CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20762

MEDICAL REVIEW(S)

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: Alexander S. Walker M.D.	**Date:** 09/04/97
Medical Team Leader: see secondary review memo M. Blumenthal	**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

2.0. TABLE OF CONTENTS

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, 02/13/97, 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 $\mu g/m^2$ 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. 4].

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:

(I) 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[a]	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=112)	BDP (n=116)	Placebo (n=116)	Overall Treatment P-Value[a]
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	60	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	98-270	
Duration of Condition (Years)				
Mean	19	20	20	0.97
Median	16	18	17	
Range (Min-Max)	2-68	2-68	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	61	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

(I) 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].

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-(
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 1-15																
--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	0.09	<.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 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 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	4.8	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 nasal																
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 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 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 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	0.06	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	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 16-30																
--am & pm nasal																
RAW	108	4.4	2.5	112	3.8	2.3	112	5.2	2.6	2.5	<.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	0.65	
%CHG	106	-36	50.4	112	-49	31.1	112	-30	36.7							
--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 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	E
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	
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$_{DAY\ 1\text{-}15}$ (Yes=Y/No=N)	Statistically Significant Response$_{DAY\ 16\text{-}30}$ (Y/N)	Statistically Significant Response$_{Endpoint}$ (Y/N)
NASAL			
--Rhinorrhea	Yes	No (p=0.06)[2]	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 ($p \leq 0.01$).

(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$_{DAY16-30}$	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]:

AM & PM AVERAGED DIARY TOTAL SYMPTOM SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

	(A) MOMETASONE			(B) FAMCIRASE 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	112	13.1	4.4	116	12.8	4.6	116	13.1	4.1	4.2	0.86	<.01	0.95	0.4	0.93	0.44
1-15 RAW	112	8.4	4.4	116	7.8	3.8	116	10.2	3.6	3.9	<.01	<.01	0.66	<.01	0.09	<.01
CHG	112	-4.7	4.4	116	-4.8	3.9	116	-2.8	3.7	4.0	<.01	0.27	0.96	0.99	0.98	<.01
%CHG	112	-33	41.9	116	-36	28.5	116	-19	26.5							
16-30 RAW	108	7.6	4.8	112	6.1	4.4	112	8.4	4.8	4.8	<.01	<.01	0.44	0.01	0.34	<.01
CHG	108	-5.3	4.4	112	-6.9	4.9	112	-4.7	4.8	4.8	0.97	0.01	0.84	0.98	0.37	0.01
%CHG	108	-38	36.6	112	-49	34.4	112	-34	34.6							
ENDPT RAW	112	8.0	4.9	116	6.3	4.4	116	9.0	4.8	4.5	<.01	<.01	0.4	<.01	0.36	<.01
CHG	112	-5.1	4.4	116	-6.4	4.9	116	-4.1	4.9	4.9	0.91	0.02	0.62	0.08	0.38	<.01
%CHG	112	-33	35.2	116	-48	34.9	116	-32	34.5							

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)
@ SUM OF THE 6 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
%CHG PERCENT CHANGE VALUES WERE NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

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

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

INTENT-TO-TREAT POPULATION

AM DIARY TOTAL SYMPTOM SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

	(A) MOMETASONE			(B) VANCERASE 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	112	13.2	4.4	116	12.8	4.6	116	13.3	4.1	4.1	0.46	<.01	0.83	0.24	0.81	0.34
1-15 RAW	112	8.4	4.6	116	7.8	3.9	116	10.4	3.9	4.0	<.01	<.01	0.80	<.01	0.15	<.01
CHG	112	-4.8	4.2	116	-4.7	3.9	116	-2.8	3.7	4.0	<.01	0.18	0.86	0.85	0.99	<.01
%CHG	112	-33	40.5	116	-34	30.0	116	-18	28.0							
16-30 RAW	108	7.6	4.9	112	6.3	4.4	112	8.6	4.7	4.5	<.01	<.01	0.38	0.01	0.4	<.01
CHG	108	-5.3	4.4	112	-6.9	4.9	112	-4.7	4.8	4.8	0.86	0.01	0.83	0.10	0.34	0.02
%CHG	108	-36	40.5	112	-48	34.2	112	-34	34.8							
ENDPT RAW	112	-8.1	5.1	116	6.5	4.4	116	9.0	4.7	4.6	<.01	<.01	0.32	<.01	0.49	<.01
CHG	112	-5.1	4.6	116	-6.3	4.4	116	-4.1	4.9	4.9	0.83	0.01	0.81	0.08	0.37	0.01
%CHG	112	-34	40.4	116	-47	34.4	116	-32	36.4							

ATTACHMENT 1--continued

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

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

INTENT-TO-TREAT POPULATION

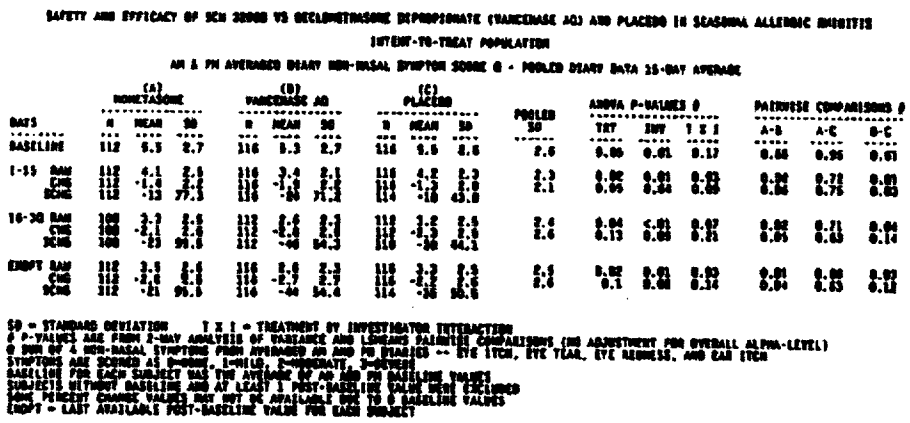
PM DIARY TOTAL SYMPTOM SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

	(A) BECLOMETHASONE			(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	111	12.8	4.5	118	12.6	4.8	116	13.0	4.4	4.5	0.84	0.81	0.12	0.7	0.86	0.57
1-15 RAW	111	-3.1	4.3	118	-2.8	4.8	116	-0.8	4.0	3.9	<.01	<.01	0.06	0.06	0.03	<.01
SCORE	111	-3.0	4.7	118	-2.8	5.3	116	-0.8	3.9	4.3	<.01	0.88	0.05	0.06	0.03	<.01
	111	-19	60.0	118	-33	35.3	116	-10	31.7							
16-30 RAW	108	-2.7	4.8	111	-2.9	4.4	112	-0.3	4.3	4.3	<.01	<.01	0.04	0.01	0.3	<.01
SCORE	108	-2.8	5.5	111	-2.7	5.3	112	-0.3	4.8	4.8	0.01	0.88	0.06	0.04	0.43	<.01
	108	-29	82.1	111	-40	38.9	112	-14	37.8							
EXPT RAW	111	-2.8	4.8	118	-2.1	4.4	116	-0.5	4.0	4.1	<.01	<.01	0.03	0.01	0.02	<.01
SCORE	111	-2.9	5.5	118	-2.1	5.3	116	-0.5	4.1	4.5	0.01	0.88	0.03	0.06	0.38	<.01
	111	-30	91.2	118	-40	39.2	116	-12	38.2							

ATTACHMENT 1--continued

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

(A) Subject a.m. and p.m. combined scores [172:302]:



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

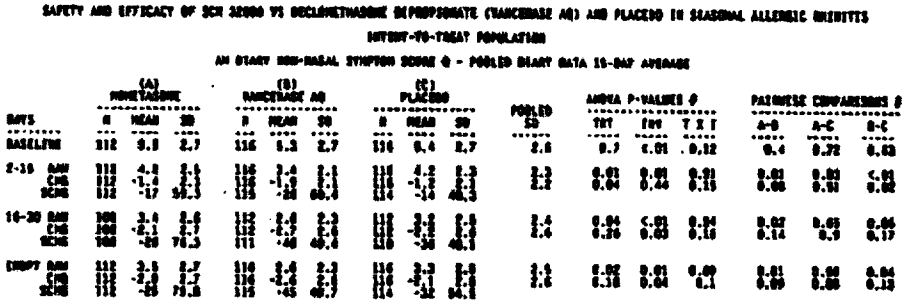
INTENT-TO-TREAT POPULATION

AM & PM AVERAGED DIARY NON-NASAL SYMPTOM SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

	(A) MOMETASONE			(B) VANCERASE 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	112	9.5	2.7	116	9.3	2.7	116	9.6	2.6	2.6	0.00	0.01	0.17	0.66	0.95	0.61
1-15 RAW	112	-4.1	2.1	116	-3.4	2.1	116	-4.2	2.3	2.3	0.02	0.01	0.03	0.20	0.72	0.03
ITT	112	-4.1	2.1	116	-3.4	2.1	116	-4.2	2.3	2.1	0.00	0.00	0.00	0.00	0.75	0.00
PCWR	112	-15	77.5	116	-30	71.2	116	-10	43.8							
16-30 RAW	108	-3.3	2.5	112	-2.6	2.3	110	-3.2	2.5	2.4	0.04	<.01	0.07	0.00	0.71	0.04
ITT	108	-3.1	2.4	112	-2.6	2.3	110	-3.2	2.5	2.4	0.13	0.00	0.21	0.00	0.63	0.14
PCWR	108	-23	99.0	112	-40	64.3	110	-30	64.1							
EMPT RAW	112	-3.5	2.5	116	-2.9	2.3	116	-3.2	2.5	2.5	0.02	0.01	0.03	0.01	0.00	0.03
ITT	112	-3.4	2.5	116	-2.9	2.3	116	-3.2	2.5	2.5	0.1	0.00	0.10	0.04	0.05	0.12
PCWR	112	-21	99.1	116	-44	54.4	114	-30	60.6							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LEHMANN 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
%CHG PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
EMPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

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



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

INTENT-TO-TREAT POPULATION

AM DIARY NON-NASAL SYMPTOM SCORE @ - POOLED DIARY DATA 15-DAY AVERAGE

	(A) MOMETASONE			(B) VANCERASE 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	112	9.8	2.7	116	9.3	2.7	116	9.4	2.7	2.6	0.7	<.01	0.12	0.4	0.72	0.03
2-15 RAW	111	-4.1	2.1	116	-3.4	2.1	116	-4.2	2.3	2.2	0.01	0.01	<.01	0.02	0.03	<.01
ITT	111	-4.1	2.1	116	-3.4	2.1	116	-4.2	2.3	2.2	0.04	0.01	0.15	0.06	0.01	0.02
PCWR	112	-17	99.3	116	-30	60.4	114	-14	45.3							
16-30 RAW	108	-3.4	2.6	112	-2.6	2.3	110	-3.2	2.5	2.4	0.04	<.01	0.04	0.02	0.03	0.05
ITT	108	-3.1	2.7	112	-2.6	2.3	110	-3.2	2.5	2.4	0.16	0.00	0.10	0.14	0.9	0.17
PCWR	108	-26	98.3	111	-40	60.4	110	-30	60.1							
EMPT RAW	111	-3.5	2.7	116	-2.9	2.3	116	-3.2	2.5	2.5	0.02	0.01	0.09	0.01	0.00	0.04
ITT	111	-3.4	2.7	116	-2.9	2.3	116	-3.2	2.5	2.5	0.10	0.04	0.1	0.04	0.06	0.13
PCWR	111	-26	98.8	115	-45	60.7	114	-32	64.1							

ATTACHMENT 1--continued

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

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

INTENT-TO-TREAT POPULATION

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

	(A) NONETASONE			(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	111	5.3	2.0	116	5.3	2.0	116	5.5	2.2	2.0	0.61	0.84	0.22	>.99	0.50	0.50
1-15 RAW	111	3.9	2.4	115	3.4	2.2	111	4.1	2.3	2.3	0.04	<.01	0.03	0.08	0.02	0.01
1-15 SCHE	107	3.6	1.9	114	3.0	1.8	113	3.9	2.1	2.0	0.11	0.08	0.04	0.07	0.08	0.07
16-30 RAW	108	3.3	2.3	111	2.9	2.3	111	3.5	2.5	2.5	0.04	<.01	0.01	0.03	0.01	0.04
16-30 SCHE	104	3.0	1.9	110	2.7	2.0	108	3.4	2.4	2.2	0.06	0.08	0.04	0.03	0.01	0.14
SHIFT RAW	111	3.4	2.4	115	3.0	2.3	111	3.3	2.4	2.4	0.03	<.01	0.05	0.05	0.08	0.05
SHIFT SCHE	107	3.2	1.9	114	2.8	2.0	108	3.2	2.3	2.1	0.09	0.11	0.13	0.03	0.08	0.14

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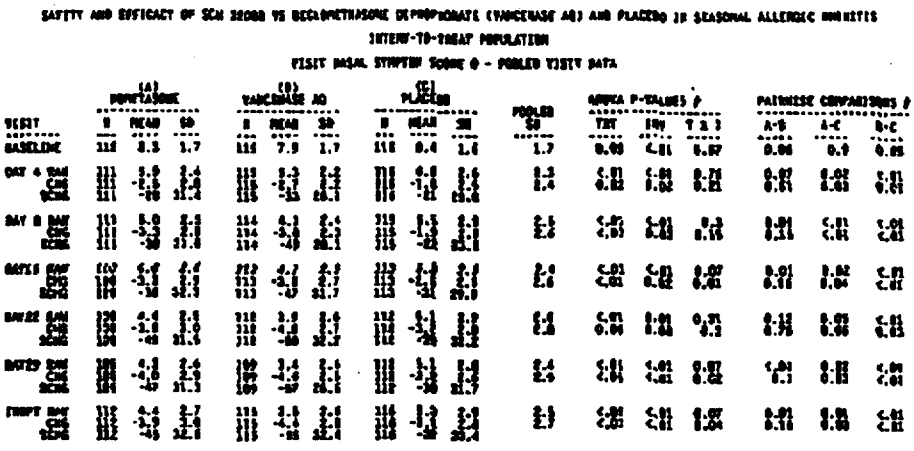
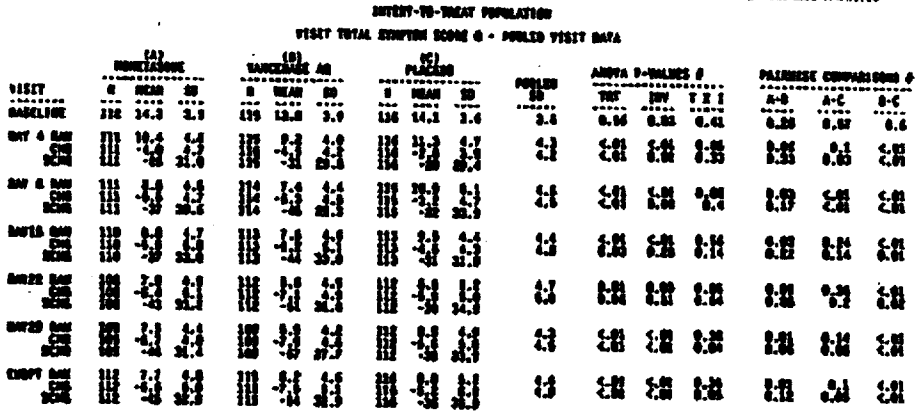
APPEARS THIS WAY
ON ORIGINAL

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

	(A) MOMETASONE			(B) VANCERASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
VISIT	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	DAY	T X D	A-B	A-C	B-C
BASELINE	112	0.0	2.4	115	0.0	2.0	116	0.7	2.6	2.3	0.07	0.04	0.26	0.74	0.26	0.10
DAY 4 RAW	[illegible]			[illegible]			[illegible]									
DAY 8 RAW	[illegible]			[illegible]			[illegible]									
DAY15 RAW	[illegible]			[illegible]			[illegible]									
DAY22 RAW	[illegible]			[illegible]			[illegible]									
DAY29 RAW	[illegible]			[illegible]			[illegible]									
ENDPT RAW	[illegible]			[illegible]			[illegible]									

SD = STANDARD DEVIATION T X D = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LEAST-SQUARES PAIRWISE COMPARISONS AND 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
RAW: PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

ATTACHMENT 1--continued

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

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 CONDITION (POOLED)

VISIT	(A) BECLOMETHASONE N	MEAN	SD	(B) VANCERASE 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	2.3	0.6	115	2.2	0.6	116	2.3	0.6	0.6	0.25	<.01	0.80	0.16	0.96	0.14
DAY 4 RAW	111	-1.7	0.7	113	-1.3	0.7	116	-1.0	0.7	0.9	0.01	0.1	0.56	0.21	0.05	<.01
DAY 4 CHG	111	-1.7	0.8	113	-1.3	0.8	116	-1.0	0.8	0.9	0.09	0.33	0.80	0.33	0.08	0.06
DAY 8 RAW	111	-1.9	0.6	114	-1.6	0.6	114	-1.3	0.7	0.6	<.01	<.01	0.29	0.11	<.01	<.01
DAY 8 CHG	111	-1.9	0.6	114	-1.6	0.7	114	-1.3	0.6	0.7	<.01	<.01	0.01	0.32	<.01	<.01
DAY15 RAW	110	-1.9	0.7	113	-1.6	0.7	113	-1.3	0.7	0.7	<.01	<.01	0.10	0.08	<.01	<.01
DAY15 CHG	110	-1.9	0.8	113	-1.6	0.8	113	-1.3	0.8	0.8	<.01	<.01	0.1	0.18	0.05	0.01
DAY22 RAW	109	-1.9	0.7	111	-1.7	0.7	112	-1.5	0.7	0.7	0.01	<.01	0.8	0.4	0.03	<.01
DAY22 CHG	109	-1.9	0.8	111	-1.7	0.8	112	-1.5	0.8	0.8	<.01	<.01	0.56	0.04	0.07	0.06
DAY29 RAW	105	-1.9	0.7	109	-1.6	0.8	111	-1.4	0.7	0.8	<.01	<.01	0.1	0.07	0.01	<.01
DAY29 CHG	105	-1.9	0.8	109	-1.6	0.9	111	-1.4	0.8	0.8	<.01	<.01	0.02	0.11	0.04	<.01
EXPT RAW	111	-1.9	0.8	115	-1.7	0.7	115	-1.3	0.7	0.7	<.01	<.01	0.02	0.06	0.03	<.01
EXPT CHG	111	-1.9	0.8	115	-1.7	0.8	115	-1.3	0.8	0.8	<.01	<.01	0.02	0.06	0.03	<.01

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND ADJUSTED PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
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
MODEL: SCORE = TREATMENT (TRT) INVESTIGATOR (INV) TREATMENT X INVESTIGATOR (T X I)

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

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 CONDITION (POOLED)

VISIT	(A) BECLOMETHASONE N	MEAN	SD	(B) VANCERASE 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	2.3	0.6	115	2.2	0.6	116	2.2	0.6	0.6	0.65	0.46	0.62	0.88	0.88	0.96
DAY 4 RAW	111	-1.6	0.7	113	-1.3	0.7	113	-1.1	0.7	0.9	0.04	<.01	0.65	0.17	0.01	0.03
DAY 4 CHG	111	-1.6	0.8	113	-1.3	0.8	113	-1.1	0.8	0.9	<.01	0.11	0.61	0.03	<.01	<.01
DAY 8 RAW	111	-1.7	0.7	111	-1.4	0.7	113	-1.2	0.8	0.7	<.01	<.01	0.16	0.03	<.01	<.01
DAY 8 CHG	111	-1.7	0.8	111	-1.4	0.7	113	-1.2	0.8	0.7	<.01	<.01	0.1	0.03	<.01	<.01
DAY15 RAW	110	-1.7	0.7	111	-1.4	0.7	113	-1.2	0.7	0.7	0.01	<.01	0.16	0.02	0.10	<.01
DAY15 CHG	110	-1.7	0.8	111	-1.4	0.8	113	-1.2	0.8	0.8	<.01	<.01	0.16	0.02	0.10	<.01
DAY22 RAW	109	-1.6	0.7	110	-1.3	0.7	111	-1.1	0.7	0.8	<.01	<.01	0.04	0.03	0.01	<.01
DAY22 CHG	109	-1.6	0.8	110	-1.3	0.8	111	-1.1	0.8	0.8	<.01	<.01	0.12	0.02	0.01	<.01
DAY29 RAW	105	-1.6	0.8	108	-1.3	0.8	111	-1.1	0.8	0.8	<.01	<.01	0.12	0.02	0.01	<.01
DAY29 CHG	105	-1.6	0.8	108	-1.3	0.8	111	-1.1	0.8	0.8	<.01	<.01	0.12	0.02	0.01	<.01
EXPT RAW	111	-1.6	0.8	115	-1.3	0.8	116	-1.1	0.8	0.8	<.01	<.01	0.06	0.03	0.01	<.01
EXPT CHG	111	-1.6	0.8	115	-1.3	0.8	116	-1.1	0.8	0.8	<.01	<.01	0.06	0.03	0.01	<.01

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND ADJUSTED PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
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
MODEL: SCORE = TREATMENT (TRT) INVESTIGATOR (INV) TREATMENT X INVESTIGATOR (T X I)

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) FLUTICASONE			(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 RAN	111	3.3	1.0	115	3.2	1.0	116	3.0	0.9	0.9	0.01	<.01	0.04	0.4	0.03	<.01
DAY 8 RAN	111	3.0	1.0	114	2.7	1.0	111	2.5	1.0	1.0	<.01	<.01	0.37	0.04	<.01	<.01
DAY15 RAN	110	3.0	1.1	113	2.8	0.9	113	2.3	1.0	1.0	<.01	<.01	0.31	0.05	0.03	<.01
DAY22 RAN	108	2.9	1.1	112	2.7	1.1	112	2.2	1.1	1.0	<.01	<.01	0.04	0.08	0.1	<.01
DAY29 RAN	105	3.0	1.1	108	2.6	1.0	111	2.3	1.1	1.0	<.01	<.01	0.32	0.01	0.02	<.01
ENDPT RAN	112	3.0	1.2	115	2.7	1.1	116	2.4	1.1	1.1	<.01	<.01	0.13	0.03	0.01	<.01

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
@ P-VALUES ARE FROM F-TEST ANALYSIS OF VARIANCE AND LEAST SQUARES 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) FLUTICASONE			(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 RAN	111	3.1	1.2	115	3.2	1.1	116	3.0	1.1	1.0	0.06	<.01	0.36	0.29	0.23	0.02
DAY 8 RAN	111	3.0	1.2	114	2.7	1.1	111	2.5	1.1	1.0	<.01	<.01	0.49	0.04	<.01	<.01
DAY15 RAN	110	3.0	1.2	113	2.8	1.0	113	2.3	1.0	1.0	<.01	<.01	0.11	0.07	0.02	<.01
DAY22 RAN	108	2.9	1.1	112	2.7	1.1	112	2.1	1.2	1.1	0.02	<.01	0.37	0.02	0.04	0.01
DAY29 RAN	105	2.9	1.2	108	2.6	1.2	110	2.2	1.2	1.1	<.01	<.01	0.03	0.01	0.04	<.01
ENDPT RAN	112	2.9	1.2	115	2.5	1.2	116	2.3	1.3	1.1	<.01	<.01	0.02	0.01	0.02	<.01

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
@ P-VALUES ARE FROM F-TEST ANALYSIS OF VARIANCE AND LEAST SQUARES 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 in 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. C93-013).

	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.

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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 also 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	-6.78	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	-6.89	83	-4.01	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	-7.96	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	-6.89	95	-6.49	97	-7.66	95	-7.44	95	-4.61	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	8.4	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 specification 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:

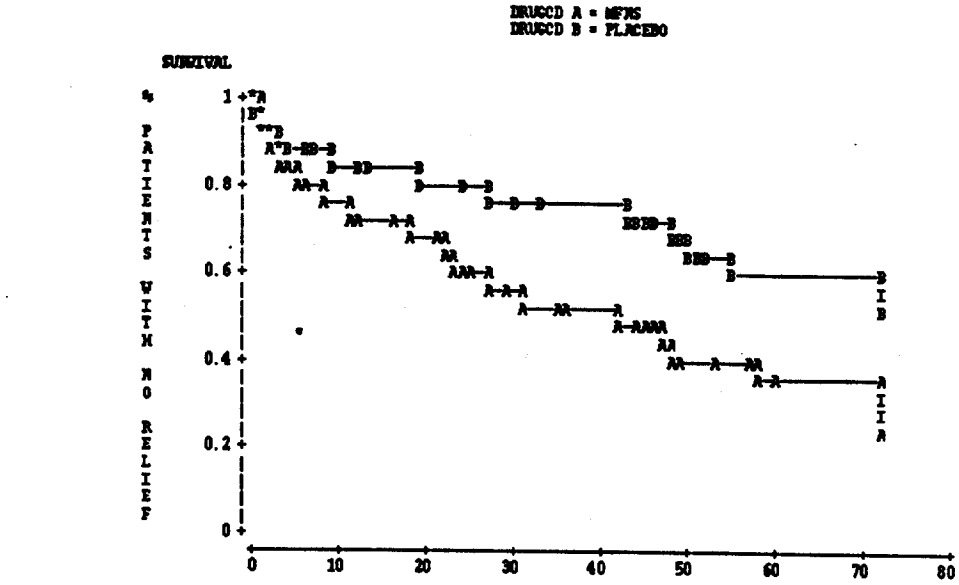
A total of 201 subjects were enrolled into the study, with 1 immediate dropout post-randomization, leaving 200 subjects in the safety (intent-to-treat) population. Three additional subject exclusions resulted in 197 subjects analyzed in the efficacy population. For the ITT population, 101 subjects comprised 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	17.000844	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	-	-	-
[1]–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	<.01
	CHANGE	-2.2	-1.1	<.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	<.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.

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.