both plasma and bone marrow at 6 hr postdosing. The concentrations of 3H-SCH 32088 in bone marrow suggested that ^{3}H-SCH 32088 and/or its metabolites may readily penetrate into the bone marrow.

Dose (mg/kg)	Mice used in each interval	Plasma Dug Levels*		Bone Marrow Drug Levels*	
		at 6 hr.	at 168 hr.	at 6 hr.	at 168 hr.
500	20	32	0	40	1
1000	20	78	1	215	6

* Data were presented as the concentration of radioactivity (µg equivalent of SCH-32088/ml)

By LC/MS analysis, ^{3}H-SCH 32088 was present in bone marrow at both 6 and 24 hr postdosing In the 1000 mg/kg group, 6-hydroxy mometasone furoate was detectable in the plasma at 6 hr postdosing, but not at 24 hr postdosing

Through the 168-hr period radioactivity was mainly eliminated via the feces and 4.7 - 6.7% of the dosed radioactivity was found in the urine. (See table below)

Total recovery (168 hr.) of Administered Radioactivities		
Dose	500 mg/kg	1000 mg/kg
Parameter	Mean (%CV*)	Mean (%CV)
Urine	4.68 (13.74)	6.36 (19.87)
Feces	96.57 (7.18)	84.80 (31.65)
Carcass	3.41 (13.57)	14.55 (35.54)
Total Recovery	104.66 (7.29)	105.71 (22.23)

* %CV coefficient of variation (SD mean x 100%)

PHARMACOKINETICS

Background: A series of pharmacokinetic studies were conducted to support this NDA submission. A recent report from the Division of Scientific Investigations (DSI, HFD-340) indicated that plasma samples obtained in several pharmacokinetic (PK) studies were initially examined by using enzyme immunoassay (EIA). However, after these EIA measurements were completed, an employee of the sponsor revealed to the management that she and two other employees had deliberately falsified some data during the validation of EIA and the conduction of the studies. Related conclusions of DSI are the following:

1. "The data generated by the mometasone furoate EIA at Schering Plough are not accepted for review."

2. "The HPLC-MS data generated by Taylor Technologies, despite our confidence in their own operations, but using specimens temporarily in the custody of the three suspect individuals at Schering Plough, be not accepted for review."

3. "Any mometasone furoate study submitted to the Agency, the audit trail be traced for any biological fluid specimens stored or handled at Schering Plough between 1992 and 1995. Such studies should be referred for our audit."

Following the DSI report, all invalid PK studies have been taken out of this review.

Single Dose Pharmacokinetic Studies:

Single-dose pharmacokinetic studies were not performed under GLP.

[redacted] were conducted by the sponsor and reviewed in this submission. In these studies, absorption, metabolism and excretion of SCH 32088 were determined.

1. Oral bioavailability in male mice (P-6111, 5/96; Vol. 136)

Male CD-1 mice (n=9/interval) were treated with a single dose of SCH 32088 by either intravenous (IV; solution, 0.3 mg/kg) or oral (PO; suspension, 0.6 mg/kg) administration. Plasma samples were collected at 0 (pre-dose), 0.08 (for IV group only), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hr postdosing. SCH 32088 concentrations in the plasma were determined by [redacted]

As demonstrated in the following table, plasma drug concentration in PO group reached the peak (Cmax =1870 pg/ml) at 0.5 hr (Tmax) postdosing. Following IV treatment, Cmax (189000 pg/ml) appeared at the first sampling timepoint (0.08 hr). After IV administration of SCH 32088, a short distribution half life ($t_{1/2}\alpha$ =0.26hr) was followed by a short elimination half life ($t_{1/2}\beta$ = 1.88 hr) in mice. Mean AUC levels for PO and IV groups were 2551 and 74603 pg.hr/ml, respectively. When AUCs were normalized by the dose administered, the absolute oral

Parameter	Unit	Oral Dose (0.6 mg/kg)	Intravenous Dose (0.3 mg/kg)
Cmax/C5min	pg/ml	1870	189000
Tmax	hr	0.5	0.08
t½α	hr	NC	0.26
t½β	hr	NC	1.88
AUC(0-12 hr)	pg-hr/ml	2551	74603
Absolute bioavailability (dose normalized)	%	1.7	NA

NC - Not calculated for this route
NA - Not applicable for this route

2. Pharmacokinetic study of ^{14}C-SCH 32088 in rats following a single intranasal dose (P-5352, 3/89; Vol. 134)

To determine the disposition and excretion of ^{14}C-SCH 32088, 14 male Sprague Dawley rats were treated intranasally with a single dose of ^{14}C-SCH 32088 suspension (Batch No. unknown) at 240 µg/kg. Blood samples were taken from 6 rats at 0.25, 0.5, 1, 2, 4, 6, 24, 48 and 96 postdosing. Urine and feces from 8 other rats were collected every 24 hr up to 168 hr postdosing. All samples were assayed for radioactivity content.

(≤ 1ng equiv. SCH 32088/ml) following intranasal drug administration. At 168 hr postdosing, approximately 2.4% and 93.5% administered radioactivity were recovered in urine and feces, respectively. Excretion of administered radioactivity was nearly complete within 48 hr of dosing.

3. Pharmacokinetic studies in male rats of ^{3}H-SCH 32088 following a single oral or intravenous dose of ^{3}H-SCH 32088 (P-5941, 4/96 and P-6368, 5/96; Vol. 137)

Seven groups of male Sprague Dawley rats were treated with a single PO (Batch #: 31177-133) or IV dose (Batch #: 32136-05) of ^{3}H-SCH 32088 and then sacrificed at different intervals. (See table below.) Rats in Groups 1 and 2 were used to determine the pharmacokinetics and excretion of radioactivity. Rats in Groups 3 and 4 were used to determine the metabolite profile. Rats in Group 5 were used only for the collection of blank plasma. Rats in Groups 6 and 7 (n = 1)

served as the controls. Drug-derived radioactivity was normally analyzed by a liquid scintillation spectrometer Plasma samples from Groups 1 and 2 were also assayed by HPLC-MS/MS.

Group # (Rat #)	Dose (Route)	Blood Sampling
1 (60)	0.3 mg/kg (IV)	*
2 (56)	0.6 mg/kg (PO)	**
3 (15)	0.3 mg/kg (IV)	1, 2, 4 hr postdosing
4 (15)	0.6 mg/kg (PO)	1, 2, 4 hr postdosing
5 (10)	0	For blank samples only
6 (1)	Vehicle (IV)	1, 2, 4 hr postdosing
7 (1)	Vehicle (PO)	1, 2, 4 hr postdosing

* At 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 168 hr postdosing
** At 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 168 hr postdosing

Results:

Absorption: Drug-related radioactivity was evaluated, and the mean parameters are summarized in the following table:

Phamacokinetic parameters for total radioactivity		
Parameter	IV	PO
Dose (mg/kg)	0.3	0.6
Cmax(ng eq/g)	328	5.2
Tmax(hr)	0.08*	3.0
AUC(tf; ng eq.hr/g)	748	249

* The first sampling time (0.08 hr) after IV dosing

Plasma samples were re-analyzed by LC-MS/MS (LOQ = 50 pg/ml; P-6368). Comparing the AUC values in the above table, AUC values measured by the LC-MS/MS method were much smaller than the AUC values determined by radioactivity. (See table below.)

Phamacokinetic parameters measured by LC-MS/MS		
Parameter	IV	PO
Dose(mg/kg)	0.3	0.6
Cmax(ng/g)	364	1.14
Tmax(hr)	0.08*	3.0
AUC(tf; ng.hr/ml)	192	5.23
tf (hr)	12	24
t½ (hr)	1.56	4.19

* The first sampling time after IV dosing

Based on the above table, bioavailability of SCH 32088 following oral dosing was approximately 1.4% of the IV doses when plasma AUC levels were normalized for the dose administered.

Tissue distribution: The liver, lungs and gastrointestinal tissues collected from Groups 1 and 2 rats were analyzed for radioactivity. Following IV administration, radioactivity was rapidly observed in the small intestine, suggesting rapid biliary excretion of ^{3}H-SCH 32088 and/or its metabolites. The Cmax levels in the lungs and liver were detected at 0.08 hr after IV dosing.

Following PO administration, the highest concentrations of drug-derived radioactivity were found in the gastrointestinal tract. Cmax in liver or lungs was found at 6 hr after PO administration. The concentrated gastrointestinal radioactivity may be contributed by the unabsorbed drug and drug excreted into the bile.

In both IV and PO groups, drug-related radioactivity was peaked at 6 hr postdosing. (See tables below.)

Mean Percent of Administered Radioactivity in Tissues of Male Sprague Dawley Rats Following a Single Intravenous Dose of ^{3}H-SCH 32088

	Time of Sacrifice (hr)									
	0.08		1.0		6.0		12		24	
Tissue	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV
Lungs	0.869	12	0.146	25	0.0248	20	0.0116	18	0.0085	26
Liver	13.8	34	3.39	38	0.16	25	2.81	36	2.09	39
Stomach[a]	0.779	22	1.05	74	0.0256	37	0.720	105	0.0287	41
Large Intestine[a]	0.847	4	0.758	62	61.8	12	14.7	64	1.84	41
Small Intestine[a]	16.6	20	67.5	16	12.9	67	2.32	40	0.853	61

Mean Percent of Administered Radioactivity in Tissues of Male Sprague Dawley Rats Following a Single Oral Dose of ^{3}H-SCH 32088

	Time of Sacrifice (hr)									
	0.25		1.0		6.0		12		24	
Tissue	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV
Lungs	0	NC	0.0006	200	0.0039	12	0.0035	17	0.0013	13
Liver	0.108	62	0.103	40	0.053	20	0.015	24	0.032	41
Stomach[a]	44.14	41	28.0	68	0.110	78	0.793	108	0.7896	80
Large Intestine[a]	0.0481	126	0.0036	127	78.8	12	28.2	42	2.01	66
Small Intestine[a]	34.3	74	61.2	30	2.39	17	0.880	46	0.160	64

Results are expressed in terms of percent of administered dose and represent mean and %CV where n = 4

[a] Including contents

NC Not calculated

%CV Coefficients of variation expressed as a percent

Excretion: Feces and urine were collected at different intervals for up to 168 hr postdosing. Excretion of drug-derived radioactivity was rapid following both IV and oral dosing. Approximately 86% of the dose was recovered in the feces and urine within 24 hr. By 168 hr, the total radioactivity excreted from the IV and PO groups was 90% and 91%, respectively. (See table below.)

Percentage of administered radioactivity		
Samples	IV	PO
Urine	3.28	0.54
Feces	86.2	90.1
Cash Wash	0.25	0.16
Total	89.7	90.8

Metabolism: In both IV and PO groups, unchanged SCH 32088, metabolites similar in polarity to 6β-hydroxy mometasone furoate and 21-hydroxymometasone were detected in plasma (1-4 hr) by using HPLC methods. There was no unchanged SCH 32088 found in urine of IV and PO dosed rats or feces of IV dosed rats. The high-level of SCH 32088 was observed only in the feces of PO groups. However, the Sponsor did not conduct any quantitative study to determine the quantity of SCH 32088 or its metabolites in any samples.

4. Disposition of ^{3}H-SCH 32088 in rat and dog following a single IV or PO dose (P-5313, 11/88; Vol. 138)

Disposition of ^{3}H-SCH 32088 suspension (Batch #: 21120-31-20, in 0.4% methylcellulose) was evaluated in male rats (n=6/group; Dose = 1 mg/kg) and male dogs (n=4/group; Dose = 0.6 mg/kg) following a single dose IV or PO drug administration. Urine and fecal samples were collected up to 168 postdosing. Radioactivities of all samples were measured using scintillation spectrometry (LOQ ≈ 1 ng eq/ml)

In both species, parent compound and/or metabolites were eliminated mainly through the feces. However, IV-dosed radioactivity in either rats or dogs was not completely eliminated within a 168 hr period. In contrast to IV administration, PO-dosed radioactivity in rats or dogs was completely eliminated through urine and feces. (See table below.)

Recovery of Administered Radioactivity (%)

Rat	Time	0-24Hr	24-48Hr	48-72Hr	72-96Hr	96-120Hr	120-144Hr	144-168Hr	C.W*	Total	Total Recovery
IV	URINE (±SD)	0.50 (0.37)	0.56 (0.41)	0.41 (0.31)	0.26 (0.22)	0.22 (0.16)	0.16 (0.13)	0.12 (0.07)	0.22 (0.12)	2.46 (1.75)	72.31 (5.25)
	FECES (±S.D.)	5.53 (4.08)	12.16 (7.51)	11.83 (8.50)	8.35 (5.41)	5.30 (2.74)	3.81 (1.91)	3.16 (1.64)	NS@	50.14 (24.9)	
PO	URINE (±SD)	0.38 (0.07)	0.24 (0.25)	0.12 (0.14)	0.09 (0.10)	0.05 (0.05)	0.02 (0.02)	0.02 (0.02)	0.12 (0.08)	1.04 (0.65)	113.85 (8.21)
	FECES (±SD)	92.87 (29.9)	10.96 (9.20)	6.08 (9)	3.02 (5.6)	0.71 (1.27)	0.10 (0.16)	0.10 (0.12)	NS@	113.9 (8.2)	
Dog	**Time**	**0-24Hr**	**24-48Hr**	**48-72Hr**	**72-96Hr**	**96-120Hr**	**120-144Hr**	**144-168Hr**	**C.W***	**Total**	**Total Recovery**
IV	URINE (±SD)	0.09 (0.02)	0.67 (0.17)	1.18 (0.05)	0.88 (0.18)	0.74 (0.12)	0.74 (0.17)	0.55 (0.10)	0.38 (0.06)	5.4 (0.52	80.92 (3.32)
	FECES (±SD)	NS@	7.30 (4.82)	25.56 (2.72)	14.64 (5.01)	9.61 (2.02)	8.04 (4.49)	7.34 (2.15)	3.04 (0.23)	75.5 (2.8)	
PO	URINE (±SD)	0.31 0.14	0.12 (0.06)	0.05 (0.02)	0.02 (0.01)	0.02 (0.02)	0.01 (0.01)	0.02 (0.01)	0.11 (0.12)	0.66 (0.36)	93.8 (15.4)
	FECES (±SD)	89.00 (16.8)	3.56 (2.57)	0.34 (0.17)	0.09 (0.02)	0.11 (0.16)	0.02 (0.01)	0.02 (0.01)	NS@	93.15 (15.4)	

* Cage washing fluid. @ NS No sample

Multiple-Dose Pharmacokinetic Studies:

5. One-month nose-only inhalation pharmacokinetic studies in rats (P-6137, Vol. 143)

A one-month study was conducted to evaluate pharmacokinetic parameters in rats treated with SCH 32088 by nose-only inhalation. The concentrations of SCH 32088 in this study were 0.25, 0.5, 1 and 2 µg/L. Toxic effects of SCH 32088 were not reported in this study. The design of this study is presented in the following table:

Report # (time)	P-6137 (4/96)
Animal	SD rats
Laboratory	Battelle Pacific
Formulation	MDI
Route	Nose-only Inhalation
Duration	1- month
Daily doses on Day 1	♂: 2.6, 4.1, 10, 17µg/kg ♀: 3.7, 8.7, 14, 33 µg/kg &
Daily doses on Day 30	♂: 3.2, 6.7, 14, 24µg/kg ♀: 3.7, 8.7, 14, 33 µg/kg &
Batch #	26951-133
Blood sampling	Days 1, and 30*
Assays (LOQ= 50 pg/ml)	HPLC-APCI/MS/MS (50 pg/ml)

* 80 or 84 rat sex time point at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 7, 9, 11, 14, 18, 23, 35 (Day 1 only) and 43 hr (Day 1 only) postdosing

After rats inhaled SCH 32088, pharmacokinetic parameters were gender-independent. Following

either single dose (Day 1) or multiple doses (Day 30), both Cmax and AUC were generally increased almost proportionally with the dose administered. Tmax values were approximately 1 hr postdosing. (0.75 -1.5 hr; See table below.)

Parameter	Units	Target Exposure Concentration (µg/L)											
		0.25			0.50			1.0			2.0		
		M	F	M+F	M	F	M+F	M	F	M+F	M	F	M+F
Day 1													
Dose*	µg/kg/day	2.81	3.79	NC	4.89	6.72	NC	10.2	14.0	NC	18.7	25.9	NC
Cmax	pg/mL	666	872	769	1300	799	993	1730	1870	1800	7040	4230	5640
Tmax	hr	1.00	0.50	1.00	1.25	1.25	1.25	1.00	1.00	1.00	1.00	1.00	1.00
AUC(t)	pg•hr/mL	869	484	679	3779	2993	3486	6940	6916	6891	20883	17388	18807
t	hr	3.00	16.0	16.0	16.0	16.0	16.0	24.0	16.0	24.0	24.0	24.0	24.0
Day 30													
Dose	µg/kg/day	3.24	5.89	NC	6.71	9.31	NC	13.8	18.1	NC	24.0	37.1	NC
Cmax	pg/mL	667	719	648	2000	1000	2000	3000	2100	2700	6940	3000	4960
Tmax	hr	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.75	1.00	1.25	1.25	1.25
AUC(t)	pg•hr/mL	2346	1663	2104	6486	3981	6104	13446	7880	10571	40488	12339	18889
t	hr	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	24.0	24.0	24.0
R	-	8.27	4.16	5.70	1.87	1.24	1.46	1.89	1.28	1.63	0.666	0.715	0.845

Key: F = Female; M = Male; NC = Not calculated

t Estimated total dose calculated from minute volume measurements and based on total deposition

6. One-month nose-only inhalation pharmacokinetic studies in mice (P-6122, Vol. 140)

A 1-month nose-only inhalation study was conducted to evaluate pharmacokinetic parameters in Swiss CD-1 mice at 0.25, 0.5, 1 and 2 µg/L of SCH 32088. After a single dose exposure, blood samples (5 mice/sex/time point) were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 7, 9, 11, 14, 18, 23, 35 and 47 hr postdosing. On Day 30, blood samples (15 mice/sex/time point) were taken at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 7, 10, 14 and 23 hr postdosing. The design of this study is presented in the following table:

Report # (time)	P-6137 (7/95 - 4/96)
Animal	Swiss CD-1 mice
Laboratory	
Formulation	MDI
Route	Nose-only Inhalation
Duration	1- month
Predicted daily doses on Day 1 and Day 30	♂: 32, 64, 128, 255µg/kg ♀: 36, 71, 142, 284 µg/kg
Batch #	26951-133
Blood sampling	Days 1 and 30
Assays	HPLC-APCI/MS/MS (LOQ= 50 pg/ml)

The results showed that plasma drug concentrations were gender-independent. Following either a single exposure or a 30-day multiple-dose inhalation, plasma drug concentrations increased non-proportionally with administered doses. Except the low dose group (0.25 µg/L), plasma SCH 32088 levels were generally similar following a single dose and 30-daily doses, suggesting that the pharmacokinetics of SCH 32088 were not dependent on the treatment duration. (See table below.)

Parameter	Units	Target Exposure Concentration (µg/L)							
		0.25		0.5		1.0		2.0	
		Day 1	Day 30	Day 1	Day 30	Day 1	Day 30	Day 1	Day 30
Cmax	(pg/mL)	882	341	709	672	1910	1178	2087	3180
Tmax	(hr)	3.00	1.00	0.75	1.00	1.00	1.00	1.00	1.00
AUC(t)	(pg•hr/mL)	1171	686	1538	1440	3804	3206	6321	10281

This study displayed a dose-related systemic exposure in Swiss CD-1 mice. This mouse strain has been also used in an oncogenicity study (P-6006) conduced by . Since the predicted SCH 32088 doses in this study were similar to the predicted doses in the study P-6006, the data from this study may predict plasma drug exposure in the oncogenicity study.

7. A 28-day oral inhalation pharmacokinetic study in dogs (P-6096, Vol. 145)

Beagle dogs were treated for 28 days by oral inhalation at 20, 80 and 160 µg/kg/day. On Days 1, 15 and 28, blood samples (4 dogs/sex/group) were collected at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hr postdosing. The design of this study is presented in the following table:

Report # (time)	P-6196 (2/95 - 3/96)
Animal	Beagle dog
Laboratory	
Formulation	MDI
Route	oral Inhalation
Duration	28-day
Predicted daily doses	20, 80 and 160µg/kg
Batch #	26951-110
Blood sampling	Days 1, 15 and 28
Assays	HPLC-APCI/MS/MS (LOQ= 50 pg/ml)

The results showed that plasma drug concentrations of 20 µg/kg/day group were under the

quantifiable levels (50 pg/ml). Pharmacokinetic parameters in the 80 and 160 µg/kg/day groups were not affected by gender or treatment duration. Following the treatment of 80 and 160 µg/kg, plasma levels of SCH 32088 were increased non-proportionally with administered doses. (See table below.)

Days of Postdosing	Pharmacokinetic Parameters	Treatment			
		80 µg/kg/day		160 µg/kg/day	
		Mean	%CV	Mean	%CV
Day 1	Cmax (pg/ml)	67.5	17	121	29
	AUC (0-24hr; pg.hr/ml)	124	48	321	81
Day 15	Cmax (pg/ml)	82	28	197	30
	AUC (0-24hr; pg.hr/ml)	418	--*	790	65
Day 28	Cmax (pg/ml)	79.2	22	143	34
	AUC (0-24hr; pg.hr/ml)	228	45	445	41

* n = 1

This study showed that plasma concentrations of SCH 32088 were under the quantifiable levels after beagle dogs were treated with 20 µg/kg/day; dose-related systemic exposures were seen in the dogs treated with 80 and 160 µg/kg/day.

8. Three-month nose-only inhalational studies in 2 species (P-5836 & P-5837; Vol. 139)

After rats and dogs were treated with SCH 32088 for 3 months by nose-only inhalation, blood and tissue samples were collected. The designs of these studies are presented in the following table:

Report # (time)	P-5836 (3/94)	P-5837(3/94)
Animal	SD rats	Beagle dogs
Laboratory		
Formulation	Dry powder	Dry powder
Route	Nose-only Inhalation	Nose-only Inhalation
Daily dose	♂: 3.4 13, 56µg/kg ♀:4.5, 17, 74µg/kg	♂: 35, 93, 192µg/kg ♀: 57, 161, 250µg/kg
Batch #	92-MMF-DDPX-01	92-MMF-DDPX-01
Blood sampling	Weeks 1, 7 and 12*	Days 1 and 91**
Assays (LOQ)	EIA (50 pg/ml)	EIA (50 pg/ml)

* 4 rats sex time point at 0.25, 0.5, 1, 1.5, 2, 4 and 24 hr
** 3 dog/sex/time point at 0.25, 1, 3, 6 and 22 hr on Days 1 and 91

After the animals in both st. dies were dosed inhalationally with SCH 32088 dry powder. pharmacokinetic parameters were measured by EIA between 1992 to 1995. Based on the repon from the Division of Scientific Investigations (HFD-340), the results from these pharmacokinetic studies were not acceptable. The livers and lungs in both studies were also collected at 24 hr after the final dose and were used to evaluate enzyme induction.

1. In the rat study (P-5836), SCH 32088 has almost no effect on the induction of liver and lung enzymes. The following table demonstrated the quantities of total microsomal protein, cytochrome P-450 and benzphetamine N-demethylase (BND) in the livers or lungs from the control and high dose-treated groups (56 µg/kg for the males and 74 µg/kg for the females) after a 3-month inhalational exposure. (See table below)

		Liver Enzymes (Mean±SD)		Lung Enzymes (Mean±SD)	
Treatment (Concentrations)		0 (Control)*	4 µg/L *	0 (Control)*	4 µg/L *
Liver weight (g)	♂	15.4±2.6	13.4±2.2	1.4±0.1	1.1±0.0
	♀	8.9±0.6	7.8±0.5	1.2±0.1	1.0±0.2
Total microsomal protein (mg/g tissue)	♂	31.2±1.1	31.1±3	13.6±1.6	13.5±1.2
	♀	29.9±0.9	29.8±1.5	12.4±1	12.9±2.4
Cytochrome P-450 (nmol/g liver)	♂	18.6±1	17.7±2.2		
	♀	12.5±1.3	12.4±0.3		
BND (nmol/min/g tissue)	♂	347±38	365±75	24.7±6	15.4±5.4
	♀	127±17	137±10	30.1±8.9	15.9±5.4

* n=6 sex group time point treated with the vehicle
a n=4 sex group time point treated with the drug at the concentration of 4 µg/L. This was equivalent to 56 µg/kg for the males or 74 µg/kg for the females

2. Although liver weights in the dog study (P-5837) were increased following a 3-month SCH 32088 exposure (16 µg/L, or 192 µg/kg for the males and 250 µg/kg for the females), the concentrations of total microsomal protein, cytochrome P-450 and benzphetamine N-demethylase (BND) were not increased in the drug-treated livers or lungs. (See table below.)

		Liver Enzymes (Mean±SD)		Lung Enzymes (Mean±SD)	
Treatment (Concentrations)		0 (Control)*	16 µg/L *	0 (Control)*	16 µg/L *
Tissue weight (g)	♂	235±2.4	658±158	93.2±6.6	90±7
	♀	218±42	498±22	77.7±5.6	78±6.1
Total microsomal protein (mg/g tissue)	♂	22.1±0.9	20.4±2.1	9.0±1.1	12.3±0.6
	♀	20.6±1.1	18.9±2.2	7.2±0.1	9.9±0.3
Cytochrome P-450 (nmol/g liver)	♂	6.2±1	5.4±1	N/A	N/A
	♀	10±1.8	7.2±1.1	N/A	N/A
BND (nmol/min/g tissue)	♂	92.5±19.6	67.4±6.2	3.3±0.5	9.9±1.6
	♀	134±13	82±22	7.0±2.2	10.1±2.8

* n=3 sex group time point treated with the vehicle

n=3 sex group interval, treated with the drug at the concentration of 16 µg/L. This was equivalent to 192 µg/kg for the males or 250 µg/kg for the females

9. Three-month oral pharmacokinetic studies in 3 species (P-6104, P-6138 in Vol. 145; P-6007 in Vol. 148)

Pharmacokinetic parameters were measured after mice, rats and dogs were treated orally with a SCH 32088 suspension for 3 months. The designs of these studies are summarized in the following table:

Report # (time)	P-6140 (8/96)	P-6138 (8/96)	P-6007 (94/96)
Animal	CD-1 mice	SD rats	Beagle dogs
Laboratory			Shering-Plough
Formulation	Suspension *	Suspension *	Suspension *
Route	oral gavage	oral gavage	oral gavage
Daily dose	0, 50, 150, 450, 650 µg/kg	0, 50, 150, 450, 650 µg/kg	0, 10, 150, 650 µg/kg
Study Duration	3-month	3-month	3-month
Batch #	92-MMF-DDPX-01	92-MMF-DDPX-01	92-MMF-DDPX-01
Blood sampling	Days 28 and 90**	Days 1, 28 and 90 ***	Days 1, 43 and 91@
Assays (LOQ)	HPLC-APCI-MS/MS (50 pg/ml)	HPLC-APCI-MS/MS (50 pg/ml)	HPLC-MS/MS (50 pg/ml)

* In 0.4% methylcellulose

** n = 61 mice sex interval. Blood was collected at 0 (predose) 0.5, 1, 2, 4, 6, 12 and 24 hr p.d. on Day 28, and then at 1, 2, 4 and 6 hr p.d. on Day 90

*** n =50 rats sex interval. Blood was collected at 0 (predose) 0.5, 1, 2, 4, 6, 12 and 24 hr p.d. on Days 1 and 28, and then at 1, 2, 4 and 6 hr p.d. on Day 90

@ N= 4 or 6 dogs sex interval. Blood was collected at 0.25, 0.5, 1, 2, 4, 6, 9 (except Day 43), 12 (except Day 43) and 24 hr postdosing

1. Plasma SCH 32088 concentrations in mice were generally increased with dose (P-6140).

Except for the 50 µg/kg group, plasma AUC(tf) levels on both Days 28 and 90 were consistently higher in females than in males. Tmax values were normally longer in the females than in males. When both AUC and Cmax values were compared between Day 28 and 90, it was found that there was no drug accumulation, and plasma SCH 32088 concentrations were not influenced by the duration of treatment. (See table below.)

Dose	Gender	Day 28 C_{max}	Day 28 T_{max}	Day 28 tf	Day 28 AUC(tf)	Day 28 AUC (0-6 hr)	Day 90 C_{max}	Day 90 T_{max}	Day 90 tf	Day 90 AUC (0-6 hr)
50	M	812	2	2	331	331[a]	0[c]	-	-	0[c]
	F	171	1	4	376	376[b]	262	1	2	283[a]
	M+F	351	2	4	69-1	694[b]	151	1	2	185[a]
150	M	311	1	4	836	836[b]	138	1	6	515
	F	693	2	6	1788	1788	813	1	6	1479
	M+F	383	2	6	1427	1427	476	1	6	1010
450	M	655	1	6	1522	1522	694	1	6	1332
	F	1310	2	12	5781	4374	2880	1	6	4782
	M+F	888	1	12	4092	2963	1663	1	6	2838
800	M	688	1	12	2940	2190	1270	1	6	2874
	F	1490	2	12	5407	4823	1850	2	6	5373
	M+F	1054	2	12	4272	3505	1247	2	6	4204

Units: Dose, µg/kg/day; C_{max}, ng/ml; T_{max} and tf, hr; AUC, ng.hr/ml
a: tf = 2 hr
b: tf = 4 hr
c: Plasma SCH 32088 concentrations were not quantifiable

2. Plasma drug concentrations in the gavaged-rats did not vary between males and females (P-6138). Tmax values were between 1 and 2 hours. In all three sampling days, Cmax and AUC values were increased in a dose-related fashion. AUC (tf) values on Day 28 were approximately 2-fold higher than those on Day 1. However, AUC(0-6 hr) were similar on Days 28 and 90. (See table below.)

Table 4 Mean Pharmacokinetic Parameters in Male and Female Rats Following Single- and Multiple-Dose Oral Gavage Administration of SCH 32088 as a Suspension.

Parameter	Day	50 µg/kg/day M	50 µg/kg/day F	50 µg/kg/day M+F	150 µg/kg/day M	150 µg/kg/day F	150 µg/kg/day M+F	450 µg/kg/day M	450 µg/kg/day F	450 µg/kg/day M+F	800 µg/kg/day M	800 µg/kg/day F	800 µg/kg/day M+F
Cmax	1	180	218	200	433	736	872	1680	1310	1487	2010	1480	1744
	28	1000	260	999	981	1680	1290	1820	2880	2048	2430	4810	3430
	90	477	808	484	1040	1440	1158	4050	2880	2814	3010	4660	3613
Tmax	1	2	2	2	1	2	2	2	2	2	2	2	2
	28	1	2	1	1	2	2	1	2	1	1	2	2
	90	2	1	1	1	2	2	2	1	2	1	2	2
AUC(tf)	1	474	716	823	1431	3151	2370	6808	7117	6984	8421	7908	7884
	28	2137	1122	1681	3728	6438	4682	7208	16224	12261	11731	20672	16151
AUC(0-6 hr)	28	2137	884	1501	3125	4203	3654	6888	10487	8587	7752	13476	10610
	90	1851	1662	1808	3786	4026	3822	11081	8613	11301	10079	13836	11951
tf	1	4	6	6	6	12	12	12	12	12	12	12	12
	28	6	12	12	12	12	12	12	24	24	24	24	24
	90	6	6	6	6	6	6	6	6	6	6	6	6

Units: Cmax-ng/ml, Tmax-hr, AUC-ng hr/ml, tf-hr. PK parameters were calculated with mean data, thus no estimate of variability can be

3. After dogs were dosed orally (P-6007), plasma drug concentrations on Day 1 were below the LOQ in all groups except for one 150 µg/kg male. Plasma SCH 32088 levels were also below the LOQ on Days 43 and 91 for the 10 µg/kg dose group, indicating a poor oral bioavailability in dogs. The concentrations of SCH 32088 were detected with a greater frequency at 600 µg/kg than at 150 µg/kg, suggested that the exposure in dogs was elevated with dose. Gender-related differences in plasma drug levels were not found. Both Cmax and AUC values on Day 91 were lower than those on Day 43.

Parameters in orally dosed dogs (Mean+%CV)

Parameters in orally dosed dog	Days	10 µg/kg/day		150 µg/kg/day		600 µg/kg/day	
		M	F	M	F	M	F
Cmax (pg/ml)	1	0*	0	770	0	0	0
	43	0	154	0	0	184	207
	91	0	0	70	0	43.6	48.4
AUC(0.25-24hr; pg hr/ml	1	N/A**	N/A	22608	N/A	N/A	N/A
	43	NC#	NC	NC	NC	2363	2219
	91	NC	NC	NC	NC	347	90.2
Tmax(hr)	1	N/A	N/A	1	N/A	N/A	N/A
	43	N/A	24	N/A	N/A	0.5	0.25
	91	N/A	N/A	4	NC	9	0.5

* The mean value below the LOQ (50 pg/ml) are presented as 0
** Not applicable
# Not calculated

Tissue Distribution:

The following studies were not conducted under GLP.

Three single-dose and one multiple-dose tissue distribution study were conducted in male rats treated by intravenous, oral or intranasal route of administration. Excretions of radioactive-labeled SCH 32088 to rat placenta and milk were also determined following a single oral dose administration. Finally, biliary excretion and enterohepatic circulation of SCH 32088 were studied in rats.

10. Tissue distribution studies in rats following a single dose administration (D-24338, D-24339 and P-5367 in Vol. 149)

Three tissue distribution studies were conducted in rats following administration of a single dose of radio-labeled SCH 32088. Radioactivity was measured. The designs of these studies are briefly summarized in the following table:

Report # (time)	D-24338 (8/90)	D-24339 (8/90)	P-5367 (3/89)
Animal	♂ SD rats	♂ SD rats	♂ SD rats
Laboratory			Schering Co.
Test Article	^{3}H-SCH 32088	^{3}H-SCH 32088	^{14}C-SCH 32088
Batch #	23650-119-9	23650-119-9	Unknown
Route	Intravenous	Oral	Intranasal
Dose level	0.12 mg/kg	0.12 mg/kg	240 µg/kg
Blood sampling	0.5, 3, 6, 24, 72, 168 hr postdosing. *	0.5, 3, 6, 24, 72, 168 hr postdosing. *	0.5, 2, 4, 24, 72, 120 hr postdosing.**
Tissue sampling	0.5, 3, 6, 24, 72, 168 hr postdosing. *	0.5, 3, 6, 24, 72, 168 hr postdosing. *	0.5, 2, 4, 24, 72, 120 hr postdosing.**
Urine & Feces	24, 48, 72, 96, 120, 144, 168 hr postdosing. *	24, 48, 72, 96, 120, 144, 168 hr postdosing. *	24, 72, 120 hr postdosing.*
Assays	Liquid Scintillation Counter	Liquid Scintillation Counter	Liquid Scintillation Counter

* n=5 rat sex time point
** n= 6 rats time point
@ Plasma samples were collected from males or females at Weeks 1, 7 and 12/13 and then pooled together

1. After intravenous administration (D-24338), blood radioactivity was decreased throughout the study period. The highest concentrations of radioactivity were observed in the small and large intestine at 3 and 6 hr postdosing, respectively. (See table below.) It suggests that biliary excretion of SCH 32088 and/or its metabolites. At 24 hr postdosing, radioactivity recovered from feces and urine was 78% and 3% of the administered dose, respectively.

2. After oral administration (D-24339). ^{3}H-SCH 32088 was rapidly distributed throughout the body. At 24 postdosing, 91.5% and 2.9% radioactivities were recovered from feces and urine, respectively. The highest tissue concentrations of radioactivity were found in the stomach, liver, small and large intestines. A consistent secondary increase in the radioactivity at 6 hr postdosing may be due to biliary recirculation of SCH 32088 and/or its metabolites.(See table below.)

	TIME (h)											
TISSUE/ORGAN	0.5		3.0		6.0		24.0		72.0		168.0	
Stomach	37.3035	(34)	48.6144	(68)	8.6126	(19)	0.7788	(176)	0.0431	(39)	0.0168	(36)
Small Intestine	39.4191	(31)	42.3985	(41)	15.0998	(68)	1.7862	(56)	0.1391	(33)	0.0452	(45)
Large Intestine	5.0983	(219)	1.8319	(166)	24.2994	(33)	7.4188	(62)	1.0391	(118)	0.0469	(39)
Liver	7.6788	(84)	2.4257	(65)	4.3834	(34)	1.9351	(37)	0.1884	(7)	0.2499	(65)
Kidney	0.1921	(73)	0.0998	(36)	0.0842	(28)	0.0435	(14)	0.0088	(16)	0.0116	(34)
Adrenals	0.0000	(00)	0.0006	(00)	0.0012	(61)	0.0000	(65)	0.0000	(35)	0.0000	(00)
Pituitary Gland	0.0000	(00)	0.0007	(85)	0.0001	(39)	0.0000	(286)	0.0000	-	0.0000	-
Thyroid	0.0000	(31)	0.0000	(00)	0.0000	(36)	0.0001	(00)	0.0001	(17)	0.0000	-
Mesenteric Lymph	0.0000	(00)	0.0000	(00)	0.0004	(79)	0.0015	(82)	0.0004	(16)	0.0000	(00)
Pancreas	0.0057	(00)	0.0001	(00)	0.0009	(41)	0.0028	(18)	0.0004	(36)	0.0013	(00)
Lungs	0.0168	(00)	0.0001	(00)	0.0010	(00)	0.0111	(21)	0.0003	(36)	0.0003	(00)
Urinary Bladder	0.0032	(91)	0.0144	(37)	0.0012	(00)	0.0004	(00)	0.0002	(21)	0.0002	(00)
Harderian Gland	0.0004	(145)	0.0010	(69)	0.0001	(00)	0.0004	(00)	0.0000	(00)	0.0000	(00)
Heart	0.0000	(00)	0.0000	(00)	0.0001	(51)	0.0004	(78)	0.0000	(00)	0.0016	(39)
Spleen	0.0034	(00)	0.0007	(00)	0.0000	(00)	0.0001	(17)	0.0000	(00)	0.0010	(00)
Gland	0.0158	(102)	0.0004	(00)	0.0073	(45)	0.0009	(00)	0.0000	(00)	0.0000	(00)
Cervical Lymph	0.2069	(37)	0.1089	(00)	0.2116	(17)	[illegible]	[illegible]	0.1160	(11)	0.0018	(00)
Prostate	0.0000	(00)	0.0000	(00)	0.0010	(00)	0.0000	(00)	0.0000	(00)	0.0000	(00)
Seminal Vesicle	0.0000	(00)	0.0000	(00)	0.0004	(00)	0.0001	(00)	0.0010	(00)	0.0013	(00)
Thymus	0.0051	(00)	0.0000	(00)	0.0004	(00)	0.0004	(00)	0.0000	(00)	0.0000	(00)
Ovary	0.0003	(00)	0.0007	(00)	0.0009	(00)	0.0003	(00)	0.0000	(00)	0.0000	(00)
Testis	0.0011	(00)	0.0000	(00)	0.0011	(00)	0.0012	(00)	0.0012	(00)	0.0000	(00)
Eye	0.0011	(67)	0.0000	(00)	0.0010	(17)	0.0000	(00)	0.0000	(00)	0.0000	(00)
Thymus	0.0000	(00)	0.0000	(00)	0.0000	(00)	0.0004	(00)	0.0007	(00)	0.0000	(00)
Prostate	0.0000	(00)	0.0000	(00)	0.0000	(00)	0.0000	(00)	0.0000	(00)	0.0000	(00)
Brain	0.0044	(00)	0.0000	(00)	0.0000	(00)	0.0000	(00)	0.0002	(00)	0.0000	(00)
Carcass	2.1168	(36)	1.1000	(37)	0.0000	(00)	0.0713	(00)	0.0001	(00)	0.0000	(00)

Values represent group means (CV) where n = 5 except [illegible] where n = 4

[illegible] no aliquot taken

Note: Skin, fat and muscle values are not given in this table since these values are included in the carcass values

	TIME (h)											
TISSUE/ORGAN	0.5		3.0		6.0		24.0		72.0		168.0	
Small Intestine	38.7773	(00)	78.1127	(34)	12.2220	(19)	2.6037	(100)	0.1100	(39)	0.0433	(36)
Liver	7.4444	(74)	7.6609	(38)	6.4162	(30)	3.0164	(4)	1.0936	(00)	0.5341	(16)
Kidney	1.2243	(44)	0.4519	(17)	0.1775	(19)	0.0918	(40)	0.0379	(15)	0.0212	(19)
Adrenal	0.0175	(44)	0.0052	(24)	0.0023	(22)	0.0006	(34)	0.0002	(25)	0.0001	(46)
Pituitary	0.0017	(73)	0.0008	(20)	0.0003	(7)	0.0000	(132)	0.0000	-	0.0000	-
Harderian Gland	0.1104	(81)	0.0339	(24)	0.0108	(20)	0.0039	(34)	0.0013	(17)	0.0008	(23)
Pancreas	0.1721	(73)	0.0484	(22)	0.0173	(31)	0.0008	(41)	0.0004	(22)	0.0021	(7)
Mesenteric Lymph Node	0.0772	(93)	0.0251	(34)	0.0085	(43)	0.0025	(128)	0.0004	(11)	0.0002	(57)
Stomach	0.4018	(63)	0.0771	(76)	0.2508	(78)	0.4369	(138)	0.0179	(61)	0.1271	(117)
Thyroid	0.0039	(89)	0.0013	(10)	0.0009	(15)	0.0004	(33)	0.0001	(61)	0.0008	(137)
Lung	0.2113	(56)	0.1217	(5)	0.0331	(16)	0.0038	(41)	0.0163	(38)	0.0178	(88)
Cervical Lymph Node	0.0093	(73)	0.0048	(22)	0.0031	(29)	0.0004	(26)	0.0002	(32)	0.0002	(46)
Large Intestine	0.7488	(88)	1.3076	(99)	88.3731	(15)	5.7272	(51)	0.1618	(34)	0.0547	(77)
Spleen	0.0084	(76)	0.0047	(18)	0.0179	(22)	0.0079	(81)	0.0032	(16)	0.0027	(27)
Heart	0.1140	(62)	0.0298	(22)	0.0145	(20)	0.0004	(37)	0.0039	(11)	0.0021	(25)
Thymus	0.0066	(88)	0.0048	(27)	0.0017	(18)	0.0045	(75)	0.0008	(61)	0.0002	(204)
Prostate	0.0540	(78)	0.0257	(24)	0.0108	(19)	0.0000	(43)	0.0004	(204)	0.0000	-
Urinary Bladder	0.0099	(73)	0.0049	(20)	0.0024	(23)	0.0009	(33)	0.0003	(0)	0.0002	(14)
Seminal Vesicle	0.0064	(77)	0.0051	(27)	0.0021	(20)	0.0008	(31)	0.0001	(42)	0.0007	(61)
Gland	0.0474	(70)	0.0199	(20)	0.0135	(14)	0.0769	(11)	0.0004	(17)	0.0020	(63)
Testis	0.1220	(61)	0.0951	(23)	0.0017	(14)	0.0045	(17)	0.0136	(23)	0.0002	(28)
Eye	0.0076	(70)	0.0041	(28)	0.0025	(18)	0.0010	(16)	0.0009	(21)	0.0005	(37)
Brain	0.0424	(76)	0.0155	(24)	0.0089	(19)	0.0008	(23)	0.0014	(22)	0.0008	-
Carcass	48.4435	(60)	15.7687	(121)	3.3498	(22)	0.1681	(137)	0.0000	(00)	0.7098	(71)

Values represent group means (CV) where n = 5

Note: Skin, fat and muscle values are not given in this table since these values are included in the carcass values

3. At 0.5 hr after rats were treated intranasally with ^{14}C-SCH 32088 (P-5367), the highest radioactivity concentrations were found in the esophagus, trachea, nasal passage and mouth. Peak concentrations of radioactivity were then observed in the stomach, small intestine and large intestine at 2, 4, and 24 hr postdosing, respectively. This finding may be due to oral ingestion of the drug. Very little radioactivity was present in the lungs and other tissues. At 24 hr postdosing, 34.4% and 2.7% of the dosed radioactivity were recovered from the feces and urine, respectively. Approximately 50% of the radioactivity was excreted from the feces (49.9%) and urine (1.9%) at 120 hr postdosing. Results from this study demonstrated that drug-related radioactivity can be extensively distributed and rapidly eliminated following intranasal administration.

11. Tissue distribution and excretion of ^{14}C-SCH 32088 in male rats following a 21-day oral administration (P-5976, 5/96; Vol. 150)

Male SD rats were dosed orally with 0.6 mg/kg of ^{14}C-SCH 32088 suspension (Batch #: 32230-70-10) for 21 consecutive days. Control rats were treated with vehicle (0.4% methylcellulose) only. The study design is presented in the following table:

Group	Activity	Dosing Day	Time (hr) After Daily Dose
1 (n=99)	Blood Collection	1 3-6 8-13 15-20 21	0.5,1,2,3,4,8,48,96,120 24 24 24 0.5,1,2,3,4,8,48,96,120
2 (n=54)	Tissue Distribution and Blood Collection	1 7 14 21	1,3,8,12,24,72,168,240 24 24 1,3,8,12,24,72,168,240
3 (n=28)	Whole Body Autoradiography	1 7 14 21	1,8,24,72,168,240 24 24 1,8,24,72,168,240
4 (n=6)	Mass Balance	3-20	24 hr collection collection at 24 hr intervals to Day 21
5 (n=1)	Tissue Control	1	ca 24 hr
6 (n=1)	Whole Body Autoradiography Control	1	ca 24 hr

After treatment, plasma, tissues and carcasses were collected at several time intervals. Radioactivity was measured using a liquid scintillation spectrometer. Plasma radioactivity was examined by an enzyme immunoassay (EIA). Profiles of 14C-SCH 32088 and its metabolites were determined by HPLC.

The concentration of radioactivity in whole blood were consistently greater than those in plasma. Following a single dose, drug-related radioactivity was not detectable in plasma or blood. However, after a 21-day oral treatment, drug-related radioactivity was quantifiable in the plasma at 24 hr postdosing and in the blood at 240 hr postdosing. Pharmacokinetic parameters are presented below:

Pharmacokinetics of ^{14}C-SCH 32088-Derived Radioactivity in Plasma of Male Albino Rats Following a Single or 21 Consecutive Daily Oral Doses of ^{14}C-SCH 32088 (0.6 mg/kg/day)

Parameter (units)	Day 21[a]
Cmax (μg eq/g)	0.006
Tmax (hr)	1.5
$t_{1/2}$ (hr)	12.1
AUC(tf) (μg eq·hr/g)	0.085
AUC(I) (μg eq·hr/g)	0.130

a Drug-derived radioactivity not detectable following single dose (Day 1)

Following a single dose administration, most of the radioactivity was observed in the gastrointestinal tract. The liver also contained significant radioactivity. At 168 hr after the single dose, radioactivity was not found in any tissue or carcass.

At 24 hr following 7 or 14 consecutive doses, radioactivities in tissues were greater than that at 24 hr following a single daily dose. This suggests that the concentrations of tissue radioactivity were increased with the length of the exposure period. (See table below.)

Ratio Analysis of Mean Concentrations (C24hr) of Radioactivity in Tissues of Male Albino Rats Following a Single or Multiple Oral Doses of ^{14}C-SCH 32088 (0.6 mg/kg/day)

Tissue	µg equivalents/g			Ratio		
	Day 1	Day 7	Day 14	Day 7:1	Day 14:1	Day 14:7
Carcass	NC	NC	NC	NC	NC	NC
Skin	NC	NC	NC	NC	NC	NC
Plasma	NC	NC	NC	NC	NC	NC
Blood	NC	0.006	0.008	NC	NC	1.5
Eyes	NC	NC	NC	NC	NC	NC
Bone Mar.	NC	NC	NC	NC	NC	NC
Brain	NC	NC	NC	NC	NC	NC
Epidid. Fat	NC	NC	NC	NC	NC	NC
Perit. Fat	NC	NC	NC	NC	NC	NC
Subcut. Fat	NC	NC	NC	NC	NC	NC
Brown Fat	NC	NC	NC	NC	NC	NC
Skel. Musc.	NC	NC	NC	NC	NC	NC
Heart	NC	NC	NC	NC	NC	NC
Lungs	NC	NC	0.002[a]	NC	NC	NC
Spleen	NC	NC	NC	NC	NC	NC
Liver	0.013	0.094	0.093	7.2	7.2	1.1
Kidney	NC	0.011	0.017	NC	NC	1.5
Stomach	NC	0.010	0.015	NC	NC	1.5
Stom. Cont	0.001[a]	0.010[b]	0.008[b]	10.0	8.0	0.8
Lge Intest.	0.008	0.022	0.057	2.4	6.3	2.6
L.I. Cont	0.073	0.117	0.215	1.6	2.9	1.8
Small Int.	0.009	0.009	0.020	1.0	2.2	2.2
S.I. Cont	0.006	0.009	0.019	1.5	3.2	2.1
Hypophysis	NC	NC	NC	NC	NC	NC
Thyroid	NC	NC	NC	NC	NC	NC
Thymus	NC	NC	NC	NC	NC	NC
Saliv. Glan	NC	NC	NC	NC	NC	NC
Testis	NC	NC	NC	NC	NC	NC
Harder. Gl.	NC	NC	NC	NC	NC	NC
Pancreas	NC	NC	0.002[a]	NC	NC	NC
Adrenals	NC	NC	NC	NC	NC	NC
Bladder	0.006[a]	NC	NC	NC	NC	NC
Cerv. Lymp	NC	NC	NC	NC	NC	NC
Mes. Lymp	NC	0.002[a]	0.003[a]	NC	NC	1.5
Epididymis	NC	NC	NC	NC	NC	NC
Prostate	NC	NC	NC	NC	NC	NC
Semin. Ves.	NC	NC	NC	NC	NC	NC

(24hr Concentration measured 24 hours after dose
[a] Two samples below the limit of detection; 0 used in calculation of mean
[b] One sample below the limit of detection; 0 used in calculation of mean
NC Could not be obtained from existing data
ND All samples below the limit of detection (< 2 x background)

After 21 consecutive oral doses, the highest concentration was present in the gastrointestinal tract. In comparison with a single dose, Cmax and AUC values for liver and kidneys were increased following 21 consecutive doses. Except for the liver, kidney and gastrointestinal tract, the concentrations of radioactivity were also elevated in other tissues following 21-day treatment, including skin, bone, lungs, spleen and pancreas. The terminal phase half-life of the drug-derived radioactivity in plasma, estimated after 21 days of dosing, was approximately 12 hr. (See the tables below.)

Cmax, Tmax and Ratio Analysis of Maximum Mean Concentrations (Cmax) of Radioactivity in Tissues of Male Albino Rats Following a Single Dose or 21 Consecutive Daily Oral Doses of ^{14}C-SCH 32088 (0.6 mg/kg/day)

	Day 1		Day 21		Ratio
Tissue	Cmax µg equiv/g	Tmax hr	Cmax µg equiv/g	Tmax hr	Cmax Day 21:1
Carcass	0.026[a]	12	0.007[b]	24	0.3
Skin	ND	NC	0.015[a]	3	0.6
Plasma	ND	NC	0.006	3	0.3
Blood	ND	NC	0.021	24	0.8
Eyes	0.001[a]	6	ND	NC	NC
Bone Mar.	ND	NC	0.004[a]	3	0.2
Brain	ND	NC	ND	NC	NC
Epidid. Fat	ND	NC	ND	NC	NC
Pert. Fat	ND	NC	ND	NC	NC
Subcut. Fat	ND	NC	ND	NC	NC
Brown Fat	ND	NC	ND	NC	NC
Skel. Musc.	ND	NC	ND	NC	NC
Heart	0.006[a]	12	0.004[a]	3	0.7
Lungs	ND	NC	0.012	3	0.5
Spleen	ND	NC	0.008	3	0.3
Liver	0.056	6	0.225	3	4.0
Kidney	0.009	6	0.038	3	4.2
Stomach	2.63	1	1.30	1	0.5
Stom. Cont.	2.73	1	2.30	1	0.8
Upp Intest	0.232	6	0.055	6	0.2
L.I. Cont	3.09	6	4.49	6	1.5
Small Int	1.09	3	2.21	1	2.0
S.I. Cont	3.89	3	2.84	1	0.7
Hypophysis	ND	NC	ND	NC	NC
Thyroid	ND	NC	ND	NC	NC
Thymus	ND	NC	ND	NC	NC
Saliv. Glan	ND	NC	0.005[b]	3	0.5
Testes	ND	NC	ND	NC	NC
Harder. Gl.	ND	NC	ND	NC	NC
Pancreas	ND	NC	0.010	3	0.5
Adrenals	0.025[a]	24	ND	NC	NC
Bladder	0.008[a]	6	0.002[a]	3	0.3
Cerv. Lymph	ND	NC	0.010[a]	3	0.5
Mes. Lymph	0.019	6	0.003	3	0.2
Epididymis	ND	NC	ND	NC	NC
Prostate	ND	NC	ND	NC	NC
Semin. Ves.	ND	NC	ND	NC	NC

ND All samples below the limit of detection (< 2 x background)
NC Could not be obtained from existing data
[a] Two samples below the limit of detection; 0 used in calculation of mean
[b] One sample below the limit of detection; 0 used in calculation of mean

Area Under the Tissue Concentration vs Time Curves, Ratio Analysis and Estimated Half-Life of Radioactivity in Tissues of Male Albino Rats Following a Single Oral Dose for 21 Consecutive Doses of ^{14}C-SCH 32088 (0.6 mg/kg/day)

Tissue	Day 1 AUC(tf) µg equiv-hr/g	Day 1 Half-Life Hr	Day 21 AUC(tf) µg equiv-hr/g	Day 21 Half-Life Hr	Ratio AUC(tf) Day 21:1
Carcass	0.083	NC	0.089	NC	1.2
Skin	NC	NC	0.474	NC	NC
Plasma	NC	NC	0.086	121	NC
Blood	NC	NC	3.62	NC	NC
Eyes	0.002	NC	NC	NC	NC
Bone Mar.	NC	NC	0.016	NC	NC
Brain	NC	NC	NC	NC	NC
Epidid. Fat	NC	NC	NC	NC	NC
Perit. Fat	NC	NC	NC	NC	NC
Subcut. Fat	NC	NC	NC	NC	NC
Brown Fat	NC	NC	NC	NC	NC
Skel. Musc.	NC	NC	NC	NC	NC
Heart	0.018	NC	0.004	NC	NC
Lungs	NC	NC	0.959	6	NC
Spleen	NC	NC	0.546	NC	NC
Liver	1.55	16.2	16.2	23.5	10.5
Kidney	0.073	NC	3.95	NC	54.1
Stomach	5.82	5.58	5.58	NC	1.0
Stom. Cont.	8.17	8.54	8.54	NC	1.0
Up Intest	3.06	10.2	10.2	NC	3.3
LI Cont	39.2	58.5	58.5	NC	1.5
Small Int	5.94	10.3	10.3	NC	1.7
S.I. Cont	17.4	16.8	16.8	NC	1.0
Hypophysis	NC	NC	NC	NC	NC
Thyroid	NC	NC	NC	NC	NC
Thymus	NC	NC	NC	NC	NC
Salv. Glan	NC	NC	0.005	NC	NC
Testes	NC	NC	NC	NC	NC
Harder. Gl.	NC	NC	NC	NC	NC
Pancreas	NC	NC	0.410	NC	NC
Adrenals	0.695	NC	NC	NC	NC
Bladder	0.048	NC	0.003	NC	NC
Cerv.Lymph	NC	NC	0.010	NC	NC
Mes. Lymph	0.116	NC	2.12	NC	18.2
Epididymis	NC	NC	NC	NC	NC
Prostate	NC	NC	NC	NC	NC
Semin. Ves.	NC	NC	NC	NC	NC

NC Could not be obtained from existing data

HPLC profiles showed that the metabolism of SCH 32088 in rats was qualitatively similar after either single or multiple oral doses. Unchanged SCH 32088 and moderately polar metabolites similar in retention to 6β-hydroxymometasone furoate and 21-hydroxymometasone were detected in the plasma collected on Days 1 and 21. Due to the small sample quantity, SCH 32088 and metabolites were not studied quantitatively.

Radioactivity was detectable in urine until 22 days postdosing. However, radioactivity was measurable in feces until 26 days postdosing. (See table below.) Most of the drug-related radioactivity was recovered in the feces (89.3%) and less than 0.4% of the dose was recovered in

urine. At the end of the study, total recovered dose was approximately 90% of administered dose. (See table below.)

Mean Daily Recovery (%) of Radioactivity in Excreta of Male Albino Rats Following Once Daily Oral Administration of ^{14}C-SCH 32088 (0.6 mg/kg/day) for 21 Consecutive Days

	Percent of Administered Dose			
	Urine		Feces	
Study Day	Mean	%CV	Mean	%CV
2	0.01	89	3.37	2
3	0.01	22	3.38	8
4	0.01	28	3.63	4
5	0.01	21	3.84	6
6	0.01	27	4.05	7
7	0.01	37	4.04	6
8	0.01	38	3.87	4
9	0.01	18	3.81	2
10	0.02	21	4.15	9
11	0.02	26	4.17	2
12	0.02	16	4.40	5
13	0.02	28	4.74	4
14	0.02	27	4.05	13
15	0.02	30	4.53	2
16	0.01	27	4.21	8
17	0.02	36	4.60	6
18	0.02	33	4.30	8
19	0.02	31	4.89	2
20	0.02	30	4.87	4
21	0.02	24	5.02	3
22	0.02	29	5.19	2
23	0	27	0.24	34
24	0	NC	0.02	32
25	0	NC	0.01	16
26	0	NC	0.01	39
27	0	NC	0	NC
28	0	NC	0	NC
29	0	NC	0	NC
30	0	NC	0	NC
31	0	NC	0	NC

Results are expressed as a percentage of the total dose administered during the 21 consecutive days of dosing
Results represent mean and %CV where n = 6
%CV Coefficient of variation expressed as a percent
NC Not calculated

12. Distribution and excretion of ^{14}C-SCH 32088 into rat placenta following a single oral dose (P-6000, 5/96; Vol. 151)

Femals SD rats (n=2 or 3/interval) on Day 18 pregnancy were treated orally with a single dose of ^{14}C-SCH 32088 suspension (Batch #: 32230-97-30) at 0.6 mg/kg. Blood and tissue samples were collected at 0, 1, 4, 12, 24 and 48 hr postdosing. Urine, feces and cage wash fluid were collected only from the rats sacrificed at 48 hr postdosing. Radioactivities were determined by using Liquid Scintillation Spectrometry. (LOQ = 0.18 ng eq/g)

Plasma radioactivity in dams was detectable until 24 hr postdosing, but not at 48 hr postdosing. PK parameters in dams are presented in the following table:

Parameters	Values
Cmax (ng eq/g)	4.27
Tmax (hr)	4
AUC (0-24hr:ng/eq.hr/ml	63.8.1

In tissues, most of the radioactivity was found in the gastrointestinal tract and its contents. Lower levels of radioactivity were observed in the liver, uterus and kidneys. Radioactivity concentrations in the placenta, ovaries and amnions were just above the LOQ, indicating that SCH 32088 and/or its metabolites are able to cross the placenta. (See table below)

Tissues	Mean Concentration ng eq/g (%CV)[a]									
	Time (hr)									
	1		4		12		24		48	
Liver	8.76	(42)	36.8	(4)	24.4	(83)	20.7	(83)	10.8	(20)
Lg Intestine	16.7	(122)	3.82	(83)	80.3	(72)	8.72	(32)	1.34	(20)
Lg Int Contents	1.37	–[b]	65.6	(166)	1780	(38)	46.3	(37)	81.5	(102)
Sm Intestine	522	(98)	282	(61)	24.3	(66)	14.4	(42)	0.880	(8)
Sm Int Contents	7230	(9)	3360	(38)	181	(122)	89.7	(82)	3.40	(8)
Stomach	891	(58)	384	(82)	4.21	(119)	8.23	(131)	0.153	(87)
Stomach Contents	7420	(80)	8280	(36)	79.3	(132)[c]	382	(166)	ND	–
Cecum	9.83	(81)	54.2	(142)	38.4	(46)	3.85	(37)	2.72	(41)
Cecum Contents	28.1	(66)	3340	(78)	1410	(32)	99.0	(70)	37.5	(46)
Urinary Bladder	1.01	(173)	8.88	(38)	4.15	(84)	0.626	(173)	ND	–
Kidneys	1.10	(46)	3.11	(10)	1.48	(82)	1.84	(66)	0.788	(20)
Lungs	ND	–	0.737	(23)	0.442	(87)	46.0	(173)	2.81	(173)
Heart	ND	–	0.228	(173)	0.178	(173)	ND	–	ND	–
Brain	ND	–	ND	–	ND	–	ND	–	ND	–
Mammary Glands	0.071	(173)	1.20	(18)	0.888	(46)	0.188	(87)	ND	–
Uterus	1.48	(166)	1.43	(13)	1.33	(82)	0.617	(20)	0.180	(87)
Placentas	0.877	(110)	1.73	(37)	1.88	(88)	0.638	(34)	0.244	(13)
Amnions	4.58	(173)	1.98	(82)	2.01	(84)	2.25	(48)	1.16	(46)
Amniotic Fluid	ND	–	ND	–	ND	–	ND	–	ND	–
Ovaries	1.87	(25)	4.88	(4)	3.22	(48)	1.56	(40)	ND	–
Blood	1.22	(41)	3.42	(5)	3.37	(47)	2.86	(62)	1.88	(13)
Plasma	1.10	(40)	4.27	(7)	3.05	(50)	1.27	(33)	ND	–

a Means based on n=3
b Mean calculated on n=1 due to failed duplicate test
c Mean and %CV calculated on n=2 due to failed duplicate test
ND = Samples below the limit of quantitation (<2 X background)
– Not calculated

Radioactivity was also detectable in fetal liver, brain, lungs, blood and body. Radioactivity in the fetal liver was decreased over time. Compared with the dams, radioactivity in fetal liver was lower. However, radioactivity in fetal brain and lungs was higher than the levels in the dams.

Table 7 Mean Concentration of Radioactivity in Tissues of Fetal Rats Following a Single Oral Dose of ^{14}C-SCH 32088 to 18-Day Pregnant Rats

Tissue	Concentration (ng eq/g) (%CV)									
	1 hr		4 hr		12 hr		24 hr		48 hr	
Liver	0.741	(173)	1.83	(8)	1.23	(87)	0.405	(129)	0.044	(173)
Heart	ND		ND		ND		ND		ND	
Kidney	ND		ND		ND		ND		ND	
Brain	ND		ND		1.032	(173)	ND		ND	
Blood	ND		ND		ND		0.414	(173)	ND	
Lung	ND		ND		0.282	(173)	0.142	(173)	ND	
Carcass	0.813	(173)	ND		0.379	(173)	ND		ND	

ND = Samples below the limit of quantitation (< 2x background, ~ 0.02 ng eq/g)

In the dams, most of the administered radioactivity was excreted in the feces (75.9%). Only a small portion of dosed radioactivity was recovered in the urine (1.7%).

13. Excretion of ^{14}C-SCH 32088 in rat milk following a single oral dose administration (P-6010, 5/96; Vol. 151)

Lactating rats (n=3/interval; Mean bodyweight= 396g) at 14-day post-partum were treated orally with 0.6 mg/kg of ^{14}C-SCH 32088 suspension (Batch No. 32230-97-30). Plasma and milk samples from the dams were collected at 0, 0.5, 1, 4, 24, and 72 hr postdosing. Blood and plasma samples were also obtained at each time-point from 6 pups/dam selected at random from individual litters. Radioactivity was measured by using a liquid scintillation analyzer. Metabolite profiles of SCH 32088 were analyzed using HPLC.

Plasma radioactivity was observed in the dam for up to 24 hr postdosing, but no radioactivity was detected in the plasma of the pups. Radioactivity was detected in the milk of 1/3 rats at 0.5 and 1 hr postdosing, but in all 3 rats at 4 hr postdosing. Pharmacokinetic analysis of plasma and milk radioactivity is presented in the following table:

Parameter		Mean Plasma Radioactivity	Mean Milk Radioactivity
Cmax	ng equiv/ml	3.2	2.6
Tmax	hr	4	4
AUC(0-12 hr)	ng equiv·hr/ml	31.6	14.8
AUC(tf)	ng equiv·hr/ml	47.3	4.65
tf	hr	24	4

Based upon the average daily milk consumption (2 ml/pup) and the maximum milk concentration observed (2.5 ng eq/ml), daily drug exposure to each pup can be calculated as the following:

$$\frac{2.5 \text{ ng eq/ml} \times 2 \text{ ml/pup}}{0.6 \text{ mg/kg} \times 0.396 \text{ kg}} \times 100\% = 0.002\%$$

Based on the above calculation, the daily dose for each pup would be approximately 0.002% of the daily dose administered to the dam. If a pup at birth was 6 g, the daily dose would be 4.75 ng eq/per pup (0.00792 mg/kg). Therefore, only 1.3% of the administered SCH 32088 was given to each pup.

14. Biliary excretion and enterohepatic circulation in rats following a single oral dose administration of ^{14}C-SCH 32088 (P-6009, 6/95; Vol. 151)

Two groups of fasted and bile-duct-cannulated male SD rats (n=4/group) were used in this study. To test biliary excretion, rats in Group 1 (donors) were treated PO with a single dose of ^{14}C-SCH 32088 suspension (Batch # 32230-97-30). To assess enterohepatic circulation, rats (recipients) in Group 2 were treated intraduodenally (ID) with the bile collected from Group 1 rats. The study design is presented in a table below.

Group	Treatments	Route	Dose
Donor	^{14}C-SCH 32088	PO	0.6 mg/kg
Recipient	0-24 hr pooled donor bile	ID	4.5 ml/rat

After treatment, bile was collected at 0-2, 2-4, 4-6, 6-8, 8-24 and 24-48 hr, and urine and feces were collected up to 48 hr postdosing. Gastrointestinal tissues and contents, and carcasses were pooled at 48 hr postdosing. Radioactivities in all samples were assayed by liquid scintillation counter. Metabolites of SCH 32088 in the bile and fecal samples were analyzed using both liquid scintillation counter and HPLC.

As demonstrated in the following table, approximately 14% of the oral-dosed ^{14}C-SCH 32088 was excreted through the bile. About 27% of the absorbed dose was reabsorbed and underwent enterohepatic circulation. In both groups, drug-related radioactivity was mainly eliminated through the feces. Approximately 0.5 and 3% of radioactivity were excreted in the urine of donor and recipient groups, respectively.

Excretion of radioactivity: % of Dosed ^{14}C-SCH 32088 (Mean(%CV)

Samples	Donor Group	Recipient Group
Bile	13.68 (37)	27.11 (7)
Urine	0.48 (43)	3.12 (34)
Feces	60.71 (29)	56.09 (7)
GI Tract	8.13 (121)	9 (66)
Carcass	1.65 (124)	0 (0)
Total	84.65 (6)	95.32 (10)

SCH 32088 was found in fecal samples of the donors, but not in the recipient group. In the bile samples collected from the donor and recipient groups, radioactivity was present in several peaks, including those coincident with standards for 21-hydroxy mometasone, 6β-hydroxy mometasone furoate and mometasone. However, SCH 32088 was not observed in any bile sample, suggesting that absorbed SCH 32088 was completely metabolized.

Protein Binding and in vitro Drug Metabolism:

These studies were not conducted under GLP.

15. In vitro protein binding of SCH 32088 in rat, mouse, rabbit, dog and human plasma (P-6004, 7/95; Vol. 149)

Drug-free plasma samples from rat, mouse, rabbit, dog and human were spiked with ^{3}H-SCH 32088 (Batch # 30329-46-10) at therapeutically relevant concentrations of 5 to 500 ng/ml plasma. After the spiked plasma samples were prepared, liquid scintillation radiometry (LOQ = 250 ng/ml) was used to determine the extent of protein binding. The means of plasma protein binding of ^{3}H-SCH 32088 in each species are shown in the following table:

SCH 232088 (ng/ml)	Rat		Mouse		Rabbit		Dog		Human (Frozen)		Human (Fresh)	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
500	99.0	0.10	99.4	0.03	98.4	0.11	99.6	0.04	99.1	0.07	99.5	0.06
250	98.9	0.07	99.5	0.05	98.4	0.02	99.6	0.02	99.0	0.36	99.3	0.05
100	98.9	0.11	99.5	0.04	98.4	0.20	99.6	0.01	99.2	0.12	99.3	0.02
25	98.7	0.11	99.2	0.09	98.2	0.21	99.6	0.07	99.0	0.04	99.2	0.06
5	BQL	-	BQL	-	97.2	0.28	BQL	-	BQL	-	BQL	-

* BQL - Below quantifiable limits

Several reference compounds (chloramphenicol, lidocaine, warfarin and indomethacin) were

utilized as positive controls for system validation; the values obtained were within the ranges previously reported for each compound.

In summary of the above finding, ^{3}H-SCH 32088 was highly bound to rat (98.9%), mouse (99.4%), rabbit (98.3%), dog (99.6%) and human (99.1%) plasma proteins. There was no significant difference for the protein binding potentials at 100 to 500 ng/ml.

16. In vitro metabolism in pulmonary and hepatic tissues (P-5642, 8/92; Vol. 152)

To determine SCH 32088 metabolisms in rat or mouse pulmonary and hepatic tissues, ^{3}H-SCH 32088 (Batch #: 23650-49-7) was incubated in vitro with the supernatant of lung and liver fractions. After culture, the supernatant was analyzed using HPLC-LC/MS. Each incubation was divided into three groups. Group I represented the live protein, 30 min incubations which were analyzed to identify metabolic products. Groups II (Live protein + 0 min incubation) and III (denatured protein + 30 min incubation) were used as controls. Only the peaks in Group I (but not in other groups) were identified as the metabolites. If a metabolic product appeared in all groups, it was considered an artifact.

Results showed that no metabolism of ^{3}H-SCH 32088 was found in rat or mouse lung S9 incubations. Since SCH 32088-9, 11-epoxide was found in all mouse incubation groups, it was considered to be an artifact. (See table below.)

LUNG S9 METABOLIC PROFILE

(Mean (%CV) percent of total peak area)

Incubation	Epoxide*	SCH 32088
Rat Lung		
Ia**	-	99.02 (1.7)
Ib	-	100
IIa	-	100
IIb	-	100
IIIa	-	100
IIIb	-	100
Mouse Lung		
Ia	2.5 (12)	97.5 (0.3)
Ib	1.2 (21)	98.8 (0.3)
IIa	2.9 (75)	97.1 (2)
IIb	1.1 (25)	98.9 (0.3)
IIIa	2.8 (4)	97.2 (0.1)
IIIb	1.2 (3)	98.8 (0)

Epoxide*: SCH 32088-9,11-epoxide

In rat liver S9 incubation, SCH 32088 was extensively metabolized. Approximately 40% of SCH 32088 (0.05mM substrate) was converted to 6-hydroxy SCH 32088. Mometasone and two unknown metabolites (UK1 and UK2) were also detected. In mouse liver, 6-hydroxylation, ester hydrolysis and metabolism to an unidentified product were observed. (See table below)

LIVER S9 METABOLIC PROFILE

(Mean (%CV) percent of total peak area)

Incubation	6-OH*	UK1	Mometasone	Epoxide	UK2	SCH 32088
Rat Liver						
Ia**	38.5 (3)	0.8 (24)	0.7 (42)	1.9 (20)	2.1 (18)	55.9 (3)
Ib	5.1 (4)	0.3 (15)	0.3 (9)	0.7 (6)	0.3 (18)	93.5 (0.3)
IIa	–	–	–	0.7 (12)	–	99.3 (0.1)
IIb	–	–	–	0.5 (4)	–	99.5 (0.02)
IIIa	–	–	–	2.2 (8)	–	97.8 (0.2)
IIIb	–	–	–	0.9 (15)	–	99.1 (0.1)
Mouse Liver						
Ia	3.2 (9)	1.0 (31)	0.8 (5)	1.9 (2)	–	93.0 (0.6)
Ib	1.4 (17)	0.3 (26)	0.5 (12)	1.5 (18)	–	96.2 (0.4)
IIa	–	–	–	2.6 (76)	–	97.4 (2)
IIb	–	–	–	1.3 (12)	–	98.7 (0.2)
IIIa	–	–	–	2.7 (23)	–	97.3 (0.6)
IIIb	–	–	–	1.2 (5)	–	98.8 (0.1)

6-OH*: 6β-Hydroxy Mometasone Furoate
UK1: Unknown 1
Epoxide: SCH 32088-9,11-epoxide
UK2: Unknown 2
a**: 0.05 mM substrate concentration
b: 0.50 mM substrate concentration
I: live protein, 30 min incubation
II: live protein, 0 min incubation
III: denatured protein, 30 min incubation

The above results showed that SCH 32088 in rats or mice was extensively metabolized by liver S9, but not by lung S9 system in vitro. This result can be attributed to low concentrations of metabolic enzymes in the lungs in comparison with the livers.

17. Other studies

1) The following studies were briefly summarized in the following table:

Study	Report No./ Labs	Animals/sex group (Batch #)	Method	SCH32088 Daily dose	AUC (pg.hr/ml) ♂/♀
Rat: 14-day nose-only inhalation (dry powder/ lactose)		16 (25387-023)	HPLC*	♂: 4.9 µg/kg ♀: 4.5, µg/kg	824**
				♂: 17 µg/kg ♀: 16 µg/kg	4293**
Young rat: 1-mon oral study	P-6045/Schering, Lafayette, NJ	16 (93-MMF-DDPX-01)	HPLC*	♂ & ♀: 0.5 µg/kg	AUC (Day 1) 133/162; AUC (Day 30) ND/ND@
				♂ & ♀: 5 µg/kg	AUC (Day1) 125/356; AUC (Day 30) ND@/16
Young dog: 1-mon oral study	P-6008 /Schering, Lafayette	5 (92-MMF-DDPX-01)	HPLC	♂ & ♀:0.15, µg/kg	(Day 26) ND/ND@
				♂ & ♀: 0.6 µg/kg	(Day 26) 1034/1849
Dog: 3-wk oral study	P- 6045/ Schering	4 ♂ only (93-MMF-DDPX-01)	HPLC*	600 µg/kg	Plasma SCH 32088 was below the LOQ

*LOQ = 10 to 50 pg/ml ** Only mean AUC from both males and females were provided
@ND Plasma SCH32088 was either not detectable or below LOQ
* In this study, the dogs in the low-dose group were treated inhalationally at 20 µg/kg; plasma drug concentration in this group was below the quantifiable level

2) The following studies were conducted by Schering-Plough between 1992 and 1995. Pharmacokinetic parameters in these studies were measured by using the unacceptable EIA technique.

Study	Report No./ Labs.	Method	Conclusion
Rat: 3-mon nose-only inhalation (powder)	P-5836/ & Schering	EIA	Invalid study
Rat: 3-mon nose-only inhalation (MDI)	P-5737/ & Schering	EIA	Invalid study
Rat: 3-mon nose-only inhalation (MDI)	P-5738/ & Schering	EIA	Invalid study
Beagle Dog: 14-day mouth-only inhalation (dry powder/ lactose)	P-6078/ & Schering	EIA	Invalid study
Beagle Dog: 3-month mouth-only inhalation (dry powder/ lactose)	P-5837/ & Schering	EIA	Invalid study
Mouse: 1-mon nose-only inhalation (MDI)	P-5739/ & Schering	EIA	Invalid study
Mouse: 1-mon oral study	P-5967/ Schering, Lafayette	EIA	Invalid study
Beagle Dog: 4-wk oral inhalation (powder)	P-5994 & Schering	EIA	Invalid study
Single IP dose in mice	P-5486/Schering	EIA	Invalid study
Single PO and IV dose study in mice	P-5494/Schering	EIA	Invalid study
Single dose inhalation in mice	D-26298/Schering	EIA	Invalid study
Single PO and SC dose study in dog	P-6001/Schering	EIA	Invalid study
Single dose PO and IV study in dog	P-6001/Schering	EIA	Invalid study

CARCINOGENICITY STUDIES

1. Two-year nose-only inhalation carcinogenicity study in rats (Report #: P-6005; Study #: 88050; 5/96; Vol. 119)

2. Two-year nose-only inhalation carcinogenicity study in mice (P-6006; Study #: 88051; 5/96; Vol. 119)

Laboratory: GLP: Yes

Study Date: July 30, 1992- May 15, 1996

Inhalational carcinogenicity studies in rat and mouse were previously reviewed. The dose levels selected in rats were based on the MTD obtained from 3- and 6-month inhalational toxicology studies. When mice were treated inhalationally with SCH 32088 for 3 months, mortality was present in the 0.5 and 4.0 μg/L groups, but steroid-like toxicities were only found in the 4.0 μg/L group. The designs of both rat and mouse carcinogenicity studies were previously accepted by the agency. The dose levels used for the studies are present in the following 2 tables:

Dose Levels used in Rats		
Concentration of SCH 32088	Predicted Daily Dose (μg/kg/day)	Predicted Daily Dose(μg/m² body surface #)
0 (Filtered Air)	0	0
0 (Vehicle *)	0	0
0.25 (±0.03) μg/L	9	53.1
0.5 (±0.05) μg/L	17	100.3
1.0 (±0.1) μg/L	34	200.6
2.0 (±0.2) μg/L	67	395.3

A conversion factor of 5.9 was used to convert mg/kg to mg/m²

Dose Levels used in Mice		
Concentration of SCH 32088	Predicted Daily Dose (μg/kg/day) for ♂/♀	Predicted Daily Dose (μg/m² body surface #) for ♂/♀
0 (Filtered Air)	0/0	0/0
0 (Vehicle)	0/0	0/0
0.25 (±0.03) μg/L	26/20	78/60
0.5 (±0.05) μg/L	51/40	153/120
1.0 (±0.1) μg/L	102/80	306/240
2.0 (±0.2) μg/L	204/160	612/480

A conversion factor of 3.0 was used to convert mg/kg to mg/m².

In these studies, both rats and mice were exposed to aerosolized SCH 32088. Survival rates in both species were acceptable. The death rates were not tumor-related. The causes of death were mainly attributed to the non-neoplastic changes.

Most clinical abnormalities (including clinical signs, reduced bodyweight and food consumption, hematological changes) were more severe in the high dose-treated animals, but less obvious in the 0.25 and 0.5 μg/L groups. Dose-related necropsy findings were mainly present in the skin and eyes. These abnormalities were possibly related to direct drug exposure. Pancreatic islet cell and mammary gland hyperplasia, and enlarged pituitary glands were dose-dependent in rats. However, these findings were not observed in mice, suggesting that mice may be less sensitive to SCH 32088.

Due to falsification of EIA results and sample preparation, plasma concentrations of SCH 32088 may not be reliable. However, the data obtained from the exposure chamber filters showed that the concentrations of SCH 32088 on the filters increased with dose. In contrast, SCH 32088 was not present on the filters used for control groups.

Dose-related tumors were noted in the mammary gland and pancreas in rats, and in the urinary bladder and lymphoid tissues in mice. The incidence of mammary gland adenoma in rats and malignant lymphoma in mice were seen within the Sponsor's and Charles River's historical control ranges. Based on the available literatures, benign mesenchymal tumor of mouse urinary bladders is also referred to as a leiomyosarcoma which is a unique tumor type for CD-1 or related mouse strains (Chandra M and Firth CH. Toxicol Pathol. 19: 164-76, 1991). This tumor type is not found in B6C3F1 mice, rats, domestic animals or humans. This neoplastic lesion was also reviewed by Dr. Leopold Koss, MD, Chairman of Dept. of Pathology, the University Hospital for the Albert Einstein College of Medicine. He stated that the morphology of this tumor type was not seen to any human urinary bladder. Therefore, urinary bladder tumor seen in mice was not considered to be relevant to human cancer risk.

The occurrence of pancreatic mixed islet cell tumors was not dose-related. When the incidence of this tumor type was combined with other pancreatic islet cell tumors, the combined incidences were present within the historical control ranges.

In a previous clinical study (C95-050-01), both Cmax and AUC were not quantifiable following intranasal administration at 400 μg/kg/day. In this NDA submission, the proposed clinical dose of SCH 32088 nasal suspension is 200 μg/day, which is equivalent to 4 μg/kg/day on the basis of body weight or 125 $\mu g/m^2$/day on the basis of body surface areas. Since the human AUC values are not available, the exposure rates of 2 carcinogenicity studies are compared with the proposed clinical dose based on the body weight and body surface area. (See table below.)

Species/Duration	Study #	Predicted dose		Safety Margin	
		µg/kg/day	µg/m ^{2}	µg/kg/day	µg/m ^{2}
Rats/2-year	P-6005	9-67	54 -402	2.3-16.8	0.4 -3.2
Mice/19-month	P-6006	20 -160	60-480	5 -40	0.5 -4

As shown in the above table, the dose levels used in rat and mouse carcinogenicity studies were up to 3- and 4-times the maximum recommended daily intranasal dose in adults (125 $\mu g/m^2$/day) on a $\mu g/m^2$ basis, respectively.

In summary, the appearance of most dose-related tumor types were found within the available historical control ranges. However, the historical control values used in this evaluation were not generated by the testing laboratory. Variability of historical ranges among the different testing laboratories should be considered. The highest incidences of most tumor types in the studies were higher than the average values of the historical controls. However, based on the body weight and body surface areas, exposure rates in both carcinogenicity studies were much higher than the proposed human clinical dose. Therefore, SCH 32088 presents a very limited cancer risk to humans.

In conclusion, based on the available data and results, SCH 32088 has none or a very limited cancer risk to human. (See attachments A and B.)

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SUMMARY AND EVALUATION

Summary and Evaluation of Pharmacology Studies

NASONEX™ (SCH 32088 or Mometasone furoate) is a potent corticosteroid. Inhalation administration of SCH 32088 can inhibit allergen-induced pulmonary eosinophil infiltration and Th cell accumulation in allergic mouse and guinea pig models. In comparison with some corticosteroid, SCH 32088 has more potency in the inhibition of cytokine releases and leukotriene productions. Anti-inflammatory activities of SCH 32088 in animals were also observed in the treatment of RPAR, and acute and chronic dermal inflammation.

Side-effects of SCH 32088 were also evaluated by the sponsor. When SCH 32088 was compared with betamethasone valerate, SCH 32088 had less potency for suppressing the HPA axis, but had greater potency for the induction of thymolysis and skin atrophy. SCH 32088 also had significant effects on female sexual maturation, and had some antiuterotrophic activity. However, SCH 32088 had no androgenic, antiandrogenic and estrogenic activity. SCH 32088 affects neither biliary secretion nor gastric acid and pepsin secretion. SCH 32088 showed mineralocorticoid activity in rats. Although SCH 32088 had no effects on the central nervous, cardiovascular, respiratory systems in the experimental animals, it did increase urine volume, creatinine release and decrease ICG (an indicator of hepatic function). Oral administration of SCH 32088 did not significantly reduce the concentration of circulating lymphocytes. Following subcutaneous injection, apparent hepatic glycogen accumulation was not seen in rats dosed up to 60 mg/kg, but was observed in mice treated at 200 mg/kg.

Finally, when all effects of SCH 32088 in different pharmacology studies were compared, the potencies of topically used SCH 32088 on the skin are much higher than systemically dosed SCH 32088.

Summary and Evaluation of Acute Toxicity Studies

Acute inhalation toxicity studies were evaluated in mice (3.16 mg/L), rats (3.31 and 5 mg/L) and dogs (♂: 139.5 μg/L; ♀: 121.5 μg/L). After treatment, bodyweight reduction was observed in rodents, and food consumption was slightly decreased in dogs. After sacrifice, small spleens were found in rats; discoloration of lung, liver, kidney and skin were seen in both rodent species. Death was only seen in the mice (♂: 1/5; ♀: 1/5) exposed for 4 hours to SCH 32088 at a concentration of 3.16 mg/L.

Acute oral and subcutaneous toxicity studies were conduced in rats and mice administered at 20, 200 and 2000 mg/kg. Following a single oral dose treatment at 2000 mg/kg, SCH 32088 was well tolerated by mice and rats; a target organ of toxicity was not identified. When the animals were treated subcutaneously, lethal doses for the rats and mice were 2000 and 200 mg/kg, respectively. Target organs of toxicities were the injection site, abdominal viscera, gastrointestinal tract and kidney.

Based on the results of the acute toxicity studies, subcutaneous administration of SCH 32088 produced much higher systemic toxicity when compared with orally administered SCH 32088. This finding may be attributed to poor oral bioavailability of SCH 32088.

Summary and Evaluation of Intranasal Toxicity Studies

Summary of Intranasal Toxicity Studies:

The intranasal irritation potential was determined by using SCH 32088 nasal suspension at the concentration of 0.05% or 1%. Intranasal administration either at 400 μg/kg/day for 3 days or at 180 μg/kg/day for 1-month did not produce nasal irritation in dogs.

Intranasal toxicity studies were conducted in rats and dogs treated with SCH 32088 nasal suspension for 6 months or 1 year. The objective of these studies was to investigate the potential systemic and nasal toxicities following intranasal administration of SCH 32088.

In a 6-month intranasal toxicity study, Sprague-Dawley rats were dosed intranasally with SCH 32088 at 0.017, 0.05, 0.15 or 0.6 mg/kg/day. The formulation of SCH 32088 used in this study was the same as the proposed final clinical formulation. Alopecia was found mainly in the 0.6 mg/kg rats, but was also seen in the 0.05 and 0.15 mg/kg groups. Nasal irritation was not reported in any group. Constant bodyweight reductions were only present in the 0.6 mg/kg group. Plasma cholesterol levels were statistically increased in the 0.15 (24-53%) and 0.6 mg/kg (16-31%) males. Skin hypotrichosis was only seen in the 0.6 mg/kg group. No pathological alteration was found in other organs. Therefore, the NOAEL dose was established as 0.05 mg/kg/day for the rats. SCH 32088 at 0.15 mg/kg/day was considered as a tolerated dose with mild glucocorticoid effects. At 30 days postdosing, AUC levels of the 0.05 and 0.15 mg/kg/day groups were 322 and 772 pg/hr/ml, respectively. No target organ of systemic toxicity was identified in this study.

Beagle dogs were also treated for 6 months by intranasal administration of SCH 32088 at

0.0075, 0.015, 0.045 and 0.15 mg/kg/day. The formulation of SCH 32088 used in this study was the same as the proposed final clinical formulation. No dose-related clinical sign or nasal irritation was reported in any group. Decreased eosinophil count and increased plasma cholesterol were only found in the 0.15 mg/kg group. Plasma cortisol levels in the 0.15 mg/day group were generally lower than the vehicle-treated controls. After animals were treated for 26 weeks, serum cortisol concentration in the 0.045 mg/kg group was also decreased. In comparison with the control values, ACTH response was normal in the 0.045 mg/day group, but was lower in the 0.15 mg/kg group. No dose-related pathological changes were observed in the nasal cavity or other organs. In conclusion, target organs of systemic toxicity were not identified in this study. The NOEL dose was 0.015 mg/kg/day in dogs. The intranasal dose of 0.045 mg/kg/day can be considered a tolerated dose with mild glucocorticoid effects. For the animals treated with SCH 32088 at 0.015 and 0.045 mg/kg/day, plasma drug concentrations were below the quantifiable levels.

In a 1-year intranasal toxicity study, dogs received intranasal doses of 0.1, 0.2, 0.6 or 2.0 mg/day. (Doses for the male dogs: 0.0075, 0 015, 0.045 and 0.15 mg/kg/day, respectively; doses for the female dogs: 0.0089, 0.018, 0.054 and 0.179 mg/kg/day, respectively.) The formulation of SCH 32088 used in this study was the same as the proposed final clinical formulation. Alopecia was found in 6 high-dose animals (2 mg/day: ♂ = 3/5, ♀ = 3/5), but also seen in the 0.2 mg/day group (♂ = 1/5, ♀ = 1/5). No other dose-related clinical signs or nasal irritations were seen. Significant reductions (>20%) in the leukocyte and lymphocyte counts were noted only in the 2 mg/day group. Two 0.06 mg/day males had undetectable pre-ACTH values and normal post-ACTH cortisol responses. Adrenal cortex atrophy was found in one of them. The association between the reduction of ACTH output and morphological alterations of the adrenal cortex indicated that adrenocortical insufficiency could be induced in dogs treated with SCH 32088 at 0.6 mg/day. Both basal and post-ACTH cortisol responses were significantly decreased in the 2 mg/day dogs. Small adrenal glands and low adrenal weights were observed only in the 2 mg/day males and females. Pathological changes in the thymus, skin and adrenal glands were mainly found in the 2 mg/day dogs, but also in some 0.6 mg/day dogs. Absences of lymphoid aggregates were mainly seen in the 0.6 and 2 mg/kg dogs. This morphological change was considered a corticosteroid-related effect. Based on the results of this study, the NOAEL dose was 0.1 mg/day. Intranasal administration at 0.2 mg/day can be considered a tolerated dose with mild glucocorticoid effects. AUC levels of 0.1 and 0.2 mg/kg/day groups were not quantifiable. Although adrenal cortex atrophy and undetectable pre-ACTH values were found in one 0.6 mg/day male, average cortisol levels were comparable between the 0.6 mg/day and control groups. Therefore, if close clinical monitoring is available, dose levels between 0.2 and 0.6 mg/day can be also acceptable.

In summary, following a 12-month intranasal administration, target organ toxicities in dogs were in the thymus, skin and adrenal glands. All intranasal irritation and intranasal toxicity studies are summarized in the following table.

Summary of Relevant Intranasal Studies			
Study Name	**Report No. (#/sex/group)**	**Daily dose (μg/kg)**	**Observation**
Dog: 1-week Nasal Irritation study	P-5995 (3)	♂: 47, 93, 187 ♀: 61, 122, 244	NOEL: ♂: 187; ♀ 244 μg/kg Target organ: not determined AUC data: None
Dog: 1-month Nasal Irritation study	P-5336 (3)	♂: 180, 360 ♀: 220, 440	NOEL: ♂: 180; ♀: 220 μg/kg Target organ: not determined AUC data: None
Dog: 1-month Nasal Irritation study	P-5474 (3)	♂: 210, 430 ♀: 250, 510	NOEL: ♂: 210; ♀: 250 μg/kg Target organ: not determined AUC data: None
Rat: 6-month intranasal toxicity study	D-6117 (25)	17, 50, 150, 600	NOAEL: 50 μg/kg; Tolerated dose: 150 μg/kg Target organ: not determined AUC data (Day 30): 322 pg.hr/ml (50 μg/kg group) 772 pg.hr/ml (150 μg/kg group)
Dog: 6-month intranasal toxicity study	D-6118 (5)	7.5, 15, 45, 150	NOEL: 15 μg/kg; Tolerated dose: 45 μg/kg Target organ: not determined AUC data (Day 180): unquantifiable (15 and 45 μg/kg groups)
Dog: 1-year intranasal toxicity study	D-6116 (5)	♂: 7.5, 15, 45, 150 ♀: 8.9, 18, 54, 179	NOAEL: 7.5/8.9 μg/kg; Tolerated dose: 15/18 μg/kg Target organ: not determined AUC data (Day 363): unquantifiable (7.5/8.9 and 15/18 μg/kg groups)

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Evaluation of Intranasal Toxicity Studies:

In this NDA submission, the proposed human daily dose of SCH 32088 is 200 μg/day. When the NOEL or NOAEL dose levels obtained from dog intranasal irritation studies were compared with the proposed human dose by using nasal surface area, the intranasal doses in dogs were approximately 7- to 15-times higher than the proposed human dose. (See table below.) Therefore, results from the dog intranasal irritation studies provide a safety margin for the proposed human intranasal dose.

Comparison of intranasal doses between dog and human

Animal (Duration)	NOEL* or NOAEL@ dose in dog (μg/kg) ♂/♀	Daily dose (μg/animal) ♂/♀	Daily dose(μg/cm² of nasal surface area)* ♂/♀	Human dose (μg/cm² of nasal surface area)**	Margin of Safety
Dog (3-day)	400* / 520*	4280/4264	19.4/19.3	1.25	15
Dog (7-day)	187* / 244*	2001/2001	9.05/9.05	1.25	7
Dog (1-mon)	180* / 220*	1998/2002	9.04/9.05	1.25	7
Dog (1-mon)	210@ / 250@	1974/175	8.93/8.93	1.25	7

* NOEL dose level
@ NOAEL dose level
* Nasal surface areas (cm²): Man = 160, Dog = 221, Rat = 14 (Acta Pharm Nord. 2: 1990)
** Human dose is calculated based on the proposed clinical dose (200 μg person day)

In pharmacokinetic studies from intranasal toxicity studies, AUC in the dog was below the quantifiable level (BQL) following treatment up to 45 μg/kg/day. AUC levels were detectable in the rats treated at 50 μg/kg/day (NOAEL dose) or 150 μg/kg/day (a tolerated dose with mild glucocorticoid effects). In a previous clinical study (C95-050-01), both Cmax and AUC were not quantifiable in humans following the intranasal administration at 400 μg/kg/day. In the NDA submission, the proposed clinical dose of SCH 32088 nasal suspension is 200 μg/day or 4 μg/kg/day.

In the 6-month and 1-year intranasal toxicity studies, the formulation of SCH 32088 used in animals was the same as the proposed human clinical formulation. When dose levels used in animals were compared with the proposed human dose, the NOEL or NOAEL doses obtained from animals were approximately 2- to 12-times greater based on bodyweight and 1.2- to 2.4-times greater based on body surface area; the tolerated doses obtained from animals were approximately 4- to 38-times greater based on bodyweight and 2.4- to 7-times greater based on body surface area.

Species (Duration)	Preclinical data				Margin of Safety	
	Dose levels	Daily dose (µg/kg bodyweight)	Daily Dose (µg/m² body surface area)*	AUC(tf) (pg/hr/ml)	µg/kg bodyweight**	µg/m² body surface area**
Rat (6 mon)	NOAEL	50	300	137 - 322	12	2.4
	Tolerated dose	150	900	487 - 772	38	7
Dog (6 mon)	NOEL	15	300	BQL	4	2.4
	Tolerated dose	45	900	BQL	11	7
Dog (12 mon)	NOAEL	7.5	150	BQL	2	1.2
	Tolerated dose	15	300	BQL	4	2.4

* Body surface area Rat = 0.025 m², Dog= 0.4 m², Human = 1.6 m²

** 50 kg bodyweight person was used for the calculation. Daily dose 4 µg/kg bodyweight or 125 µg/m² body surface areas

In conclusion, tolerated doses from rat and dog intranasal studies were greater than the proposed clinical dose of SCH 32088. Therefore, the preclinical data from intranasal studies support the proposed intranasal dose in humans.

Summary and Evaluation of Inhalation Toxicology Studies

Summary of Inhalation Toxicology Studies:

In a 26-week oral inhalation study (P-5591), dogs were treated with SCH 32088 at 21 (low-dose), 37 (mid-dose) and 74 (high-dose) µg/kg/day. After treatment, dose-related death and clinical signs were not noted. Statistically decreased bodyweight and food consumption were observed in the high-dose group. Total leukocyte counts were comparable among the groups. However, leukocyte differentiation was not performed in this study. Therefore, the suppression of lymphocyte or other leukocytes could not be evaluated. Blood cortisol levels in the test groups were generally lower, but was only statistically reduced in the high-dose males. This finding was associated with the decreased adrenal weight in the high-dose males (48%↓). Morphologically, adrenal cortex atrophy was observed in 2/4 mid-dose males, 3/4 high-dose males, and 4/4 high-dose females. This study suggested that the inhalation dose of 21 µg/kg/day in dogs is the tolerated dose with mild glucocorticoid effects. The target organ of toxicity was adrenal glands, based on pathological observation.

In another 26-week inhalation study, rats were treated inhalationally at 50, 93 or 214 µg/kg/day for the males, and at 55, 102 or 234 µg/kg/day for the females. The animals had dose-related alopecia (8%, 75%, 83% and 97% of rats in the control to high-dose group) and scabbing of the muzzle, neck and other skin regions (5%, 50%, 61% and 57% of the rats in the control to high-dose group). Between Weeks 12 to 26, 16 animals were sacrificed following observation of

progressive respiratory abnormalities (wheezing, gasping and labored breathing), and the frequency increased with dose level (1, 4 and 11 rats in the low-, mid- and high-dose group, respectively). Decreased bodyweight and food consumption were also induced by the treatment. Hematological examination revealed dose-related increases in neutrophils and decreases in lymphocyte and total leukocyte counts. Organ weight reductions were observed in the spleen, thymus, uterus and adrenal glands. Atrophy was found in the adrenal, spleen, thymus and lymph nodes at all dose levels. A dose-related secondary lesion in several animals was a pulmonary fungal infection. This infection may be attributed to SCH 32088-induced immunosuppression. Subtle perturbations of the estrous cycle and enhanced mammary gland lobuloalveolar development were reported in all dosed groups. Based on the above results, a NOEL or a tolerated dose with mild glucocorticoid effects was not established for low-dose animals (50 µg/kg/day for the males or 55 µg/kg/day for the females). Major target organs of toxicity were liver, spleen, lungs, thymus, heart, kidney, uterus and thyroid, adrenal and mammary glands.

In a 3-month inhalation dog study, animals were exposed to SCH 32088 aerosols at 44, 79 or 158 µg/kg/day. After the treatment, there were no dose-related deaths, clinical signs, body weight decreases and food consumption changes. Significant reductions in leukocyte counts were found in the mid- and high dose females. Serum cortisol levels in all test groups were generally lower than the control group, particularly in the mid- and high-dose groups. Liver weights were increased in a dose-related manner. The histopathology evaluation showed that liver glycogen accumulation was found in all high-dose dogs and about 50% of the mid-dose and low-dose dogs. Dose related changes in the zona glomerulosa of adrenal glands was also observed. In this study, target organs of systemic toxicity were the liver, thymus and adrenal gland. The NOEL was not established.

In a 3-month inhalation rat study (conducted by), rats received inhalation doses at 48, 102 or 273 µg/kg/day. Treatment-related alopecia and changes in body weight and food consumption were seen in all test groups in a dose dependent manner. Dose-related significant decreases in leukocyte and lymphocyte counts were present in the mid- and high-dose groups. Increases in plasma cholesterol, glucose and reduction in cortisol were observed in the mid-dose and high dose group. Reduced spleen, adrenal, thymus weights in the mid- and high-dose groups were associated with morphological alterations. Therefore, the inhalation dose at 48 µg/kg was considered as the NOAEL in rats. Target organs of systemic toxicity were defined in thymus, spleen and adrenal glands.

Another 3-month inhalation rat study was performed by

Rats in this study were treated at the concentrations of 0.25, 0.5, 1, 2 or 4 µg/L. The target doses were 8, 17, 18, 34, 67 or 134 µg/kg/day for the males, and were 8, 18, 37, 73 or 146 µg/kg/day for the females. Dose-related clinical signs were not found in any group. Body weights were reduced statistically in the 1, 2 and 4 µg/L groups. Decreased liver, spleen and lung weights were mainly present in the two high-dose groups. Microscopic examination demonstrated that treatment-related tracheal globule cell decrease occurred in 100% of the test animals, but not in any of the control rats. Uterine granulocytic leukocytes were also decreased in

a dose-related manner. Based on the results of this study, a NOEL dose was not established.

In a 2-week inhalation study (D-22607), dogs were exposed to SCH 32088 aerosols at 80 (low-dose), 240 (mid-dose) and 800 (high-dose) µg/kg/day. The results showed that SCH 32088 did not affect mortality, clinical signs, body weight change, food consumption and parameters of clinical pathology. Plasma cortisol levels were not measured in this study. Histopathological changes in the liver, adrenal cortex, mammary gland, lymph nodes and thymus were observed in the mid- and high-dose group. Since no other obvious abnormalities were seen in the low-dose group, except adrenal atrophy (♂: 1/3; ♀: 1/3), the inhalation dose at 80 µg/kg/day in dogs was considered a tolerated dose with mild glucocorticoid effects. Target organs of toxicity were the liver, adrenal, lymph nodes, mammary glands and thymus.

In another 2-week inhalation study (D-22680), rats were treated at 80, 240 and 800 µg/kg/day, respectively. Achieved daily doses were 0, 68, 239 and 636 µg/kg/day for male rats and 0, 76, 268 and 710 µg/kg/day for female rats. Treatment-related changes were mainly found in the mid- and high-dose groups, including reduced body weight and food consumption, decreased leukocyte and lymphocyte counts, decreased GPT, GOT and alkaline phosphatase levels. Spleen, adrenal and thymus weights were reduced in the mid- and high-dose groups. Obvious atrophy was seen in the adrenal and thymus of the mid- and high-dose groups, but also seen in one low-dose female. Since adrenal atrophy was only seen in one low-dose animal (1/20), 68 µg/kg for the male rats and 76 µg/kg for the female rats can be considered a tolerated dose with mild glucocorticoid effects. Target organs of systemic toxicity were the thymus, spleen and adrenal glands.

Pharmacokinetic parameters were not measured in the above inhalation studies. In an inhalation pharmacokinetic study, when beagle dogs were treated by 28-day oral inhalation (P-6096), plasma concentrations of SCH 32088 were under the quantifiable levels in the 20 µg/kg group, and the AUC level in the 80 µg/kg group was 228 pg/hr/ml on Day 28. In a 1-month pharmacokinetic study, inhalation doses were up to 24 µg/kg/day for male rats and up to 33 µg/kg/day for female rats. The AUC value in the high dose rats (♂: 24 µg/kg or ♀: 33 µg/kg) was 15898 pg.hr/ml. However, the highest inhalation doses in this rat PK study were lower than tolerated doses given to the rats in the inhalation studies. All inhalation toxicity studies are summarized in the following table:

Summary of relevant Inhalation Toxicity Studies			
Study Name	**Report No.(#/sex/group)**	**Daily dose (μg/kg)**	**Observation**
Dog: 26-week inhalation study	P-5591 (4)	21, 37, 74	NOEL dose: not established Tolerated dose: 21 μg/kg Target organ: adrenal AUC data: None
Rat: 26-week inhalation study	P-5598 (20)	♂: 50, 93, 214 ♀: 55, 102, 234	NOEL dose: not established Tolerated dose: ♂: 50 μg/kg; ♀: 55 μg/kg Target organ: liver, spleen, lungs, thymus, heart, kidney, uterus, thyroid, adrenal, mammary gland AUC data: None
Dog: 3-month inhalation study	D-22796 (4)	44, 79, 158	NOEL or tolerated dose: not established Target organ: liver, thymus, adrenal AUC data: None
Rat: 3-month inhalation study	D-22797 (15)	48, 102, 273	NOEL dose: not established NOAEL dose: 48 μg/kg. Target organ: adrenal, spleen, thymus AUC data: None
Rat: 3-month study	P-5736 (10)	♂: 8, 17, 34, 67, 134 ♀: 8, 18, 37, 73, 146	NOEL or tolerated dose: not established Target organ: trachea, spleen, lungs, uterus AUC data: None
Dog: 2-week inhalation study	D-22607 (3)	80, 240, 800	NOEL dose: not established Tolerated dose: 80 μg/kg Target organ: liver, lymph nodes, thymus, adrenal AUC data: None
Rat: 2-week inhalation study	D-22680 (10)	♂: 68, 239, 636 ♀ 76, 268, 710	NOEL dose: not established Tolerated dose, ♂: 68 μg/kg, ♀:76 μg/kg Target organ: liver, spleen, thymus, adrenal AUC data: None
Rat: 1-month inhalation PK study	P-6137 (80 or 84)	♂: 3.2, 6.7, 14, 24μg/kg ♀: 3.7, 8.7, 14, 33 μg/kg	NOEL or Tolerated dose: not determined Target organ: not determined AUC data (Day 30): 2164 pg.hr/ml (3.2/3.7 μg/kg group); 15898 pg.hr/ml (24/33 μg/kg group)
Dog: 1-month inhalation PK study	P-6096 (4)	20, 80, 160μg/kg	NOEL or Tolerated dose: not determined Target organ: not determined AUC data (Day 28): Not quantifiable (20 μg/kg group); 445 pg.hr/ml (160 μg/kg group)

Evaluation of Inhalation toxicology studies:

In the 6-month and 3-month inhalation toxicity studies, systemic toxicities in dogs were produced following treatment of 34 µg/kg. The NOEL or NOAEL dose level was not established in these studies. A tolerated inhalation dose with mild glucocorticoid effects was 21 µg/kg in dogs. However, the dose level at 80 µg/kg was tolerated by dogs in a 2-week inhalation study. The studies indicated that systemic toxic effects of SCH 32088 increased with the dose and the duration of treatment. Target organs of toxicity in dogs were mainly the liver, thymus and adrenal glands. For this NDA submission, the proposed human daily dose is 200 µg/day, which is equal to a daily dose of 4 µg/kg bodyweight or 125 µg/m^2 body surface area. Based on the available pharmacokinetic data, the plasma drug concentration was below the quantifiable level (50 pg/ml) when dogs were treated inhalationally at 20 µg/kg/day for 28 days (P-6096). An undetectable plasma drug level was also observed in humans treated with an intranasal dose of SCH 32088 of 400 µg/day (C95-050-01). To further evaluate the data from the 6-month dog inhalation study, a tolerated inhalation dose is compared with the proposed human intranasal dose on the basis of bodyweight or body surface area. As demonstrated in the following table, a tolerated inhalation dose with mild glucocorticoid effects was 3.4- to 5-time higher in dogs than the proposed human intranasal dose.

Tolerated dose in dogs		Margin of safety *	
µg/kg bodyweight**	µg/m^2 body surface area***	µg/kg	µg/m^2 body surface area
21	420	5	3.4

* 50 kg bodyweight person was used for the calculation. Daily dose 4 µg/kg body weight or 125 µg/m^2 body surface area
** Based on mean bodyweight = 10 kg
*** Body surface area Rat = 0.025 m^2, Dog= 0.4 m^2, Human = 1.6 m^2

In a 2-week rat study, the inhalation dose at 68 µg/kg/day was established as a tolerated dose with mild glucocorticoid effects. A 6-month inhalation study showed that systemic toxicities can be induced in rats at 50 - 55 µg/kg/day. Major target organs of toxicity in the 6-month study were the liver, spleen, lungs, thymus, heart, kidney, uterus and thyroid, adrenal and mammary glands. Two 3-month inhalation toxicity studies were conduced in rats by 2 different laboratories. In one 3-month inhalation toxicity study (D-22797), the NOAEL dose in rats was defined as 48 µg/kg/day and toxic effects were noticed at 102 µg/kg/day. In another study (P-5736), decreased tracheal globule cells were found in all test animals, although systemic toxicity was not obvious in the rats at 34 µg/kg. Since decreased tracheal globule cells were not confirmed in adult rats by other short- or long-term toxicity studies, the importance of this observation is not clear.

The NOAEL dose (48 µg/kg) from one 3-month inhalation study (approximately 288 µg/m^2 on a body surface basis) is compared to the proposed clinical dose. As shown in the table below, the

NOAEL dose obtained from the rats was 2.3- to 12-times higher than the proposed human intranasal dose.

NOAEL dose in rat		Margin of safety *	
µg/kg bodyweight**	µg/m² body surface area***	µg/kg	µg/m² body surface area
48	288	12	2.3

* 50 kg bodyweight person was used for the calculation. Daily dose: 4 µg/kg body weight or 125 µg/m² body surface areas
** Based on mean bodyweight = 0.2 kg
*** Body surface area: Rat = 0.0313 m², Dog= 0.4 m², Human = 1.6 m²

As demonstrated by the above inhalation studies, tolerated inhalation doses with mild glucocorticoid effects were much higher than the proposed human intranasal dose. Therefore, the data from preclinical inhalation studies is sufficient to support the proposed clinical intranasal dose.

Summary and Evaluation of Pediatric Studies

In a 1-month inhalation study, 2-week-old pediatric rats were exposed to SCH 32088 powder at the concentrations of 0.01, 0.05, 0.25 or 1 µg/L. No treatment-related deaths or clinical signs were observed in any group. Statistically significant decreased bodyweight and hematological changes were present in the 1 µg/L group. In comparison with the controls, serum corticosterone levels were statistically higher in the treated males, but not the treated females. Major pathological alterations were decreased tracheal globule cells, nasal goblet cell hyperplasia and increased bone marrow adipose cells. Alveolar histiocytic infiltration and enhanced mammary gland development were observed in all dosed male and female groups, respectively. Based on the results of this study, a NOEL was not established in the females. Although pulmonary alveolar histiocytic infiltration was found in 1/24 treated males, a tolerated dose with mild glucocorticoid effects was 0.2 µg/kg/day for the male rats. Major target organs of toxicity were trachea, nasal cavity, bone marrow, mammary gland and lungs on the basis of pathological findings.

In another inhalation study, 6-week-old dogs were treated for 7 weeks at the concentration of 0.04, 0.2 and 1 µg/L. There were no drug-related death and clinical signs after the treatment. Significant reduction in bodyweight gains was present in the high-dose group during the treatment, but was fully recovered after a 9-week recovery period. Elevated serum potassium, GGT, ALT and ALP were observed in the high-dose animals. The high-dose dogs had a low pre-ACTH value and a normal post-ACTH value, suggesting the normal response of adrenal cortices to ACTH. The PK study showed that plasma drug levels was not quantifiable in the low-dose group, and was detectable in the mid-dose group only in the Week 5. For the high-dose group, Cmax and AUC levels in Week 5 were higher than in Week 1, which suggests

drug accumulation. Organ weight changes in the lungs, epididymis, thyroid, spleen and thymus were observed in all drug-treated groups, particularly in the high-dose group. Decreased adrenal weight was only found in the high-dose group. After a 9-week recovery period, epididymis weight remained decreased, however, the weights of other organs were similar between the high-dose and control groups. Morphologically, pulmonary hemorrhage, alveolar edema as well as acute cellular infiltration were present as primary pathological changes in all groups, including the control group. These acute structural changes may be attributed to the mechanical damage produced by an improperly used exposure mask. There were no dose-related pathological findings in other organs. Based on the results of this study, oral inhalation at 0.2 µg/L can be accepted as a tolerable dose for pediatric dogs. The inhalation dose at the concentration of 0.2 µg/L was equal to 7.1 µg/kg/day for male dogs or 7.3 µg/kg/day for the female dogs.

Based on the above inhalation toxicology studies in pediatric animals, a tolerated dose with mild glucocorticoid effects was not established in rats, but was defined as 7.1-7.3 µg/kg/day in dogs. Currently, SCH 32088 is not indicated for a pediatric population.

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Summary and Evaluation of Reproductive Toxicology Studies

Segment II studies were conducted in rats, rabbits and mice by oral, topical and subcutaneous routes of administration.

In a pilot oral Segment II study, a tolerated oral dose with mild glucocorticoid effects was greater than 600 μg/kg/day in pregnant rats. However, a subcutaneous Segment II rat study demonstrated that reduced fetal and maternal body weights and delayed ossification were seen at 15 and 30 μg/kg. In this rat subcutaneous study, the NOEL dose was at 2.5 μg/kg/day for both dams and fetuses.

In an oral Segment II study, the incidences of malformations in the rabbits were 2.3%, 4.8% and 6.9% in the control, 140 μg/kg/day and 700 μg/kg/day groups, respectively. Conjoined twin, extra sternebra and fused ribs were observed in the 140 μg/kg/day rabbits. An oral dose at 700 μg/kg/day increased the incidences of resorption and malformations, including cleft palate and/or head malformations (consisting of hydrocephaly or domed head). A dose level at 2800 μg/kg/day caused pregnancy failure in most rabbits. The malformation rate in the 140 μg/kg/day group was considered to be comparable to the control value (2.3%). Since the daily oral dose at 140 μg/kg did not produce significant toxic effects to either the dams or their offsprings, it was accepted as a NOAEL.

In a subcutaneous Segment II mouse study, SCH 32088 at 60 or 180 μg/kg/day caused body weight loss and an increased incidence of cleft palate. The NOEL in mice was 20 μg/kg/day for both the dams and the offsprings

When SCH 32088 at 300, 600 and 1200 μg/kg was used dermally (topical) in a rat Segment II study, fetal growth suppression and delayed ossification occurred in all treated groups. However, umbilical hernia and cleft palate were observed in the 600 and 1200 μg/kg rats.

After rabbits in a dermal Segment II study were treated topically at 150 and 300 μg/kg, maternal and fetal toxicities were induced in rabbits. Observed malformations in the animals were gallbladder agenesis, umbilical hernia and flexed front paws.

Segment I and III studies were conducted in rats treated with a subcutaneous dose at 2.5, 7.5 or 15 μg/kg. Impairment of fertility in rat was not produced by subcutaneous dose up to 15 μg/kg/day. Prolonged gestation, and prolonged and difficult labor were produced by the subcutaneous dose at 15 μg/kg. The treatment at 15 μg/kg also caused significant reductions in the offspring delivered, litter size and survival rats, as well as increase resorption. In both Segment I and III studies, a subcutaneous dose at 2.5 μg/kg was the NOEL, and at 7.5 μg/kg was considered as a tolerated dose with mild glucocorticoid effects.

All reproductive toxicology studies and related PK studies are summarized in the following table:

Summary of Reproductive Toxicity Studies			
Study Name	**Report**	**Daily dose (μg/kg)**	**Observation**
Rabbit: oral segment II study	P-5991	140, 700, 2800	NOAEL: Not established Tolerated dose: 140 μg/kg AUC data: 2282 pg.hr/ml in the 2800 μg/kg group, but not quantifiable in the 140 and 700 μg/kg groups
Rat: subcutaneous segment II study	P-5543	2.5, 15, 30	NOEL: 2.5 μg/kg AUC data: None
Mouse: subcutaneous segment II study	P-5478	20, 60, 180	NOEL: 20 μg/kg AUC data: None
Rat: dermal segment II study	D-5054	300, 600, 1200	NOAEL: Not established AUC data: None
Rabbit: dermal segment II study	D-5066	150, 300	NOAEL: Not established AUC data: None
Rat: subcutaneous segment I study	D-5174	2.5, 7.5, 15	NOAEL: 2.5 μg/kg Tolerated dose: 7.5 μg/kg AUC data: None
Rat: subcutaneous segment III study	D-5164	2.5, 7.5, 15	NOAEL: 2.5 μg/kg Tolerated dose: 7.5 μg/kg AUC data: None
Pregnant female rat: single dose PK study	P-6084	Subcutaneous: 30 Oral: 600	NOAEL or Tolerated dose: Not determined AUC data: 8250 pg.hr/ml after subcutaneous treatment; 17595 pg.hr/ml after oral treatment
Female rat: 10-day PK study	P-6105	Subcutaneous: 2.5, 15, 30 Oral: 2.5, 15, 30	NOAEL or Tolerated dose: Not determined AUC data: On Day 1 1. PO group: Not quantifiable in the 2.5 μg/kg group; 202 pg.hr/ml in the 15 μg/kg group 2. SC group: 1248 pg.hr/ml in the 2.5 μg/kg group; 7282 pg.hr/ml in the 15 μg/kg group On Day 10: 1. PO group: Not quantifiable in the 2.5 μg/kg group; 328 pg.hr/ml in the 15 μg/kg group 2. SC group: 1457 pg.hr/ml in the 2.5 μg/kg group; 9090 pg.hr/ml in the 15 μg/kg group

In this NDA submission, pharmacokinetic parameters in pregnant rats (single dose), pregnant rabbits (14 daily doses) and female rats (10 daily doses) were determined after the exposure to

SCH 32088. In a single dose study, oral bioavailability in pregnant rats was only 11%. AUC levels were not detectable in pregnant rabbits dosed orally for 14 days at 140 μg/kg/day (NOAEL). In subcutaneous Segment I, II and III studies, NOEL doses were 2.5 μg/kg in rats. However, pharmacokinetic parameters in rats were not examined in these subcutaneous reproductive toxicology studies. AUC levels in rats were determined by another pharmacokinetic study. After female rats were treated subcutaneously at 2.5 μg/kg, AUC values were greater than the AUC levels in the rats treated intranasally at 50 (NOEL; Study #: P-6117) or 150 μg/kg (a tolerated dose with mild glucocorticoid effects; Study #: P-6117). AUC and NOEL (or a tolerated dose with mild glucocorticoid effects) obtained from different studies are compared in the following table:

	Rat (intranasal toxicity study; P-6117)		Rat (Subcutaneous PK study & Seg. I, II, III)		Rabbit (Oral Seg. II study)
	Day 1	Day 30	Day 1	Day 10	Day 14
NOEL (μg/kg/day)	50	50	2.5	2.5	N/A
AUCtf (pg/hr/ml)	137	322	1248	1457	NQ**
Tolerated dose* or NOAEL dose*** (μg/kg/day)	150*	150*	N/A	N/A	140***
AUCtf (pg/hr/ml)	487	772	N/A	N/A	N/A

* Tolerated dose with mild glucocorticoid effects
** Not quantifiable
*** NOAEL dose

The results from the above studies suggest that reproductive toxicities may not be produced in rats when they are treated intranasally at the NOEL dose and a tolerated dose with mild glucocorticoid effects. The intranasal NOEL dose (50 μg/kg) in female rats was approximately 12-times greater than the proposed human intranasal dose (4 μg/kg).

Summary and Evaluation of Genetic Toxicology Studies

Ten genetic toxicology studies were conducted by the sponsor, negative results were found in 8 of the studies. Chromosomal aberration in CHO cells was observed in 2 studies. Both studies showed that SCH 32088, but not its degradation product, may induce chromosomal aberration in CHO cells. However, SCH 32088 produced chromosomal aberration in CHO cells under toxic dose levels, and the incidence of the aberration were not dose-related. Chromosomal aberration results were negative in CHL cells in vitro, spermatogonial cells in vivo and rat bone marrow cells in vivo.

SUMMARY OF GENETIC TOXICOLOGY STUDIES

Study	Dose levels	Finding
Ames	31.25 to 500 μg/plate	Negative
Ames	100 to 2500 μg/plate	Negative
In vitro mouse lymphoma assay	3.125 to 100 μg/ml	Negative
In vitro chromosomal aberration in CHO cells	No-S9: 5 to 20 μg/ml S9: 25 to 100 μg/ml	No-S9: Positive for chromosomal aberration at 12.5 μg/ml
In vitro chromosomal aberration in CHO cells using SCH 32088 or its degradation product	No-S9: 1 to 22.5 μg/ml S9: 25 to 100 μg/ml	No-S9. Positive for chromosomal aberration at 15 μg/ml
In vitro chromosomal aberration in CHL	1.65 - 13.2 μg/ml	Negative
In vivo mouse bone marrow micronucleus	600 to 1200 mg/kg	Negative
In vivo chromosomal aberration in spermatogonial cells	378 to 1626 mg/kg	Negative
In vivo chromosomal aberration in rat bone marrow cells	378 to 1626 mg/kg	Negative
In vivo hepatocyte UDS assay	1250 to 5000 mg/kg	Negative

Based on the above results, SCH 32088 induced mutagenic changes were only found in CHO cells with no-S9 activity, but not in other studies.

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Summary and Evaluation of Phamacokinetic (PK) Studies

Summary of single dose PK studies:

In the single-dose studies, most of the administered dose was generally eliminated through the feces regardless of the animal species or route of administration. In PO-dosed animals, drug excreted through the feces (>90%) was generally greater than those in IV-dosed animals (50-86.2%). The data are summarized in the following table:

Study No.	Species/Route of administration	Period for excretion	Excretion: % of administered-dose	
			in Feces (%)	in Urine (%)
P-5352	rat/PO	168 hr	93.5	2.4
P-5941	rat/PO	168 hr	90.1	0.5
P-5313	rat/PO	168 hr	114*	1
P-5313	dog/PO	168 hr	93	0.7
P-5941	rat/IV	168 hr	86.2	3.3
P-5313	rat/IV	168 hr	50	2.5
P-5313	dog/IV	168 hr	76	5.4
Mean			86	2.3

* Based on the recovery of radioactivity in fecal samples

Tissue distribution studies indicated that drug concentrations in the gastrointestinal tract were higher than those in other tissues regardless of intravenous (P-5941) or oral (P-5941) routes of administration. Elevated drug concentrations in the feces may be due to either biliary secretion of the drug or unabsorbed drug in the gastrointestinal tract.

As summarized in the following table, plasma drug concentrations in IV-dosed groups were higher than those in PO-dosed groups. It was found that oral bioavailability was 1.7% in mice (P-6111) and 1.4 % in rats (P-6368). It suggests that oral bioavailability of SCH 32088 was very poor.

Study No.	Species/Route	Dose (µg/kg)	Cmax (ng/ml)	Tmax (hr)	AUC	
					Duration	ng.hr/ml
P-6111	mouse/PO	600	1.87	0.5	0-12hr	2.55
P-5941	rat/PO	600	1.14	3	0-tf	5.23
P-6111	mouse/IV	300	189	0.08	0-12 hr	74.6
P-5941	rat/IV	300	364	0.08	0-tf	192

After either IV or PO administration, the major metabolites were mometasone, 6β-hydroxymometasone furoate, 21-hydroxymometasone and 21-hydroxymometasone furoate (P-5941; P-6368). However, the metabolites were not determined quantitatively in any study.

Summary of multiple-dose PK studies:

In the 6-month rat and 1-year dog intranasal studies (P-6117; P-6118; P-6116), plasma drug concentrations were not detectable when the animals were dosed at 45 μg/kg or less. In both species, plasma Cmax and AUC values increased with dose, although gender or treatment duration had no effect on PK values. Drug accumulation and enzyme induction were not found in all intranasal studies.

SCH 32088 at 2.6 to 33 μg/kg was also given to rats by nose-only inhalation for a month (P-6137). Drug absorption following inhalational administration was greater than intranasal administration. After rats were treated inhalationally, plasma drug concentrations increased with dose, although gender or treatment duration had no effect on PK values. This finding was similar to the intranasal study. Following 3 months of inhalation administration, the concentrations of liver and lung enzymes were not increased in rats (P-6836) or dogs (P-6837). It suggests that SCH 32088 did not induce enzymes in the liver and lung tissues.

Following 3 months of oral administration at 10 to 650 μg/kg, gender-dependent pharmacokinetic changes were found in mice, but not in rats and dogs. Plasma AUC levels in mice were higher in females than in males. This finding was different from the results of mouse intranasal and inhalation studies. It may be due to absorption rate or metabolism differences between male and female mice. In these oral PK studies, plasma drug levels in dogs and rats were increased in a dose-related fashion. In rats, AUC(tf)s on Day 1 were almost doubled on Day 28, while AUC(0-6 hr) values on Day 28 were similar to those on Day 90. For dogs, SCH 32088 was not well-absorbed in the 150 μg/kg group, which suggests that oral bioavailability was poor in the dog.

Summary of Tissue Distribution:

In single-dose studies, male rats were treated by oral, intranasal and intravenous routes of administration. SCH 32088 was predominantly present in the gastrointestinal tract regardless of the route of administration. In the intranasal study, the highest drug concentrations were seen in the esophagus, trachea, nasal passage and mouth, but not in the lungs. Drug concentrations in the liver and kidneys were also higher than most tissues. Biliary recirculation of SCH 32088 and/or its metabolites was only observed in orally dosed rats.

In a 21-day oral study, tissue drug concentrations in male rats were progressively increased, and were mainly present in the gastrointestinal tract, liver and kidney. However, SCH 32088 did not accumulate in tissues. Drug-related radioactivity was not detectable on Day 23 in urine and on Day 27 in feces. In both single- and multiple-dose tissue distribution studies, SCH 32088 and/or its metabolites were predominantly eliminated through the feces.

Using pregnant and lactating rats, it was found that SCH 32088 and/or its metabolites are not only able to cross the placenta, but also are secreted into milk. Finally, biliary excretion and enterohepatic circulation were determined in bile-duct-cannulated rats. Approximately 14% of oral-dosed drug was excreted through the bile. About 27% of the absorbed dose in these rats was reabsorbed and underwent enterohepatic circulation.

Summary of Protein Binding and in vitro Drug Metabolism:

The in vitro protein binding potential of ^{3}H-SCH 32088 was tested using the plasma samples collected from rat, mouse, rabbit, dog and human. Results showed that ^{3}H-SCH 32088 was highly bound to rat (98.9%), mouse (99.4%), rabbit (98.3%), dog (99.6%) and human (99.1%) plasma proteins. Within the dose range from 100 to 500 ng/ml, there was no significant change in protein binding activity of ^{3}H-SCH 32088. Based on the results of this study, the fractions of unbound drug in rat, dog and human plasma were 1.1%, 0.4% and 0.9%, respectively. Free drug in human plasma was approximately 2-times higher than that in dog plasma, but was slightly lower than that in rat plasma.

In vitro metabolism of SCH 32088 was examined using pulmonary and hepatic tissues from rats and mice. It showed that SCH 32088 was extensively metabolized by hepatic enzymes, but not by pulmonary enzymes. In rat liver incubation, approximately 40% of parent compound was converted to 6-hydroxy SCH 32088. Mometasone and two other unknown metabolites (UK1 and UK2) were also detected. In mouse liver incubation, 6-hydroxylation, ester hydrolysis and metabolism to an unidentified product were found. The lack of the metabolism in the lung might be due to the low concentration of metabolic enzymes in the lungs. The results of this in vitro metabolism study agreed generally with the metabolic profile obtained from single dose pharmacokinetic studies.

OVERALL SUMMARY AND EVALUATION

NASONEX™ is the nasal spray formulation of Mometasone furoate monohydrate (SCH 32088), a potent corticosteroid. Inhalation administration of SCH 32088 inhibits allergen-induced pulmonary eosinophil infiltration and Th cell accumulation in allergic mouse and guinea pig models. Anti-inflammatory activities of SCH 32088 were also observed in the treatment of acute and chronic dermal inflammation in animals.

Compared to betamethasone valerate, SCH 32088 had less potency in suppressing HPA axis, but more potency in inducing thymolysis and skin atrophy. SCH 32088 had no mineralocorticoid, androgenic, antiandrogenic and estrogenic activities. SCH 32088 did not increase the secretions of bile, gastric acid and pepsin. SCH 32088 showed on effect on the central nervous, cardiovascular, respiratory systems of the experimental animals. It can increase urine volume, creatinine release and accumulation of hepatic glycogen. SCH 32088 possesses some antiuterotrophic activity and also may accelerate sexual maturation in the females.

Single subcutaneous doses at 200 mg/kg and 2000 mg/kg may be lethal in dogs and rats, respectively. However, single oral doses at up to 2000 mg/kg did not cause any death in rats and dogs. This suggests that subcutaneous administration of SCH 32088 is more toxic than oral administration.

Toxicity of SCH 32088 was evaluated in rats and dogs by the intranasal and inhalation routes of administration. Testing duration lasted up to one year. Like other corticosteroids, major target organs of toxicity of SCH 32088 were the liver, thymus, lymph tissues, lungs, skin, spleen, mammary and adrenal glands. Changes included increases in liver weight, atrophy of the thymus and adrenal glands, and suppression of the HPA axis. Following a 6-month inhalation, the tolerated dose with mild glucocorticoid effects in dogs was 21 μg/kg/day, which was approximately 5 and 3.4 times of the proposed human intranasal dose on a bodyweight or body surface area basis, respectively. In a 3-month rat study (P-5737), SCH 32088 at as low as 8 μg/kg/day decreased tracheal globule cells in all animals tested. However, this pathological abnormality was absent in another 3-month study at dose levels up to 48 μg/kg/day, the NOAEL of the study (D-22797). The dose level of 48 μg/kg/day was approximately 12 and 2.3 times the proposed human intranasal dose on a bodyweight or body surface area basis, respectively.

Inhalation toxicity studies of SCH 32088 showed that juvenile animals are more sensitive to the drug than adults. A one-month juvenile rat study produced toxicity in the trachea, nasal cavity, bone marrow, mammary glands and lungs. Based on the results of this study a NOEL was not established in the females. Although pulmonary alveolar histiocytic infiltration was found in 1/24 treated males, a tolerated dose with mild glucocorticoid effects was defined at 0.2 μg/kg in male rats, but not in female rats. In contrast with the rats, SCH 32088 was more

tolerable to pediatric dogs. A tolerated inhalation dose with mild glucocorticoid effects in young dogs was defined at 7.2 μg/kg/day. Currently, SCH 32088 is only for adults and adolescents 12 years of age or older.

The intranasal administration of 0.05 or 1% of SCH 32088 suspension for up to 1 year did not induce nasal irritation in dogs. These dogs received up to 180 to 520 μg/kg/day of SCH 32088, which were approximately 7 to 15 times higher than the proposed human daily dose on the basis of nasal surface area. After 6 months intranasal administration, systemic toxicity was generally not noted. Two 6-month intranasal toxicity studies failed to identify target organs of toxicity in both rat and dogs on the basis of pathological observations. Acceptable tolerated doses in the 6-month studies were 150 μg/kg/day and 45 μg/kg/day for rats and dogs, respectively. A 1-year intranasal dog study showed mild effects in thymus, skin and adrenal gland. A tolerated daily dose with mild glucocorticoid effects was defined as 15 μg/kg body weight or 300 $\mu g/m^2$ body surface area. This is approximately 4- and 2.4-times the proposed human dose on the bodyweight basis and body surface area basis, respectively. Therefore, the preclinical data from intranasal toxicity studies are sufficient to support the proposed human intranasal dose of SCH 32088.

Reproductive toxicity was evaluated by oral, dermal and subcutaneous routes of administration. Subcutaneous administered SCH 32088 produced more maternal and fetal toxicity when compared with the animals treated through dermal or oral routes of administration. In a rabbit oral Segment II study, NOAELs for both dams and offspring were 140 μg/kg/day, which produced unquantifiable AUC levels. In subcutaneous Segment I, II and III rat studies, NOEL doses were 2.5 μg/kg/day. Following a subcutaneous dose at 2.5 μg/kg/day, AUC values in the female rats were greater than the AUC levels in the rats treated with intranasal doses at 50 (NOEL) or 150 μg/kg/day (tolerated dose with mild glucocorticoid effects). When the AUC and NOEL levels from different studies are compared, reproductive toxicity is not produced in animals treated intranasally at the NOEL dose or tolerated doses with mild glucocorticoid effects.

Ten genetic toxicology studies were conducted by the sponsor. Negative results were reported in 8 out of 10 studies, including Ames test, mouse lymphoma assay, mouse bone marrow micronucleus assay, UDS assay, assays of chromosomal aberration in CHL cells and chromosomal aberration in rat bone marrow cells. Chromosomal aberration in CHO cells was reproducibly observed in 2 studies under non-S9 condition. However, SCH 32088 produced chromosomal aberration in CHO cells at cytotoxic dose levels, and incidences of the aberration were not dose-related. Chromosomal aberration was not seen on CHL cells in vitro, spermatogonial cells in vivo and rat bone marrow cells in vivo.

Two inhalation carcinogenicity studies in rat and mouse have been reviewed previously. The results of these studies demonstrated that SCH 32088 has none or a very limited cancer risk to humans.

Oral bioavailability of SCH 32088 was very poor in all test species, including mice, rats and dogs. Pharmacokinetic studies showed that plasma drug levels were undetectable in the rats and dogs treated by intranasal doses for up to 45 µg/kg. When dog or rat was treated inhalationally or intranasally (dose > 45 µg/kg), plasma AUC values were increased with dose, although gender or treatment duration had no effect on AUC values. In vitro studies demonstrated that SCH 32088 was not an inducer of hepatic or lung enzymes. More than 80% of administered dose was generally eliminated through the feces regardless of the animal species or route of administration. Drug accumulation and enzyme induction were not found in any intranasal or inhalation study. After intranasal dosing, the highest drug levels were distributed in the esophagus, trachea, nasal passage and mouth, but not in the lungs. The in vitro protein binding studies showed that SCH 32088 was highly bound to human and animal plasma proteins. The binding rate of human plasma protein (99.1%) was between that of rats (98.9%) and dogs (99.6%). The fractions of unbound drug in rat, dog and human plasma were 1.1%, 0.4% and 0.9%, respectively. This suggested that under a similar plasma drug concentration, the levels of free drug in humans and rats may be approximately 2-times higher than that in dog plasma. Therefore, rats might be more sensitive to the systemic exposure of SCH 32088 when compared with the dog model. The in vitro metabolism studies demonstrated that SCH 32088 was extensively metabolized by hepatic enzymes, but not by pulmonary enzymes. Results of PK studies indicate that intranasally dosed SCH 32088 may be predominantly concentrated in the nasal cavity and upper-airways. Due to poor bioavailability or low pulmonary concentration of SCH 32088, an tolerated intranasal dose may not be able to produce significant systemic effects.

Finally, the formulation of SCH 32088 used in three pivotal preclinical intranasal toxicity studies (6-month in rats, 6-month and 1-year in dogs) was the same as that proposed for the marketed product.

In summary, NASONEX™ is a potent anti-allergic and anti-inflammatory drug. It has greater local pharmacological activities when compared with systemic activities. After a single intranasal dose, the highest drug levels were seen in the esophagus, trachea, nasal passage and mouth, but not in the lungs. Plasma drug concentrations in animals increased with dose, but were not affected by gender or treatment duration. SCH 32088 is eliminated mainly through the feces. Experimental data from intranasal and inhalation studies show that the tolerated doses with mild glucocorticoid effects were much higher in animals than the proposed human dose. Reproductive toxicities may not be induced in animals treated intranasally at a tolerated dose with mild glucocorticoid effects. Negative results were seen in 8 out of 10 genetic toxicology studies. Although SCH 32088 produced chromosomal aberrations in CHO cells at cytotoxic concentrations, this finding may not be drug-related. Results from two 2-year carcinogenicity studies showed that NASONEX has none or a very limited cancer risk to human. Therefore, preclinical data is sufficient to support the proposed human clinical use.

RECOMMENDATION

NASONEX™ nasal spray is indicated for the prophylaxis and treatment of symptoms of seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis, in adults and adolescents 12 years of age and older. The efficacy and safety of NASONEX™ are supported by the data obtained from preclinical studies. Therefore, this product is recommended to be approved.

LABELING REVIEW

Three sections were revised from the label proposed by the sponsor, including 1) Clinical Pharmacology, 2) Carcinogenesis, Mutagenesis, Impairment of Fertility, and 3) Pregnancy.

Clinical Pharmacology: When inhibitory activity to the synthesis/release of cytokines was compared (P-5558), the potency of mometasone furoate (IC_{50} = 0.1 nM) to IL-1 was approximately 8-times higher than betamethasone valerate (IC_{50} = 0.82 nM). Therefore, the lowest inhibitory activity of mometasone furoate to cytokine production should be 8-times, but not 10-times higher than other tested steroid.

Only one study showed that in an ovalbumin sensitized and challenged mice, mometasone furoate at ≥ 13 μg/kg may reduce the numbers of eosinophils into the brochoalveolar lavage fluid, and the peribronchial and bronchiolar regions of the lung tissues. Eosinophil infiltration in the lungs is one of the important pathological alterations in asthmatic patients. In order to describe the animal model and site of eosinophil infiltrations in the study, a minor revision was made in the second paragraph of clinical pharmacology.

Carcinogenesis, Mutagenesis, Impairment of Fertility: To give a clear picture, tumor findings in the carcinogenicity studies were revised. The incidence of urinary bladder mesenchymal tumors in mice was increased with administered doses. However, no statistically significant tumors were observed in mice and rats.

Although human plasma drug concentrations were not quantifiable with the maximum recommended human daily intranasal dose (4 μg/kg), the dose levels used in the rat and mouse carcinogenicity studies were compared with the maximum recommended daily intranasal dose in adults on a body surface area basis (μg/m²). The dose levels used in rat and mouse carcinogenicity studies were up to 3- and 4-times the maximum recommended daily intranasal dose in adults (125 μg/m²/day) on a μg/m² basis, respectively.

The maximum subcutaneous dose of mometasone furoate was administered at 15 μg/kg/day in rat reproductive toxicology studies (Segment I and III). Based on the available data, impairment of fertility was not seen at ≤ 15 μg/kg/day. Prolonged gestation, prolonged and difficult labor, reduced offspring survival and body weight gain were observed following the

treatment at 15 μg/kg. The daily dose at 15 μg/kg in rats was compared with the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis.

The doses used in animals and the maximum recommended daily intranasal dose in adults are compared in the following table:

Comparison of the doses used in animals and the dose used in human*					
Carcinogenicity Studies					
Rat	μg/kg	67	N/A	N/A	N/A
	$\mu g/m^2$ **	402	N/A	N/A	N/A
	A/H ratio#	3.2	N/A	N/A	N/A
Mouse	μg/kg	20	40	80	160
	$\mu g/m^2$ **	60	120	240	480
	A/H ratio#	0.48	0.96	1.92	3.84
Subcutaneous Reproductive (Segment I and III) Studies					
rat	μg/kg	15	N/A	N/A	N/A
	$\mu g/m^2$ **	90	N/A	N/A	N/A
	A/H ratio#	0.72	N/A	N/A	N/A

* Maximum recommended daily intranasal dose in adults = 4 μg/kg or 125 $\mu g/m^2$ (Bodyweight = 50kg, Surface area = $1.6m^2$).

** Conversion factor: rat = 6, mouse = 3; rabbit = 12.

The ratio of the doses used in animal (A) and the maximum recommended daily intranasal dose in human adults (H).

Pregnancy: As shown in a table below, mometasone furoate in teratology (Segment II) studies was given to several species by using various routes of administration.

Routes	Oral	Dermal (topical)	Subcutaneous
Species	Rabbit	Rat & Rabbit	Rat & Mice

Since human plasma drug concentration was not quantifiable (< 50 pg/ml) following intranasal exposure, the dose levels used in the animal teratology studies were compared to the maximum recommended daily intranasal dose in adults (125 $\mu g/m^2$/day) on a $\mu g/m^2$ basis.

Mometasone furoate at 60 and 150 μg/kg/day was teratogenic for mouse and rabbits, respectively. Non-teratogenic subcutaneous dose levels were established at 2.5 μg/kg in rats and 20 μg/kg in mice.

In an oral teratology study, rabbits were treated with placebo and mometasone furoate at 140, 700 and 2800 μg/kg. The incidences of malformations were 2.3%, 4.8% and 6.9% for the rabbits dosed at 0 (placebo), 140 and 700 μg/kg, respectively. In the 2800 μg/kg group, there were too few fetuses (n=4) to evaluate because of a high pregnancy failure rate. At 700 μg/kg, there were increased incidences of resorptions and malformations, including cleft palate and/or head malformations (consisting of hydrocephaly or domed head). In the 140

μg/kg group, conjoined twin, extra sternebra and fused ribs were observed.

The doses used in animals and the maximum recommended daily intranasal dose in adults are compared in the following table:

Comparison of the doses used in animals and the dose used in human*					
Teratology (Segment II) Studies					
	μg/kg	2.5	600	N/A	N/A
Rat	$\mu g/m^2$ **	15	3600	N/A	N/A
	A/H ratio#	0.12	28.8	N/A	N/A
	μg/kg	20	60	180	N/A
Mouse	$\mu g/m^2$ **	60	180	540	N/A
	A/H ratio#	0.48	1.44	4.32	N/A
	μg/kg	140	150	700	2800
Rabbit	$\mu g/m^2$ **	1680	1800	8400	33600
	A/H ratio#	13.4	14.4	67.2	268.8

* Maximum recommended daily intranasal dose in adults = 4 μg/kg or 125 $\mu g/m^2$ (Bodyweight = 50kg; Surface area = 1.6m

** Conversion factor: rat = 6; mouse = 3; rabbit = 12.

\# The ratio of the doses used in animal (A) and the maximum recommended daily intranasal dose in human adults (H).

The following is the proposed revised preclinical labeling

Proposed Revised Labeling:

CLINICAL PHARMACOLOGY

NASONEX Nasal Spray, is a glucocorticosteroid demonstrating anti-inflammatory properties. The precise mechanism of glucocorticosteroid action on allergic and nonallergic rhinitis is not known. On a concentration basis (nM of IC_{50}), mometasone furoate in cell culture was shown to be at least 8 times more potent than several other steroids (beclomethasone dipropionate, betamethasone, hydrocortisone, and dexamethasone) at inhibiting the synthesis/release of IL-1, IL-6 and TNFα. Mometasone furoate (0.12 nM) in cell culture was also at least ten times more potent than BDP and betamethasone dipropionate at inhibiting IL-5 production. In cultured human blood CD4+ T-cells, mometasone furoate was a potent inhibitor of the production of IL-4 and IL-5 (0.27 nM). Also, in mixed leukocytes from atopic patients, mometasone furoate inhibited the release of leukotrienes.

In an allergic mouse model, inhaled mometasone furoate (at 13 μg/kg) inhibited

allergen-induced eosinophil infiltration into brochoalveolar lavage fluid, and the peribronchial and bronchiolar regions of the lung tissues. Additionally, mometasone furoate reduced the number of lymphocytes, and the levels of messenger RNA for the proallergic cytokines IL-4 and IL-5.

In two clinical studies utilizing nasal antigen challenge, NASONEX Nasal Spray has shown anti-inflammatory activity in both the early- and late- phase allergic responses. This has been demonstrated by decreases (vs placebo) in histamine and eosinophil activity, and reductions (vs baseline) in eosinophils, neutrophils, and epithelial cell adhesion proteins.

The effect on nasal mucosa was examined following twelve months of treatment with NASONEX Nasal Spray. There was no evidence of atrophy or other adverse effects on nasal mucosa. The epithelial mucosa integrity improved, and there was a marked reduction in inflammatory cells.

In patients with seasonal allergic rhinitis, NASONEX Nasal Spray demonstrated a clinically significant onset of action (at least moderate improvement in nasal symptoms) within 12 hours after the first dose. Maximum benefit is usually reached in several days.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No statistically significant tumors were observed when mometasone furoate was evaluated in Sprague Dawley rats at inhalation doses up to 67 μg/kg (approximately 3 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis). In a 19-month inhalation study in Swiss CD-1 mice, no statistically significant tumors were noted. A dose-related increased in mouse urinary bladder mesenchymal tumors was noted at 20, 40, 80 and 160 μg/kg (approximately 1/2, 1, 2 and 4 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis).

At cytotoxic doses, mometasone furoate produced an increase in simple chromosome aberrations in vitro in Chinese hamster ovary-cell cultures in the nonactivation phase, but not in the presence of rat liver S9 fraction. Mometasone furoate was nonmutagenic in a mouse-lymphoma assay, a Salmonella/E-coli/mammalian microsome mutation assay, a Chinese hamster lung cell (CHL) chromosomal-aberrations assay, an in vivo in the mouse bone-marrow erythrocyte-micronucleus assay, a rat bone-marrow clastogenicity assay, and the mouse male germ-cell clastogenicity assay. Mometasone furoate also did not induce unscheduled DNA synthesis in vivo in rat hepatocytes.

In rat subcutaneous reproductive toxicity studies, mometasone furoate caused prolonged gestation, prolonged and difficult labor, reduced offspring survival and body weight gain following treatment at 15 μg/kg (approximately 1/2 of the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis). Impairment of fertility in rats was not produced by subcutaneous doses up to 15 μg/kg.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Mometasone furoate was

teratogenic in mice. It caused cleft palate and reduced offspring survival in mice at subcutaneous doses of 60 and 180 μg/kg, respectively (approximately 1 and 4 times the maximum recommended daily intranasal dose in adults on a μg/m² basis, respectively). Non-teratogenic dose level in mice was established at a subcutaneous dose of 20 μg/kg (approximately 1/2 of the maximum recommended daily intranasal dose in adults on a μg/m² basis).

In rabbits, mometasone furoate was teratogenic and caused gallbladder agenesis and flexed front paws at a topical dermal dose of 150 μg/kg (approximately 14 times the maximum recommended daily intranasal dose in adults on a μg/m² basis).

In rats, mometasone furoate produced umbilical hernia, cleft palate and delayed ossification at a topical dermal dose of 600 μg/kg(approximately 30 times the maximum recommended daily intranasal dose in adults on a μg/m² basis). Non-teratogenic dose level in rats was established at a subcutaneous dose of 2.5 μg/kg (approximately 1/10 of the maximum recommended daily intranasal dose in adults on a μg/m² basis).

In these teratogenicity studies, there were also reductions in maternal body weight gains, effects on fetal growth (lower fetal body weights and/or delayed ossification) in mice (subcutaneous, 60 μg/kg), rabbits (dermal, 150 μg/kg) and rats (dermal, 600 μg/kg).

In an oral teratology study in rabbits, incidences of malformations were 2.3%, 4.8% and 6.9% for the rabbits dosed at 0 (placebo), 140 and 700 μg/kg, respectively. Conjoined twin, extra sternebra and fused ribs were observed in the rabbits at the dose level of 140 μg/kg (approximately 15 times the maximum recommended daily intranasal dose in adults on a μg/m² basis). An oral dose of 700 μg/kg increased the incidences of resorptions and malformations, including cleft palate and/or head malformations (consisting of hydrocephaly or domed head; approximately 70 times the maximum recommended daily intranasal dose in adults on a μg/m² basis). At 2800 μg/kg, pregnancy failure was observed in most rabbits (approximately 270 times the maximum recommended daily intranasal dose in adults on a μg/m² basis).

There are no adequate and well controlled studies in pregnant women. NASONEX Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Proposed Labeling Editing:

The shaded areas are the proposed addition of the sponsor's proposed labeling. The strike out is the proposed deletion.

CLINICAL PHARMACOLOGY

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mouse urinary bladder mesenchymal tumors was noted at 20, 40, 80 and 160 μg/kg, approximately 1/2, 1, 2 and 4 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis.

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Pregnancy: Teratogenic Effects: Pregnancy Category C: Mometasone furoate was teratogenic in mice. It caused cleft palate and reduced offspring survival in mice at subcutaneous doses of 60 and 180 μg/kg, respectively (approximately 1.5 and 4 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis, respectively). Non-teratogenic dose level in mice was established at a subcutaneous dose of 20 μg/kg.

approximately 1/2 of the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis.

In rabbits, mometasone furoate was teratogenic and caused gallbladder agenesis and flexed front paws at a topical dermal dose of 150 $\mu g/kg$, approximately 14 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis.

In rats, mometasone furoate produced umbilical hernia, cleft palate and delayed ossification at a topical dermal dose of 600 $\mu g/kg$, approximately 30 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis. Non-teratogenic dose level in rats was established at a subcutaneous dose of 2.5 $\mu g/kg$, approximately 1/10 of the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis.

In these teratogenicity studies, there were also reductions in maternal body weight gains, effects on fetal growth (lower fetal body weights and/or delayed ossification) in mice (subcutaneous, 60 $\mu g/kg$), rabbits (dermal, 150 $\mu g/kg$) and rats (dermal, 600 $\mu g/kg$).

In an oral teratology study in rabbits, incidences of malformations were 2.3%, 4.8% and 6.9% for the rabbits dosed at 0 (placebo), 140 and 700 $\mu g/kg$, respectively. Conjoined twin, extra sternebra and fused ribs were observed in the rabbits at the dose level of 140 $\mu g/kg$, approximately 13 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis. An oral dose of 700 $\mu g/kg$ increased the incidences of resorptions and malformations, including cleft palate and/or head malformations (consisting of hydrocephaly or domed head), approximately 67 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis. At 2800 $\mu g/kg$, pregnancy failure was observed in most rabbits, approximately 270 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis.

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Tao Tom Du, Ph.D.

Pharmacologist/Toxicologist

Original NDA
c.c. /Division File
/T. Tom Du
/Dr. Alexandra Worobec
/Dr. Hilary Sheevers
/Dr. Martin Himmel
/Dr. Graig Bertha
/Ms. D. Toyer

I concur, although final labeling comments will be addressed in the future with the sponsor.

8/21/97

1st draft: 3/5/97
2nd draft: 4/30/97
3rd draft: 6/16/97
4th draft: 6/30/97
5th draft: 8/7/97

FEB 14 1997

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-762 **CHEM. REVIEW #** 1 **REVIEW DATE:** 2/13/97

RECOMMEND ACTION: Not Approved (NA)

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9/30/96	10/1/96	10/15/96

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J.
07033

DRUG PRODUCT NAME

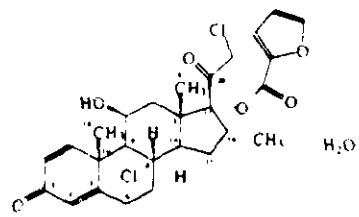
Proprietary:	NASONEX™ Nasal Spray
Nonproprietary	mometasone furoate nasal spray
USAN:	mometasone furoate
Code Name/#:	SCH 32088 Monohydrate
Chem Type/Ther Class	3S

PHARMACOL. CATEGORY/INDICATION: Anti-inflammatory corticosteroid for prophylaxis and treatment of seasonal allergic rhinitis (SAR), and treatment of perennial rhinitis (PR)

DOSAGE FORM: nasal spray
DOSE: 100 or 200 µg once daily
STRENGTHS: 50 µg mometasone furoate/actuation (100 mg formulation/actuation)

ROUTE OF ADMINISTRATION: intranasal
DISPENSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Mometasone Furoate Monohydrate

9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione Monohydrate

Molecular Formula:	$C_{27}H_{30}Cl_2O_6 H_2O$
Molecular Weight:	539.458

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review

RELATED DOCUMENTS (if applicable):

NDA 19-543 Elocon (Mometasone Furoate) Ointment (Schering, approved 30-Apr-87)*
NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (Schering, approved 06-May-87)*
NDA 19-796 Elocon (Mometasone Furoate) Lotion (Schering, approved 30-Mar-89)*

*Note: These products are for topical application.

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	11/6/96	Pending	
Microbiology	11/25/96	Pending	Evaluation of preservative effectiveness test validation and specification limits for preservatives and microbial limits tests and specs for the drug substance and drug product
Biometrics (Stability)	Not forwarded		Will be forwarded once updated stability data are submitted by the firm
Pharmacology	11/6/96 informal consult forwarded on impurities and specifications (ds and dp)	Pending	
Methods Validation	Not requested		Will not be forwarded until deficiencies addressed by firm
Environmental Assessment	Not forwarded for concurrence (see comment)		Will not be forwarded until deficiencies addressed by firm
Labeling & Nomenclature	11/13/96	Recommendations received dated 1/7/97	

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS: The application as submitted is not approvable from the standpoint of chemistry, manufacturing, and controls.

cc
Orig. NDA 20-762
HFD-570/Division File
HFD-570/CBertha/2/13/97
HFD-570/DToyer
HFD-570/GPoochikian
HFD-570/AWorobec
HFD-570/TDu
R/D Init by GPoochikian: GP 2/14/97

filename: 96-09-30 rev

Craig M. Bertha, Ph.D.
Review Chemist

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

JUL -9 1997

NDA #: 20-762 **CHEM. REVIEW #** 2 **REVIEW DATE:** 7/8/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9/30/96	10/1/96	10/15/96
AMENDMENT (BC)*	3/24/97	3/25/97	3/25/97
AMENDMENT (BC)*	4/4/97	4/7/97	4/7/97
AMENDMENT (BC)*	5/8/97	5/9/97	5/9/97
AMENDMENT (BC)*	5/14/97	5/15/97	5/19/97
AMENDMENT (AC)*	6/17/97	6/18/97	6/20/97

*Subject of this review

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J.
07033

DRUG PRODUCT NAME:

Proprietary:	NASONEX™ Nasal Spray
Nonproprietary:	mometasone furoate nasal spray
USAN:	mometasone furoate
Code Name/#:	SCH 32088 Monohydrate
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION: Anti-inflammatory corticosteroid for prophylaxis and treatment of seasonal allergic rhinitis (SAR), and treatment of perennial rhinitis (PR)

DOSAGE FORM: nasal spray

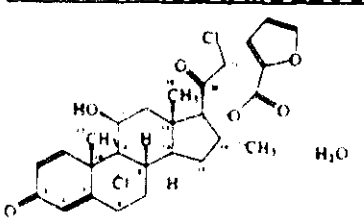
DOSE: 100 or 200 µg once daily

STRENGTHS: 50 µg mometasone furoate/actuation (100 mg formulation/actuation), 120 actuations (trade size)

ROUTE OF ADMINISTRATION: intranasal

DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Mometasone Furoate Monohydrate

9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione Monohydrate

Molecular Formula: $C_{27}H_{30}Cl_2O_6 H_2O$ Molecular Weight: 539.458

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review

RELATED DOCUMENTS (if applicable):

NDA 19-543 Elocon (Mometasone Furoate) Ointment (Schering, approved 30-Apr-87)*
NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (Schering, approved 06-May-87)[2]
NDA 19-796 Elocon (Mometasone Furoate) Lotion (Schering, approved 30-Mar-89)*

[2]Note These products are for topical application

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	11/6/96	Withhold Approval	See remark on p 6
Microbiology	11/25/96	Complete	The microbiologist recommends approval of the application in terms of microbiology (1/13/97)
Biometrics (Stability)	6/30/97	Pending	
Pharmacology	11/6/96 informal consult forwarded on impurities and specifications (ds and dp)	Pending	
Methods Validation	Not requested		Will not be forwarded until method/specification deficiencies addressed by firm and an updated package is received
Environmental Assessment	Forwarded for concurrence on 5/27/97	Concurrence pending	Revised EA from the 5/14/97 amendment was reviewed separately
Labeling & Nomenclature	11/13/96	Complete	Recommendations received dated 1/7/97 (see remark section)

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS: The amendments dated 4/4/97 and 6/17/97 provide a full response to the IR letter dated 2/28/97. The application as amended is not approvable from the standpoint of chemistry, manufacturing, and controls.

cc
Orig NDA 20-762
HFD-570/Division File
HFD-570/CBertha/7/8/97
HFD-570/DToyer
HFD-570/GPoochikian
HFD-570/AWorobec
HFD-570/TDu
R/D Init. by GPoochikian: 7/9/97

filename: 97-06-17.rev

Craig M. Bertha, Ph.D.
Review Chemist

AUG 6 1997

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-762 **CHEM. REVIEW #** 3 **REVIEW DATE:** 8/1/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9/30/96	10/1/96	10/15/96
AMENDMENT (BC)	3/24/97	3/25/97	3/25/97
AMENDMENT (BC)	4/4/97	4/7/97	4/7/97
AMENDMENT (BC)	5/8/97	5/9/97	5/9/97
AMENDMENT (BC)	5/14/97	5/15/97	5/19/97
AMENDMENT (AC)	6/17/97	6/18/97	6/20/97
AMENDMENT (BC)*	7/21/97	7/22/97	7/23/97

*Subject of this review

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J.
07033

DRUG PRODUCT NAME:

Proprietary	NASONEX™ Nasal Spray
Nonproprietary	mometasone furoate nasal spray
USAN	mometasone furoate
Code Name/#	SCH 32088 Monohydrate
Chem Type/Ther Class	3S

PHARMACOL. CATEGORY/INDICATION: Anti-inflammatory corticosteroid for prophylaxis and treatment of seasonal allergic rhinitis (SAR), and treatment of perennial rhinitis (PR)

DOSAGE FORM: nasal spray

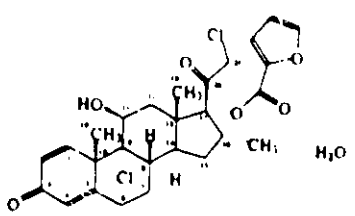
DOSE: 100 or 200 µg once daily

STRENGTHS: 50 µg mometasone furoate/actuation (100 mg formulation/actuation), 120 actuations (trade size)

ROUTE OF ADMINISTRATION: intranasal

DISPENSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Mometasone Furoate Monohydrate

9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione Monohydrate

Molecular Formula: $C_{27}H_{30}Cl_2O_6 \cdot H_2O$ Molecular Weight: 539.458

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review

RELATED DOCUMENTS (if applicable):

NDA 19-543 Elocon (Mometasone Furoate) Ointment (Schering, approved 30-Apr-87)*
NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (Schering, approved 06-May-87)[2]
NDA 19-796 Elocon (Mometasone Furoate) Lotion (Schering, approved 30-Mar-89)*

[2]Note: These products are for topical application

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	11/6/96	Withhold Approval	See remark on p 6
Microbiology	11/25/96	Complete	The microbiologist recommends approval of the application in terms of microbiology (1/13/97).
Biometrics (Stability)	6/30/97	Pending	
Pharmacology	11/6/96 informal consult forwarded on impurities and specifications (ds and dp)	Pending	
Methods Validation	Not requested.		Will not be forwarded until an updated MV package is received from firm.
Environmental Assessment	Forwarded for concurrence on 7/28/97.	Concurrence pending.	Revised EA from the 5/14/97 amendment was reviewed separately.
Labeling & Nomenclature	11/13/96	Complete	Recommendations received dated 1/7/97 (see remark section).

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS: The amendment dated 7/21/97 provides a response to our facsimile of 7/10/97 and is the subject of this review. The application as amended is not approvable from the standpoint of chemistry, manufacturing, and controls.

cc:
Orig. NDA 20-762
HFD-570/Division File
HFD-570/CBertha/8/1/97
HFD-570/DToyer
HFD-570/GPoochikian
HFD-570/AWorobec
HFD-570/TDu
R/D Init. by GPoochikian: 8/6/97
filename: 97-07-21.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

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DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-762 **CHEM. REVIEW #** 4 **REVIEW DATE:** 8/27/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9/30/96	10/1/96	10/15/96
AMENDMENT (BC)	3/24/97	3/25/97	3/25/97
AMENDMENT (BC)	4/4/97	4/7/97	4/7/97
AMENDMENT (BC)	5/8/97	5/9/97	5/9/97
AMENDMENT (BC)	5/14/97	5/15/97	5/19/97
AMENDMENT (AC)	6/17/97	6/18/97	6/20/97
AMENDMENT (BC)	7/21/97	7/22/97	7/23/97
AMENDMENT (BL)*	8/14/97	8/15/97	8/25/97
AMENDMENT (BC)*	8/22/97	8/25/97	8/26/97

*Subject of this review.

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J.
07033

DRUG PRODUCT NAME:

Proprietary:	NASONEX™ Nasal Spray
Nonproprietary:	mometasone furoate nasal spray
USAN:	mometasone furoate
Code Name/#:	SCH 32088 Monohydrate
Chem Type/Ther Class:	3S

PHARMACOL. CATEGORY/INDICATION: Anti-inflammatory corticosteroid for prophylaxis and treatment of seasonal allergic rhinitis (SAR), and treatment of perennial rhinitis (PR)

DOSAGE FORM: nasal spray

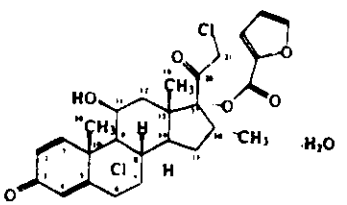
DOSE: 100 or 200 µg once daily

STRENGTHS: 50 µg mometasone furoate/actuation (100 mg formulation/actuation), 120 actuations (trade size)

ROUTE OF ADMINISTRATION: intranasal

DISPENSED: X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Mometasone Furoate Monohydrate

9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione Monohydrate

Molecular Formula: $C_{27}H_{30}Cl_2O_6 \cdot H_2O$ Molecular Weight: 539.458

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review

RELATED DOCUMENTS (if applicable):

NDA 19-543 Elocon (Mometasone Furoate) Ointment (Schering, approved 30-Apr-87)[1]
NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (Schering, approved 06-May-87)[1]
NDA 19-796 Elocon (Mometasone Furoate) Lotion (Schering, approved 30-Mar-89)[1]

[1]Note: These products are for topical application.

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	11/6/96	Withhold Approval	See remark on p. 6
Microbiology	11/25/96	Complete	The microbiologist recommends approval of the application in terms of microbiology (1/13/97).
Biometrics (Stability)	6/30/97	Pending	
Pharmacology	11/6/96 informal consult forwarded on impurities and specifications (ds and dp)	Pending	
Methods Validation	Not requested.		Will not be forwarded until an updated MV package is received from firm.
Environmental Assessment	Forwarded for concurrence on 7/28/97.	Concurrence pending.	Revised EA from the 5/14/97 amendment was reviewed separately.
Labeling & Nomenclature	11/13/96	Complete	Recommendations received dated 1/7/97 (see remark section).

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS: The amendment dated 8/22/97 provides a response to our letter of 8/11/97 and is the subject of this review. Additionally, the draft labeling and labels in the 8/14/97 amendment are reviewed herein. The application as amended is not approvable from the standpoint of chemistry, manufacturing, and controls.

cc:
Orig. NDA 20-762
HFD-570/Division File
HFD-570/CBertha/8/27/97
HFD-570/DToyer
HFD-570/GPocchikian
HFD-570/AWorobec
HFD-570/TDu
R/D Init. by GPoochikian: 8/28/97
filename: 97-08-22.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NASONEX™

(Mometasone Furoate Monohydrate)

Nasal Spray

NDA 20-762

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF PULMONARY DRUG PRODUCTS

(HFD-570)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-762

NASONEX™
(Mometasone Furoate Monohydrate)
Nasal Spray

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for NASONEX Nasal Spray, Schering-Plough Corporation has ~~conducted a number of environmental studies and~~ prepared an environmental assessment (EA, attached) in accordance with 21 CFR 25.31a (a), which evaluates the potential environmental impacts of the manufacture, use and disposal of the product. Based on the predicted market volume, the fifth year production estimate for all of the applicant's products containing Mometasone Furoate was used to calculate the Expected Introduction Concentration (EIC) of Mometasone Furoate, which is less than one (1) ppb. Thus, following the Tier 0 approach, the applicant has provided an abbreviated EA that does not contain items 7, 8, 9, 10, and 11.

Mometasone Furoate is a chemically synthesized drug which is administered as a nasal spray for the prophylaxis and treatment of symptoms of seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis in adults and adolescents 12 years of age and older. The mometasone furoate drug substance will be manufactured by Schering Plough Products, Inc. (synthesis of the crude drug substance) and Schering Corporation (purification) at their facilities in Manati, Puerto Rico and Union, NJ, respectively. The drug product will be manufactured by Schering Plough Products, Inc. and Schering Corporation at their facilities in Manati, PR and Kenilworth, NJ, respectively. The finished drug product will be used in hospitals, clinics and/or patients in their homes.

The drug substance will enter the environment through wastewater emissions at the drug substance manufacturing site in Union, NJ and through air, wastewater and solid waste from the drug product manufacturing facilities.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at licensed incineration facilities. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

7/1/97
Date

Craig M. Bertha, Ph.D.
Review Chemist
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research

1/24/97
Date

for Guirag Poochikian, Ph.D.
Chemistry Team Leader, DNDC II
Division of Pulmonary Drug Products (HFD-570)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

7/22/97
Date

Tao Du, Ph.D.
Review Pharmacologist/Toxicologist
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research

7/28/97
Date

Hilary Sheevers, Ph.D.
Pharmacology/Toxicology Team Leader
Division of Pulmonary Drug Products (HFD-570)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

8/7/97
Date

CONCURRED
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachment: Releasable Environmental Assessment (not including *confidential* appendix 1)

ENVIRONMENTAL ASSESSMENT

Pursuant to 21 CFR Part 25.31a(a)

NASONEX™ NASAL SPRAY
(Mometasone Furoate Aqueous Nasal Spray)
NDA 20-762

1. DATE: May 13, 1997

2. NAME OF APPLICANT: Schering Corporation

3. ADDRESS: 2000 Galloping Hill Road
Kenilworth, New Jersey 07033
Contact: Dr. Tobias Massa
Telephone: 908-298-5711

4. DESCRIPTION OF THE PROPOSED ACTION:

a. Request for Approval

Schering Corporation is submitting this environmental assessment (EA) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mometasone Furoate Aqueous Nasal Spray. Each spray delivers Nasonex™ Nasal Spray equivalent to 50 micrograms of Mometasone Furoate.

b. Need for Action

The proposed indications for Mometasone Furoate Aqueous Nasal Spray are prophylaxis and treatment of symptoms of seasonal allergic rhinitis and treatment of symptoms of perennial rhinitis in adults and adolescents 12 years of age and older.

c. Production Locations

Mometasone furoate will be produced at Schering-Plough Products, Inc. in Manati, Puerto Rico. This material will then be sent to Schering Corporation in Union, New Jersey where it will be purified, converted to mometasone fuorate monohydrate, and micronized. The final drug product will be manufactured (mixing, filling, packaging, and labeling) at the applicant's facility in Kenilworth, New Jersey and at the Manati facility.

The Manati facility is located at Highway 686, Km. 0.5 in Manati, Puerto Rico 00674. This is in the northern coastal region of Puerto Rico, about 2 miles from the Atlantic Ocean. The climate in the region is tropical.

The Union facility is located at 1011 Morris Avenue in Union, New Jersey 07083. The area is characterized by industrial and commercial uses and is bordered by the Elizabeth River. The terrain is flat and the climate is temperate.

The Kenilworth facility is located at 2000 Galloping Hill Road in Kenilworth, New Jersey 07033. The terrain is flat and the climate temperate. The area is characterized by industrial and commercial uses.

d. Location of Use

Through the approval of this action, Mometasone Fuorate Aqueous Nasal Suspension will be used by consumers throughout the United States.

e. Disposal Sites

Any rejected drug product or waste drug intermediate from the Manati facility which is not reprocessed will be sent off-site for incineration. The facility currently used for this purpose is:

Ogden Martin Systems of Lake, Inc.
3830 Rogers Industrial Park Road
Okahumpka, Florida 34762
USEPA ID No. FLD984258731
Permitting Authority: Florida Dept. of Env. Protection
Permit No. A035-193817
Expiration date: Indefinite extension

Any rejected drug product or waste drug substance from the applicant's facilities in Union and Kenilworth, New Jersey which is not reprocessed will be sent off-site for incineration. The facility currently used for this purpose is:

Environmental Waste Incineration, Inc.
70 Water Street
Long Beach, New York 11561
State ID No. 30-E-03
USEPA ID No. NYN100000052
Permitting Authority: New York State Dept. of Env. Conservation
Facility Permit No.1-2809-00088/00008-0
Expiration Date: February 12, 2001

Any product not used by consumers will be disposed of by users at their homes or at hospitals, pharmacies, or clinics accoding to procedures set at these facilities. Typically, the material is disposed via community waste

management systems which may include landfills or incinerators. Minimal quantities of product may be disposed of by users through sewer systems.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

a. Nomenclature

i. Established Name: Mometasone Furoate Monohydrate

ii. Brand/Proprietary Name: Nasonex™ Nasal Spray

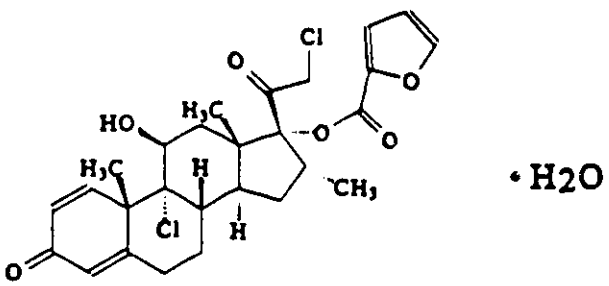
iii. Chemical Name: 9, 21-dichloro-11 beta, 17-dihydroxy-16-alpha-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) monohydrate

b. Molecular Formula: $C_{27}H_{30}Cl_2O_6 \cdot H_2O$

c. Molecular Weight: 539.45

d. CAS Number: 83919-23-7 (Mometasone Furoate Anhydrous)

e. Structural Formula:



• H2O

f. Elemental Composition:

Carbon	60.12
Hydrogen	5.93
Oxygen	20.81
Chlorine	13.14

g. **Physical Form:** White powder

h. **Melting Point:** Melts at about 220°C with decomposition.

i. **Solubility:** Practically insoluble in water (0.02 mg/mL); slightly soluble (4-8 mg/mL) in methanol, ethanol, and isopropanol; soluble (59-74 mg/mL) in acetone and chloroform; and freely soluble (>100 mg/mL) in tetrahydrofuran.

Dissociation Constant: Mometasone furoate monohydrate contains no functional groups that can be protonated or deprotonated between pH 1 and 13, and hence has no dissociation constant.

j. **Additives:**

In addition to the active substance the final dosage consists of the following ingredients:

Substance	CAS #
Microcrystalline Cellulose	9004-34-6
Carboxymethylcellulose Sodium	9004-32-4
Glycerin	56-81-5
Citric Acid Monohydrate	5949-29-1
Sodium Citrate Dihydrate	68-04-2
Polysorbate 80	9005-65-6
Benzalkonium Chloride	8001-54-5
Phenylethyl Alcohol	60-12-8
Purified Water	7732-18-5

g. **Impurities:**

There are no impurities at levels greater than 1% of the active drug substance in the product. The inactive ingredients, or additives, are all USP/NF grade materials.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

The drug intermediate will be synthesized by the applicant's facility in Manati, Puerto Rico. The starting material for this synthesis will be purchased from Pharmacia & Upjohn Inc.

The drug substance, mometasone furoate monohydrate, will be produced by the applicant at its facility in Union, New Jersey. The final manufacturing of the drug product (mixing, filling, packaging, and labeling) will be performed in Manati and at the applicant's facility in Kenilworth.

The material safety data sheet for mometasone furoate monohydrate is provided in Appendix 3. Information regarding the emissions from the operations at the manufacturing facilities is provided below in sections a through d.

a. Substances Expected to be Emitted

Information on emissions from the various production locations is provided in **Confidential Appendix 1.**

b. Controls Exercised

Manati, Puerto Rico

i. Air

Air emissions will occur during synthesis of the drug intermediate, manufacture of the drug product, and cleanout of the process equipment. Emissions are controlled by condensers and carbon absorbers. The carbon absorbers are the last control before discharge and have been measured to remove 90 percent of total hydrocarbons. Removal efficiencies for specific compounds have been measured between 66 percent (methylene chloride) and 94 percent (acetone).

ii. Wastewater/Liquid Waste

Wastewater will be generated in the synthesis of the drug intermediate, manufacture of the drug product, and cleanout of the process equipment. Liquid waste is neutralized at the facility and then discharged to the Puerto Rico Aqueducts and Sewers Authority's Barceloneta Regional Wastewater Treatment Plant, located on State Road Number 684, Km. 3.8, in Barceloneta, Puerto Rico.

iii. Solid/Hazardous Waste

There are three categories of solid waste generated at this facility: hazardous waste, pharmaceutical waste, and trash. Trash, including filter cloth, fluid bed dryer bags, tray dryer papers, silica, and any discarded clothing, is sent to a licensed landfill. The landfill currently used is:

Toa Baja Municipal Landfill
State Road 866
Barrio Candelaria Arena
Toa Baja, Puerto Rico
Permitting Authority: Puerto Rico Environmental Quality Board

Hazardous waste will be generated in the synthesis of the drug intermediate and the cleanout of the process equipment. Hazardous waste is collected and transported to a licensed waste disposal firm for incineration. The facilities currently used are:

Laidlaw Environmental Services of Bartow, Inc.
170 Bartow Municipal Airport
Bartow, Florida 33830
USEPA ID No. FLD980729610
Permit No. HO53-182726A
Issuing Authority: Florida Dept. of Env. Protection
Expiration Date: 12/10/96

Safety Kleen Envirosystems Co. of Puerto Rico, Inc.
State Road No.2, Km.51.0
Manati, Puerto Rico 00701
USEPA ID No. PRD090399718
Issuing Authority: Puerto Rico Environmental Quality Board
Expiration Date: February 16, 2000

Rollins Environmental Services Inc.
13351 Scenic Highway
Baton Rouge, Louisiana 70807
USEPA ID No. LAD010395127
Issuing Authority: Louisiana Dept. of Env. Quality
Expiration Date: March 21, 2001

Marisol, Inc.
125 Factory Lane
Middlesex, New Jersey 08846
USEPA ID No. NJD002454644
Permit No. 1211B1HP04
Issuing Authority: New Jersey Dept. of Env. Protection
Expiration Date: Indefinite extension

AETS
1 Eden Lane
Flanders, New Jersey 07836

USEPA ID No. NJD980536593
Permit No: 1427G1HP07
Issuing Authority: New Jersey Dept. of Env. Protection
Expiration Date: March 31, 1999

Clean Harbors of Baltimore, Inc.
1910 Russel Street
Baltimore, Maryland 21230
USEPA ID No. MDD980555189
Permit No. A151
Issuing Authority: Maryland Dept. of the Environment
Expiration Date: Indefinite extension

Any pharmaceutical wastes, such as rejected drug intermediate, and drug product, are collected and sent off-site for incineration. The current licensed disposal facility used is listed above in Section 4.e.

Union, New Jersey

i. Air

Air emissions will occur during manufacture of the drug substance and cleanout of the process equipment. Emissions will be controlled by a packed scrubber tower and a refrigerated vent condenser. The refrigerated vent condenser is the last control before discharge and has been designed to remove 95 percent of total hydrocarbons. Removal efficiencies for specific compounds have been calculated at between 95 percent (methylene chloride) and greater than 99 percent (acetone).

ii. Wastewater/Liquid Waste

Low levels of liquid waste will be generated in the manufacture of the drug substance and subsequent cleanout of the process equipment. Any effluents, including cleaning compounds and wash water, are pretreated by neutralization prior to discharge to the Joint Meeting of Essex and Union Counties (JMEUC) Treatment Plant. Union's discharge to the JMEUC treatment plant is in accordance with the JMEUC rules and regulations and the conditions set forth in the facility discharge permit.

iii. Solid/Hazardous Waste

There are four categories of solid waste generated at the facility: hazardous waste, pharmaceutical waste, trash, and bulky waste.

Hazardous waste will be generated in the production of the drug substance and the cleanout of the process equipment. Hazardous waste is collected

and transported to a licensed waste disposal firm for incineration. The facility currently used is:

Marisol, Inc.
125 Factory Lane
Middlesex, New Jersey 08846
EPA ID No. NJD002454544
Permit No. 1211B1HP04
Issuing Authority: New Jersey Dept. of Env. Protection
Expiration Date: Indefinite extension

Pharmaceutical wastes, such as rejected drug substance are sent to a disposal firm for incineration. The licensed disposal facility currently used is listed above in Section 4.e.

Trash, including filter cloth, fluid bed dryer bags, tray dryer papers, silica, and any discarded clothing, is sent to a licensed facility for incineration. The facility currently used is:

Union County Utilities Authority
1499 Routes 1 & 9 South
Rahway, New Jersey 07065
Permitting Authority: New Jersey Department of Environmental Protection

Permit No. 2013000835
Expiration Date: 2002

Bulky waste , including construction and demolition debris and furniture, is transported to a licensed facility for disposal. The facility currently used is:

J&J Recycling Company
625 South Front Street
Elizabeth, New Jersey 07202
Permitting Authority: New Jersey Department of Environmental Protection

Permit No. 2004001179
Expiration Date: 2000

<u>Kenilworth, New Jersey</u>

i. Air

Air emissions may occur during mixing, filling, and packaging of the drug product. However, emissions are not of a quantity or quality that require controls.

ii. Wastewater/Liquid Waste

Wastewater will be generated from the cleanout of process equipment used in the manufacture of the final drug product. Wastewater is discharged to the sewerage system of the Rahway Valley Sewerage Authority in Union County, New Jersey.

iii. Solid/Hazardous Waste

There are four categories of solid waste generated at the facility. hazardous waste, pharmaceutical waste, trash, and bulky waste.

Hazardous waste will be generated during mixing, filling, packaging and labeling of the product and from cleanout of process equipment. Hazardous waste is disposed of off the site by:

Clean Harbors of Braintree, Inc.
385 Quincy Avenue
Braintree, Massachusetts 02184
USEPA ID No. MAD053452637
Permit No.: Hazardous Waste Interim Operating Permit #80
Issuing Authority: Mass. Dept. of Environmental Protection
Expiration Date: None

Clean Harbors of Natick, Inc.
10 Mercer Street
Natick, Massachusetts 01760
USEPA ID No. MAD980523203
Permit No.: Hazardous Waste Operating Permit #26B/94
Issuing Authority: Mass. Dept. of Environmental Protection
Expiration Date: October 24, 1999

Clean Harbors of Baltimore, Inc.
1910 Russell Street
Baltimore, Maryland 21230
USEPA ID No. MDD980555189
Permit No. A151
Issuing Authority: Maryland Dept. of the Environment
Expiration Date: Indefinite extension

Pharmaceutical wastes, such as rejected drug product, are sent to a disposal firm for incineration as described in Section 4.e.

Trash, including filter cloth, fluid bed dryer bags, tray dryer papers, silica, and any discarded clothing, is sent to a licensed facility for incineration. The facility currently used is:

Union County Utilities Authority
1499 Routes 1 & 9 South
Rahway, New Jersey 07065
Permitting Authority: New Jersey Department of Environmental Protection
Permit No. 2013000835
Expiration Date: 2002

Bulky waste , including construction and demolition debris and furniture, is transported to a licensed facility for disposal. The facility currently used is:

J&J Recycling Company
625 South Front Street
Elizabeth, New Jersey 07202
Permitting Authority: New Jersey Department of Environmental Protection
Permit No. 2004001179
Expiration Date: 2000

c. Citation of and Statement of Compliance with Applicable Emission Requirements

Manati, Puerto Rico

Listed below are the laws, rules, and regulations that cover emissions and occupational requirements that are applicable to the facility in Manati, Puerto Rico:

- National Primary and Secondary Air Quality Standards (40 CFR 50)
- National Emission Standards for Hazardous Air Pollutants (40 CFR 61)
- Puerto Rico Air Pollution Control Regulations (PREQB Regulations, August 17, 1971 et. seq.)
- U.S. EPA Pretreatment Regulations (40 CFR 403 and 439)
- Puerto Rico Water Quality Standards (PREQB Regulations, January 4, 1974 et. seq.)
- Puerto Rico Aqueduct and Sewer Authority - Facility Agreement with Schering-plough Products, Inc., Maniti, Puerto Rico
- U.S. Dept. of Labor, Occupational Safety and Health Administration (OSHA), Occupational Safety and Health Standards (29 CFR 1910)

The following permits are applicable to the control of emissions from the

manufacture of mometasone furoate at the applicant's facility in Manati, Puerto Rico:

Emission	Authorizing Agency	Permit #
Air	Puerto Rico Environmental Quality Board (EQB)	PFE-47-1290-1306-1-11-0 Expiration Date: 11/12/94 [1]
Air	Puerto Rico Environmental Quality Board (EQB)	PFE-47-0692-0853-I-0 Expiration Date: 9/8/94 [1]
Process waste-water	Puerto Rico Aqueducts and Sewer Authority (PRASA)	Pretreatment Permit GDA 91-210-026 Expiration Date: 7/13/95 [2]

[1] Letters of extension granted from The "Area Calidad de Aire" dated 6/8/94 and 8/15/95, respectively. Permits are extended under Title V of the Clean Air Act and the EQB, Rule 204 Permit to Operate, with annual payment of applicable fees.

[2] Permit has been extended by the PRASA during the renewal process.

Schering-Plough Products, Inc., Maniti, Puerto Rico is registered with the USEPA (ID No. PRD 090 139536) for the handling and control of hazardous and solid waste.

The Manati facility is in compliance with emission requirements, including occupational requirements, which are applicable to the manufacturing process.

Union, New Jersey

Listed below are the laws, rules, and regulations at the federal, state, and local levels that cover emissions, including occupational requirements, and are applicable to the facility in Union:

- National Primary and Secondary Air Quality Standards (40 CFR 50)
- National Emission Standards for Hazardous Air Pollutants (40 CFR 61)
- New Jersey Air Pollution Control Regulations (N.J.A.C. 7:27 et. seq.)
- U.S. EPA Pretreatment Regulations (40 CFR 403 and 439)
- Joint Meeting of Essex and Union Counties (JMEUC) Rules and Regulations (December 20, 1989)
- Resource Conservation and Recovery Act of 1976 PL 94-580 as amended

- New Jersey Administrative Code, Title 7, Chapters 14A, 26, and 27
- U.S. Dept. of Labor, Occupational Safety and Health Administration (OSHA), Occupational Safety and Health Standards (29 CFR 1910)

The following permits are applicable to the control of emissions from the manufacture of the drug substance at the applicant's facility in Union, New Jersey:

Emission	Authorizing Agency	Permit #	Exp. Date
Air	New Jersey Dept. of Environmental Protection (NJDEP)	095068	3/29/96[1]
		082108	2/26/98
		082109	2/02/98
		102308	7/05/96
		082106	2/26/98
		082107	2/26/98
		112320	7/02/00
		115725	3/20/96[1]
Process wastewater	Joint Meeting of Essex and Union (JMEUC)	JM7145	4/14/91[2]

[1] Permits administratively extended by the New Jersey Dept. of Environmental Protection (NJDEP)

[2] Permit extended by the Joint Meeting of Essex and Union (JMEUC) until further notification

The Union facility operates under permit number (ID number) NJD001317601 for the generation, storage, and transportation of hazardous waste. This permit is issued by the Environmental Protection Agency (EPA) and the NJDEP and expires on December 30, 1996.

The facility in Union, New Jersey is in compliance with emission requirements, including occupational requirements, which are applicable to the manufacturing process.

Kenilworth, New Jersey

Listed below are the laws, rules, and regulations at the federal, state, and local levels that cover emissions, including occupational requirements, and are applicable to the facility in Kenilworth:

- National Primary and Secondary Air Quality Standards (40 CFR 50)

- National Emission Standards for Hazardous Air Pollutants (40 CFR 61)
- New Jersey Air Pollution Control Regulations (N.J.A.C. 7:27 et. seq.)
- U.S. EPA Pretreatment Regulations (40 CFR 403 and 439)
- Rules and Regulations Concerning Discharges to the Rahway Valley Sewerage Authority, effective December 1, 1989
- Resource Conservation and Recovery Act of 1976 PL 94-580 as amended
- New Jersey Administrative Code, Title 7, Chapters 14A, 26, and 27
- U.S. Dept. of Labor, Occupational Safety and Health Administration (OSHA), Occupational Safety and Health Standards (29 CFR 1910)

The following permits are applicable to the control of emissions from the manufacture of the final drug product at the facility in Kenilworth:

Emission	Authorizing Agency	Permit #	Exp. Date
Air	New Jersey Dept. of Env. Protection	NJ0001	01/01/00
Process Wastewater	Rahway Valley Sewerage Authority	RVSA035	05/31/96*
Hazardous waste	USEPA	NJD054554290	indefinite

* Permit administratively extended.

The Kenilworth facility is in compliance with emission requirements, including occupational requirements, which are applicable to the manufacturing process.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The approval of the proposed action and subsequent increase in production will not affect compliance with current emission requirements at the facilities in Manati, Union, and Kenilworth.

e. Expected Introduction Concentration

FDA regulations, 21 CFR Part 25.31a(a)6, require a prediction of the concentrations of substances entering the environment as a result of the use of the product. An estimate of the expected introduction concentration (EIC)

of the drug substance for the aquatic environment has been developed and is presented in **Confidential Appendix 1.**

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT:

Based on the Tier 0 approach under the new FDA guidance (see reference 1) for the submission of EA's, format item 7 is not normally needed if the maximum expected environmental concentration is less than 1 part per billion (ppb). The expected introduction concentration (EIC) of mometasone furoate has been calculated to be less than 1 ppb, and thus, fate information has not been provided.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Based on the Tier 0 approach under the new FDA guidance (see reference 1) for the submission of EA's, format item 8 is not normally needed if the maximum expected environmental concentration is less than 1 ppb. The EIC of mometasone furoate has been calculated to be less than 1 ppb, and thus, information on effects has not been provided.

9. USE OF RESOURCES AND ENERGY:

Based on the Tier 0 approach under the new FDA guidance (see reference 1) for the submission of EA's, format item 9 is not normally needed if the maximum expected environmental concentration is less than 1 ppb. The EIC of mometasone furoate has been calculated to be less than 1 ppb, and thus, information on the use of resources and energy has not been provided.

10. MITIGATION MEASURES:

Based on the Tier 0 approach under the new FDA guidance (see reference 1) for the submission of EA's, format item 10 is not normally needed if the maximum expected environmental concentration is less than 1 ppb. The EIC of mometasone furoate has been calculated to be less than 1 ppb, and thus, information regarding mitigation measures has not been provided.

11. ALTERNATIVES TO THE PROPOSED ACTION:

Based on the Tier 0 approach under the new FDA guidance (see reference 1) for the submission of EA's, format item 11 is not normally needed if the maximum expected environmental concentration is less than 1 ppb. The EIC of mometasone furoate has been calculated to be less than 1 ppb, and thus, information regarding alternatives to the proposed action has not been provided.

12. LIST OF PREPARERS

The information contained in this Environmental Assessment was provided by the following individuals:

Schering-Plough Corporation

Joseph A. Nusser	Sr. Dir. Env. Projects & Compliance
Carol M. Fletcher	Principal Environmental Engineer
Ravi K. Chivukula	Manager, Regulatory Affairs
Philip Apruzzese	Manager Plant Services
Judith Stettner	Environmental Engineer
Andrew R. Anderson	Environmental Engineer

Schering-Plough Products, Inc.

Samuel Laguna-Garcia	Environmental Compliance Engineer
Carlos M. Jimenez-Barber	Environmental Compliance Manager

Information on the qualifications of these individuals is presented at the end of this document in Appendix 2.

13. CERTIFICATION:

The undersigned official certifies that the information presented ' true, accurate and complete to the best of the knowledge of the Schering-, lough Corporation.

Appendix 1 of this document contains information which is considered confidential in nature and is therefore not releasable to the public.

The undersigned official certifies that the EA summary document and Appendices 2 and 3 contain non-confidential information and understands that this information will be made available to the public in accordance with 40 CFR 1506.6

Date: 5/13/97

By: for Russ Cole

Joseph A. Nusser, P.E.
Senior Director
Environmental Projects & Compliance
Schering Laboratories

14. REFERENCES:

1. *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications asn Supplements,*

Washington, D.C., Center for Drug Evaluation and Research (CDER) Food and Drug Administration, November 1995.

15. APPENDICES:

Appendix 1: Confidential EA Information Regarding the Manufacture and Production Estimates of Mometasone Furoate Aquous Nasal Suspension

Appendix 2: Qualifications of Preparers

Appendix 3: Material Safety Data Sheet (MSDS) for Mometasone Furoate Monohydrate

APPENDIX 2

Non-confidential Information

Qualifications of Preparers

APPENDIX 2

Qualifications of Preparers

Joseph A. Nusser, P.E.

Education: ME, Environmental Engineering, Manhattan College, 1971
MS, Civil Engineering, New York University, 1969
BCE, Civil Engineering, Manhattan College, 1967

Experience: Senior Director Environmental Affairs, Schering-Plough, 1985-present
Environmental Engineer, USEPA, 1984-1985
Principal Engineer, Joseph A. Nusser & Associates, 1980-1984
Project Manager, Hydroscience, Inc. 1970-1980

Carol M. Fletcher, P.E.

Education: ME, Environmental Engineering, Stevens Institute of Technology, 1996
BE, Chemical Engineering, Stevens Institute of Technology, 1985

Experience: Principal Environmental Engineer, Schering-Plough, 1993-present
Supervising Environmental Engineer, Sadat Associates, 1992-1993
Associate Engineer, Shell Oil Company, 1989-1992
Environmental Engineer, Mobil Chemical Company, 1988-1989
Assistant Environmental Engineer, NJDEP, 1986-1988

Ravi K. Chivukula

Education: MS, Pharmaceutics, University of Houston, 1987
B. Pharm, Andhra University, 1982

Experience: Mgr. Regulatory Affairs, Schering-Plough, 1992-present
Regulatory Affairs Associate, Warner Lambert/Parke-Davis, 1987-1992

Philip Apruzzese

Education: MS, Technology Management, Stevens Institute of Technology, 1993
BS, Chemical Engineering, Stevens Institute of Technology, 1970

Experience: Manager Plant Services, Schering-Plough, 1991-present
Operations Manager, Schering-Plough, 1987-1991
Engineering Manager, Schering-Plough, 1985-1987

Judith Steiner

Education: BS, Environmental Engineering, Rensselaer Polytechnic Institute, 1990

Experience: Environmental Engineer, Schering-Plough, 1993-present
Associate Engineer, Ebasco Environmental, 1990-1993

Andrew R. Anderson, P.E.

Education: ME, Environmental Engineering, Manhattan College, 1976
BS, Mechanical Engineering, Union College, 1970

Experience: Senior Associate, Malcolm Pirnie, Inc., 1990-1996
Principal Engineer, Geraghty &Miller, Inc., 1988-1990
Associate, Malcolm Pirnie, Inc., 1980-1988
Environmental Engineer, Hydroscience, Inc., 1978-1980

Samuel Laguna-Garcia, P.E.

Education: BS, Chemical Engineering, University of Puerto Rico, 1981

Experience: Env. Compliance Engineer, Schering-Plough Products, 1992-present
Environmental Engineer, Pedro Panzardi and Assoc., 1990-1992
Engineer, Puerto Rico Env. Quality Board, 1989-1990
Env. Specialist, Solid Waste Management Authority, 1987-1989

Carlos M. Jimenez-Barber

Education: MS, Physics, Unversity of Rochester
BS, Physics, University of Puerto Rico

Experience: Env. Compliance Manager, Schering-Plough Products, 1987-present
Vice President, Puerto Rico Env. Quality Board, 1985-1987
Environmental Manager, Squibb, 1976-1978
President, Puerto Rico Env. Quality Board, 1973-1976

APPENDIX 3

Non-confidential Business Information

Material Safety Data Sheet (MSDS) for Mometasone Furoate Monohydrate

rial Safety Data Sheet

NE FUROATE

Page: 1
Rev. Date 05/14/96

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

COMPANY CONTACT: Safety & Industrial Hygiene
TELEPHONE NUMBER: (908)298-5044

EMERGENCY TELEPHONE NUMBER
Safety and Industrial Hygiene (908)298-5044

PROD T NAME: MOMETASONE FUROATE
PRODUCT CODE: SCH 32088
CAS NUMBER: 83919-23-7
CHEMICAL FAMILY: Steroid
CHEMICAL FORMULA: C27 H30 C12 O6

SYNONYMS: 9-ALPHA,21-DICHLORO-11 BETA,17-DIHYDROXY-16 ALPHA-METHYLPREGNA-1,4-DIENE-3,20 DIONE 17-(2-FUROATE)
ELOCON
SCH 32088

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT NAME	EXPOSURE LIMITS	CONCENTRATION PERCENT BY WEIGHT
Mometasone Furoate	PEL	
CAS NUMBER: 83919-23-7	TLV	
	None	
	None	

3. HAZARDS IDENTIFICATION

POTENTIAL HEALTH EFFECTS

EYES
Although mometasone furoate was not irritating to the eyes in laboratory studies, it may produce eye irritation or an allergic reaction in sensitive individuals.

SKIN
May produce skin irritation in sensitive individuals. Other symptoms include burning, itching, and dryness. Systemic absorption through the skin producing suppression of adrenal gland function or target organ effects is possible.

INGESTION
Mometasone furoate is slightly hazardous by ingestion based upon the oral LD 50 in rats of greater than 2000 mg/kg. Ingestion of sufficient quantities may produce reversible suppression of the hypothalmic/pituitary/adrenal (HPA) system, manifestations of Cushing's syndrome (redistribution of fat, often with great obesity, muscular weakness, skeletal weakness, and blood pressure. The face often assumes a rounded shape, the characteristic "moon face". Other symptoms associated with HPA suppression include high blood glucose levels often concurrent with the presence of sugar in the urine.

INHALATION
The exact effects of inhalation of mometasone furoate in humans are unknown, Acute inhalation studies using laboratory animals indicate a slight hazard. Other studies indicate that systemic absorption occurs producing effects in the thymus, adrenal and mammary glands, as well as liver, spleen, and blood changes consistent with exposure to glucocoticoids.

Material Safety Data Sheet MOMETASONE FUROATE	Page: 2 Rev. Date 05/14/96

4. FIRST AID MEASURES

EYES
Flush with water for at least 15 minutes. Obtain medical attention.

SKIN
Remove contaminated clothing. Wash exposed area with soap and water. Obtain medical attention.

INGESTION
Give copious amounts of water and induce vomiting, if conscious. Obtain medical attention.

INHALATION
Remove from exposure. If not breathing, give artificial respiration. Obtain medical attention.

5. FIRE FIGHTING MEASURES

FLAMMABLE PROPERTIES
FLASH POINT: n/a°F

FIRE AND EXPLOSION HAZARDS
Under normal conditions of use this material does not pose a significant fire or explosion hazard. However, like most organic compounds, it is combustible and may form a dust explosion hazard if widely dispersed in air.

EXTINGUISHING MEDIA
Water,CO2, Dry Chemical

FIRE FIGHTING INSTRUCTIONS
Fight fire from a safe distance or protected location. Use water spray to keepcontainers and equipment cool. Wear full protective equipment including self-contained breathing apparatus (SCBA).

6. ACCIDENTAL RELEASE MEASURES

Sweep, scoop, or vacuum up spill. Minimize contact with spilled material. Keep other personnel away from the clean-up area. Wear appropriate respiratory protection and protective clothing in the spill area. Notify your supervisor immediately. Clean area with a wet mop. Dispose of spilled material and clean up materials as given in Waste Disposal Methods below.

7. HANDLING AND STORAGE

HANDLING AND STORAGE PRECAUTIONS
Store in double lined plastic in fiberboard or other appropriate container, Store in a cool, dry, well ventilated area.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

ENGINEERING CONTROLS
Provide adequate local exhaust ventilation.

EYE/FACE PROTECTION
Safety glasses/side shields.

SKIN PROTECTION
Lab Coat or uniform
Gloves- Latex.

RESPIRATORY PROTECTION
Minimum of half facepiece respirator with high efficiency cartridges.

Material Safety Data Sheet MOMETASONE FUROATE	Page: 3 Rev. Date 05/14/96

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE
White to off-white powder.

BASIC PHYSICAL PROPERTIES
MELTING POINT: 215-228°C
MOLECULAR WEIGHT: 521.40
SOLUBILITY (H2O): Insoluble

10. STABILITY AND REACTIVITY

STABILITY: Stable

HAZARDOUS DECOMPOSITION PRODUCTS
Hydrogen chloride

11. TOXICOLOGICAL INFORMATION

MISCELLANEOUS TOXICOLOGICAL INFORMATION
LD 50 oral (rats)> 2000 mg/kg. Mometasone furoate is classified as slightly hazardous via the oral route. In animal studies it was non-irritating to the skin and eyes. Acute inhalation toxicity studies at a maximum dust concentration of 0.68 mg/L did not produce any mortality although there were persistant signs of exposure during the 14 day observation period. These signs included rales, ano-genital staining, emaciation and body weight losses. Long term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility. Genetic toxicity tests with mometasone furoate (Ames test, mouse lymphoma assay, and Micronucleus test) did not show any mutagenic potential. Corticosteroids are generally teratogenic in test animals when administered systemically at relatively low dosage levels. They have also been shown to be teratogenic after dermal application in laboratory animals. There are no adequately controlled studies in pregnant women. Since risk cannot be ruled out, exposure of pregnant women to mometasone furoate should be controlled to the lowest levels possible.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE
Hypersensitivity to mometasone furoate or other corticosteroids.

12. ECOLOGICAL INFORMATION

NO DATA GIVEN

13. DISPOSAL CONSIDERATIONS

While not hazardous waste, material should be disposed in an environmentally sound manner. Incineration is the preferred disposal method.

14. TRANSPORT INFORMATION

PROPER SHIPPING NAME: N/A

15. REGULATORY INFORMATION

NO DATA GIVEN

16. OTHER INFORMATION

Hazard Rating - HEALTH: 1 Slight
- FIRE: 1 Slight
- REACTIVITY: 0 Negligible

Material Safety Data Sheet MOMETASONE FUROATE	Page: 4 Rev. Date 05/14/96

16. OTHER INFORMATION - Continued

REFERENCE DOCUMENTATION
Schering Toxicology Sourcing Document.
Physician's Desk Reference (1988)

OTHER SOLUBILITIES: Slightly soluble in octanol, very soluble in ethanol; soluble in acetone, DMF, dioxane, methanol, methylene chloride.

DISCLAIMER OF EXPRESSED AND IMPLIED WARRANTIES
Although reasonable care has been taken in the preparation of this document, we extend no warranties and make no representations as to the accuracy or completeness of the information contained therein, and assume no responsibility regarding the suitability of this information for the user's intended purposes or for the consequences of its use. Each individual should make a determination as to the suitability of the information for their particular purpose(s).

REVIEW FOR HFD-570

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review #1 of NDA 20-762
January 06, 1997

A. 1. **APPLICATION NUMBER:** NDA 20-762

APPLICANT: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

2. **PRODUCT NAME:** Nasonex (mometasone furoate) Nasal Spray

3. **DOSAGE FORM:** Mometasone furoate monohydrate (0.05% w/w) in 20 mL plastic spray bottles

4. **METHOD OF STERILIZATION:** None (non-sterile product). The product is preserved with benzalkonium chloride (0.2 mg/g) and phenylethyl alcohol (2.5 mg/g)

5. **PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION:** The proposed indication for the drug product is for the treatment of the symptoms of seasonal/perennial allergic rhinitis in adults and adolescents 12 years and older.

6. **DRUG PRIORITY CLASSIFICATION:** 3S

B. 1. **DATE OF INITIAL SUBMISSION:** Sept. 30, 1996

2. **DATE OF CONSULT:** Nov. 25, 1996

3. **RELATED DOCUMENTS:** (none)

4. **ASSIGNED FOR REVIEW:** Dec. 2, 1996

C. **REMARKS:** In addition to the microbial limits and preservative effectiveness testing review requested by HFD-570, this review addresses the microbiology content of the stability section.

APPEARS THIS WAY
ON ORIGINAL

D. CONCLUSIONS:

Preservative effectiveness testing, microbial limits testing, and the respective specifications are adequate for the drug product. The application is recommended for approval for issues concerning microbiology.

Neal Sweeney 1/6/97

Neal Sweeney, Ph.D.

PTC 1/13/97

cc:

Original NDA 20-762
HFD-570/ Division File
HFD-570/D. Toyer/C. Bertha/G. Poochikian/C. Schumaker
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, January 06, 1996
R/D initialed by P. Cooney January 06, 1996