8.10. Trial I93-133. Safety and Efficacy of Mometasone Furoate Nasal Spray in the Prophylactic Treatment of Seasonal Allergic Rhinitis (SAR).

Principal Investigator: Michael A Drouin, M.D.

Participating Centers: 18 international centers (including Canada).

8.10.1. OBJECTIVE:

1. To evaluate the efficacy of a four week course of mometasone aqueous nasal spray 200 μg qd vs. budesonide (Rhinocort Aqua) 400 μg qd, and vs. placebo in the prophylaxis of symptoms of SAR.
2. To evaluate the efficacy and safety of an 8 week course of mometasone aqueous nasal spray in the treatment of symptoms of SAR.

8.10.2. STUDY DESIGN:

This was a Phase III, randomized, multi-center, double-blind, double-dummy, active- and placebo-controlled, parallel group trial in adult subjects with seasonal allergic rhinitis. Study medications were given to SAR subjects for a total duration of 8 weeks, 4 weeks of which were prophylaxis treatment prior to the anticipated onset of the pollen season.

8.10.3. PROTOCOL:

8.10.3.1.a. POPULATION:

Significant entry criteria consisted of the following: (1) age ≥ 12 years [206:14, 208:881], (2) presence of IgE-mediated hypersensitivity to at least one seasonal allergen relevant for the site and duration of the study (i.e. tree, grass, or weed pollen but individual species were not specified in protocol), as documented by a positive skin test within 1 year of study entry via the prick testing method (≥ 3 mm in diameter than diluent control) [206:14, 208:881], and (3) asymptomatic clinical status (total nasal symptom score ≤ 2) and no nasal or non-nasal symptom rated as moderate or severe (i.e. symptom score=2 or 3) on a 0-3 scale at the Screening and Baseline visits [206:14, 208:881]. Subjects symptomatic or anticipated to become symptomatic to a perennial allergen during the study duration (e.g. molds, dust mites, animal dander) were excluded from study enrollment [206:15, 208:882].

8.10.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1. of Trial I93-133 in the NDA submission [206:13, 208:914] and is essentially identical to the study design of SAR prophylaxis study C93-215 with two exceptions [208:888-901]. In contrast to study C93-215, subjects in study I93-133 were assessed by a physician on day 15 and day 43 rather than on day 22 and day 50. Thus, subjects in study I93-133 were evaluated during the following study

visits: screening (Visit 1), baseline (Visit 2), day 8 (Visit 3), day 15 (Visit 4), day 22 (Visit 5), day 29 (Visit 6), day 36 (Visit 7), day 43 (Visit 8), day 57 (Visit 9), and day 71 (Visit 10, if an extra treatment period was necessary because of a delay in the onset of the pollen season) [206:32, 208:889]. Furthermore, subjects were allowed to use loratadine (up to 10 mg po qd) as a rescue medication after the baseline visit for control of 'intolerable' SAR symptoms [206:19, 208:880, 903]. As in all the other SAR trials for this NDA submission, SAR symptoms which consisted of individual and total nasal, non-nasal, and total (nasal + non-nasal) SAR symptoms were rated on a 0-3 symptom scale, reflectively over the previous 12 hours [206:25-26, 208:900-901, 908]. Physical examination (excluding eye exam and intraocular pressure measurements) and laboratory tests (excluding HPA-axis suppression evaluation) were performed on the first (screening) and last visit(s) (visit 9 and/or 10) of the study [206:13, 208:914]. Safety evaluations were completed at each study visit and consisted of a review by the principal investigator of any adverse events experienced by the subject and checking of vital signs of each study subject [208:914].

A double-dummy design was utilized in drug delivery for trial I93-133 using matching placebos for each bottle type, since the mometasone and budesonide medication bottles were not identical in appearance. Although subjects received bottles of differing appearance, they were blinded as to which bottles contained active drug or placebo [208:902]. The three treatment groups consisted of:

(A) Mometasone aqueous nasal spray 200 µg qd		
a.m. dosing:	Bottle 1: Mometasone	Bottle 2: Rhinocort Placebo
(B) Budesonide nasal spray (Rhinocort Aqua) 400 µg qd		
a.m. dosing:	Bottle 1: Mometasone placebo	Bottle 2: Rhinocort
(C) Placebo (0 µg qd)		
a.m. dosing:	Bottle 1: Mometasone placebo	Bottle 2: Rhinocort placebo

Given a similar study design to SAR prophylaxis trial C93-215, the primary, secondary and supplementary efficacy variables were likewise similar.

The primary efficacy variable was defined as the: **The mean proportion of minimal symptom days during the ragweed pollen season for the ITT population**--i.e. the days when the **total nasal symptom score** (defined as: the sum of individual symptom scores of: rhinorrhea, nasal congestion, sneezing, and nasal itch) was ≤ 2 based on the average of the a.m. + p.m. diary scores from the start of the pollen season, through the last day of treatment, day 57 or 71 (depending on the onset of the pollen season). The primary comparison of the study was a comparison of the mometasone treatment group vs. placebo [206:39-40, 208:908-909].

Secondary Efficacy Variables [206:40-41, 208:908-909] were defined as the following endpoints for the efficacy evaluable population (ITT data not included in the application except where otherwise noted):

(1) The proportion of minimal symptom days (total nasal symptom score ≤ 2) for the entire treatment period (ITT population).
(2) The number of days from the start of the pollen season to the first occurrence of a non-minimal symptom day (total nasal symptom score > 2).
(3) The number of days from the start of treatment to the first occurrence of a non-minimal symptom day (total nasal symptom score > 2).
(4) The proportion of minimal symptom days (total nasal symptom score ≤ 2) during the first week of the pollen season.
(5) The proportion of days during the pollen season when the total nasal symptom score=0 (i.e. the proportion of symptom-free days).

Supplementary efficacy endpoints for the efficacy evaluable population (exception (7) below) were defined in this study as the following:

(1) Mean change from baseline (*'baseline'* defined in this study as the mean of the a.m. and p.m. scores from the 7 consecutive days prior to the day of the baseline visit [206:36], 'baseline' not defined in the general study document Vol. 208) in total nasal symptom scores during the pollen season, as obtained from subject diaries (a.m. and p.m. combined) for: days 1-15 (day 1 being the first day of the pollen season), days 16-30, days 31-45, days 46-61, and the endpoint visit.
(2) Mean change from baseline in total symptom scores during the pollen season, as obtained from subject diaries (a.m. and p.m. combined) for: days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.
(3) Mean change from baseline in total non-nasal symptom scores during the pollen season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.
(4) Mean change from baseline in individual nasal symptom scores during the pollen season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.
(5) Mean change from baseline in individual non-nasal symptom scores during the pollen season, as obtained from subject diaries (a.m. and p.m. combined) for days 1-15, days 16-30, days 31-45, days 46-61, and the endpoint visit.
(6) All total (total SAR, total nasal, total non-nasal) and individual symptom scores, as determined by the physician (physician evaluations).
(7) The proportion of minimal symptom days (total nasal symptom score ≤ 2) during the prophylaxis period (ITT population).

8.10.4. RESULTS

A total of 514 subjects with SAR were enrolled into the study, with 1 subject excluded from all analyses (I93-133-14, #013) because he never received study medication. A total of 513 subjects were evaluated for safety in the intent-to-treat population; 168 subjects received mometasone, 172 subjects received budesonide, and 173 subjects received placebo [206:46]. Of the sponsor's efficacy evaluable subjects, 164 subjects received mometasone, 168 subjects received budesonide, and 168 subjects received placebo [206:46].

The treatment groups in this study were comparable with regard to demographic and disease characteristics with the exception of a statistically significant difference among the treatment groups in age (mean age of the mometasone group=31 years vs. mean age of the placebo group=35 years; p=0.01) and duration of condition (mean duration of SAR in the mometasone group=12 years vs. mean duration of SAR in the placebo group=14 years; p=0.03) [206:47]. Despite these differences, additional statistical analyses performed to assess the impact of treatment imbalance at baseline with respect to these two parameters failed to reveal an interaction of either variable with treatment (p>0.38) [209:1109]. Again, for all four treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the treatment groups was approximately equal. Furthermore, no statistically significant treatment group differences at baseline for the supplementary efficacy parameters of total symptom, total nasal and total non-nasal symptom scores [206:268, 308, 314] were detected.

An evaluation of the pollen count records (tree, grass or both) for the 18 participating centers in this study was, for the most part, consistent with findings in many of the other SAR studies of this NDA submission. One of the 18 centers (center I93-133-016) reported pollen counts for tree (cohort #02) [206:226], weed (cohort #03) [206:227], and grass (cohort #04) [206:228] which were not significantly elevated relative to baseline for at least part of the study duration. An additional problem noted in a significant number of study centers (center -06 (trees), -09 (tree/grass and weed), -12 (tree and grass), -13 (tree/grass/weed), -14 (grass), -15 (grass), -16 (weed and platanus) was that of inappropriate definition of the onset and/or peak onset and offset and/or peak offset of the pollen season where pollen counts did not correlate with the expected timepoint of the pollen season [206:208, 212-213, 216-217, 218, 221, 223, 227, and 229]. At many centers, pollen counts did not appear to be collected after the peak offset of the pollen season, consequently with the offset of the pollen season either not provided in the NDA submission or inappropriately defined [206: 205, 206, 212, 213, 214, 215, 216, 217, 221, 223, 224, 228, 229, 230, 231]. These potentially confounding issues in the NDA submission are not addressed (except in one section of the NDA where exploratory analyses were performed excluding study centers -09 and -016 [209:1110]) and given the possibility of inappropriate definition of pollen onset/offset at some study centers; make extrapolation of efficacy results across all

centers more difficult. The onset of the pollen season for any cohort at all centers was calculated to occur on average 26 days after the initiation of treatment (range 12-47 days) [206:51 and NDA 20-762, Response to FDA request on Prophylaxis studies, Schering Plough, Inc., 05/21/97, p. 2].

Analysis of the primary efficacy variable for the ITT population (the proportion of days during the 'pollen season' where the a.m. and p.m. mean total nasal symptom score ≤ 2) revealed that subjects in the mometasone treatment group had 84% of days with minimal total nasal symptoms, compared with 87% of minimal symptom days experienced by budesonide subjects, and 65% of minimal symptom days experienced by placebo subjects ($p<.01$ for mometasone vs. placebo and budesonide vs. placebo) [206:257]. While some subjects demonstrated a clinical response already during the prophylaxis period (a problem noted in study C93-215), the Sponsor used exploratory analysis to assess the impact of subjects with symptoms during the prophylaxis period by repeating the analysis of the primary efficacy variable using 2-way ANOVA but excluding those subjects who had non-minimal symptoms on at least 20%, 30%, 40% and 50% of days during the prophylaxis period [209:1110]. Results of this analysis failed to demonstrate a difference in the primary efficacy variable, with mometasone treated subjects still having a statistically greater proportion of minimal symptom days as compared with placebo ($p<.01$ for all 4 analyses) [209:1144-1148]. The Sponsor also performed exploratory analysis on the primary efficacy variable excluding 2 study centers (-09 and -016) because of possible ambiguity in the definition of the onset of the pollen season which may have led to misclassification of subjects with respect to cohort type (i.e. tree, grass, weed) [209:1110]. Results of this analysis also failed to demonstrate a difference in the primary efficacy variable with regard to clinical efficacy of mometasone in changing the proportion of minimal symptom days in subjects with SAR [209:1148].

A post-hoc analysis of the primary efficacy endpoint in subjects (n=32) receiving < 15 days of mometasone prophylaxis to determine the onset of action of mometasone revealed that even with 15 days of mometasone treatment, subjects had a statistically significantly greater proportion of 'minimal symptom days' (82%) than the placebo (n=27) group (60%, $p<.01$) [NDA 20,762, Response to FDA Request on Prophylaxis Studies, Schering, Inc., 05/21/97, p. 1-3]. Similar findings were noted for the active comparator, budesonide (n=28), in which budesonide treated subjects experienced 87% of days with minimal total nasal symptoms compared with the placebo group, [$p<.01$, Schering Response to FDA Request on Prophylaxis Studies, p. 1].

Findings for the secondary efficacy variables support those noted with the primary efficacy variable, namely that both active treatment groups displayed a greater proportion of 'minimal' or 'no symptom' days and/or a longer duration of time prior to onset of nasal symptoms, as compared with placebo [206:257, 264, 266, 209:1129,-1140, 1141-1142].

For the supplementary efficacy variables, results in general were similar to those noted in the pivotal SAR prophylaxis study C93-215. Subject symptom

scores tended to be in the same numerical range as those in study C93-215, and subjects in the 2 active treatment groups (mometasone and budesonide) demonstrated a statistically significant difference in subject evaluated total SAR, total nasal, and total non-nasal symptom scores throughout the study duration as compared with placebo. In terms of the subject rated total nasal symptom score for the day 1-15 interval of the pollen season (a.m. and p.m. combined), mometasone treated subjects exhibited a 0.3 unit increase in total nasal symptoms (a 149% increase from the prophylaxis period), compared with a 1.8 unit increase in total nasal symptoms (a 230% increase from the prophylaxis period). This difference between the mometasone treatment group and placebo was statistically significant at a p-value of <.01 [206:268]. Again, clinical efficacy of mometasone treatment (as compared with placebo) was more variable with regard to subject evaluated individual non-nasal symptoms or physician evaluated total and individual non-nasal symptoms. Nonetheless, during at least some study endpoints for each supplementary variable, mometasone treated subjects demonstrated statistically greater efficacy than the placebo group (See Table III.). While not statistically significantly different, the mean decrease in the individual non-nasal symptom scores from subject diaries and physician assessments were numerically greater for the mometasone treatment group than for placebo at some study endpoints [206:337-351] which would support prior clinical efficacy findings for mometasone.

One problem noted in study I93-133, similar to study C93-215 was again the issue of a significant decrease in study subject numbers (visit n values) for the % change in subject number (=n) for all subject evaluated symptom scores as the study progressed (total SAR, total nasal, total non-nasal, and individual nasal and non-nasal symptom scores). This decrease in subject number (=n) represented subjects who had 0 as a given symptom score with a resultant inability to compute the % change based on a denominator of 0. Acknowledging that the primary and secondary efficacy variables support the efficacy of mometasone in the prophylaxis of subjects with SAR, nonetheless the lack of incorporation of these subjects as data points into the supplementary efficacy variable analysis represents a study flaw which does not address symptom scores for all efficacy evaluable subjects.

Review of rescue medication use between the 3 treatment groups (ITT population) supported less frequent rescue medication use in the 2 active treatment groups. While 100/173 or 57.8% of placebo treated subjects used rescue medication (loratadine) >1 time during the course of the study, 73/168 or 43.5% of mometasone subjects and 54/172 or 31.4% of budesonide treated subjects used rescue medication [207:383]. Furthermore, mometasone and budesonide treated subjects who used rescue medication, tended to use it less often that the placebo group subjects; as supported by the smaller number of mometasone or budesonide subjects in the high frequency rescue medication use group [207:383].

No significant differences between a.m. and p.m. dosing of the treatment groups was detected in this study for total SAR, total nasal, total non-nasal and the individual nasal and non-nasal symptom scores; thus supporting the findings of

previous SAR studies in this NDA submission and confirming efficacy of mometasone as a once a day medication for the treatment of SAR symptoms [206:269-271, 308-310, 314-316, 325-335, 337-351]. Subject subset analysis by age, sex, and race did not reveal any significant differences from the overall subject population for the primary efficacy variable [206:260, 262]. Findings for the primary efficacy variables are summarized in Table I. below. Findings for the secondary and supplementary efficacy variables, respectively are summarized in Tables II. and III. below.

Table I. Primary Efficacy Variable of SAR and Treatment with Mometasone (ITT Population), [206:257]

1° EFFICACY VARIABLE	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1. Proportion of minimal sx days during the pollen season (total nasal sx score ≤ 2)	*Yes

sx=Symptom
* Note: Statistically significant response for 1° efficacy variable carried by 4 of the 18 study centers per the efficacy evaluable population (i.e. 14/18 centers had a statistically non-significant response [206:238-255].

Table II. Secondary Efficacy Variables of SAR and Treatment with Mometasone (Efficacy evaluable Subjects unless otherwise stated), [206:264, 209:1129, 1141]

2° EFFICACY VARIABLE	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1. Proportion of minimal sx days for the entire treatment period (ITT). (total nasal sx score ≤ 2)	Yes
2. # of days from the start of the pollen season to the first occurrence of a non-minimal sx day (total nasal sx score > 2)	Yes
3. # of days from the start of treatment to the first occurrence of a non-minimal sx day (total nasal sx score > 2)	Yes
4. Proportion of minimal sx days during the first week of the pollen season (total nasal sx score ≤ 2)	Yes
5. Proportion of asymptomatic days during the pollen season (total nasal sx score =0)	Yes

sx=Symptom, #=Number
ITT=Intent-to-treat population

Table III. Supplementary Efficacy Variables of SAR and Treatment with Mometasone (Efficacy evaluable subjects, unless otherwise specified), [206:237, 268-271, 272, 308-317, 321-335, 337-35, 358-361

Supplementary EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1.	Subject evaluated mean Δ in Total Nasal Sx Score DAY 1-15, DAY16-30, DAY 31-45, DAY 46-61, Endpoint Visit.	Yes:	Day 1-15, Day 16-30, Endpoint Visit	
		*N/E:	Day 31-45, Day 46-61	
2.	Subject evaluated mean Δ in Total SAR Sx DAY 1-15, DAY16-30, DAY 31-45, DAY 46-61, Endpoint Visit.	Yes:	Day 1-15, Day 16-30, Endpoint Visit	
		N/E:	Day 31-45, Day 46-61	
3.	Subject evaluated mean Δ in Total Non-nasal Sx DAY 1-15, DAY16-30, DAY 31-45, DAY 46-61, Endpoint Visit.	Yes:	Day 1-15, Day 16-30, Endpoint Visit	
		N/E:	Day 31-45, Day 46-61	
4.	Subject evaluated individual nasal Sx DAY 1-15, DAY16-30, DAY 31-45, DAY 46-61, Endpoint Visit.	Yes:	All 4 nasal sx: Day 1-15, Day 16-30, Endpoint Visit	
		N/E:	All 4 nasal sx: Day 31-45, Day 46-61	
5.	Subject evaluated individual non-nasal Sx DAY 1-15, DAY16-30, DAY 31-45, DAY 46-61, Endpoint Visit.	Yes:	Eye Tearing:	Day 1-15, Day 16-30, Endpoint visit
			Eye Redness:	Day 16-30, Endpoint visit
			Eye Itch:	Day 16-30, Endpoint visit
			Ear/Palatal Itch:	Day 16-30, Endpoint Visit
		N/E:	All 4 non-nasal sx: Day 31-45, Day 46-61	
6.	Physician evaluated total SAR, total nasal, total non-nasal, individual nasal and individual non-nasal sx	Yes:	Total SAR:	Day 15, 22, 36, 43, 57, Endpoint Visit
			Total Nasal:	Day 15, 22, 29, 36, 43, 57, Endpoint Visit
			Total Non-nasal:	Day 57
			Individual Nasal:	Rhinorrhea: Day 22, 36, 43, 57, Endpoint visit. Nasal congestion: Day 15, 22, 43, 57, Endpoint visit. Sneezing: Day 8, 15, 22, 29, 36, 43, 57, Endpoint visit. Nasal itch: Day 15, 22, 29, 36, 43, 57, Endpoint visit. N/E: All 4 nasal sx on Day 71.
			Individual Non-nasal:	All 4 individual non-nasal sx: Day 57
7.	Proportion of minimal sx days during the prophylaxis period (ITT).	Yes		

Δ=Change, Sx=Symptom, Rx=Treatment, ITT=Intent-to-Treat Population

NOTE: For efficacy variables 1-5, statistical assessment is based on the combined a.m. and p.m. symptom scores.

*N/E (Non-estimable): denotes numerically greater decrease in sx noted for the mometasone treatment group compared with placebo but p-value is non-estimable due to study underpowering.

8.10.4.3. ADVERSE EVENTS:

The safety analysis was based on 513 subjects in the ITT population; 168 subjects were treated with mometasone 200 µg qd, 172 subjects were treated with budesonide (Rhinocort) 400 µg qd, and 173 subjects were treated with placebo [206:66]. Adverse events were similar for all three treatment groups, with headache being the most frequently reported treatment-related adverse event.

Overall, adverse events were reported in 57% of subjects in the mometasone treatment group, 54% of subjects in the budesonide treatment group, and 57% of subjects in the placebo group [206:67-68]. Headache was reported in 20% of subjects in the mometasone group, 18% of subjects in the budesonide group, and 21% of subjects in the placebo group [206:67-68, 207:405, 211:3941-3960, 4095-4110, 4233-4249]. Again, as previously noted in the other SAR studies in this NDA submission, headache was followed by pharyngitis and epistaxis in terms of frequency of reporting by subjects [207:410]. Pharyngitis was reported in 9% of subjects in the mometasone group, 13% of subjects in the budesonide group, and 10% of placebo subjects [206:67-68]. Epistaxis was reported by 9% of subjects in the mometasone group, 12% of subjects in the loratadine group, and 9% of placebo subjects [206:67-68].

There were no reports of nasal septal perforation in either the mometasone or placebo treatment group however one subject in the budesonide treatment group (subject I93-133-08, #025) was found to have a 1 cm perforation of the anterior nasal septum and posterior margins which per biopsy report 07/27/94 revealed 'inflammatory perforation of the septum with reactive hyperplasia and squamous metaplasia of adjacent epithelium' [206:77-78, 207:476]. In addition, nasal ulcers were not reported in the mometasone treatment group however nasal ulcers were reported in the other 2 treatment groups as follows:

(1) budesonide group: reports in 5 subjects (2 subjects on Visit 9, 3 subjects on Visit 10) [211:4199, 212:5156, 5231, 5232, 5251, 5322],
(2) placebo: reports in 2 subjects (on Visit 9), [212:5162, 5256].

Glaucoma and/or cataract formation via eye examination were not specifically evaluated in this study, nor were any assessments of HPA-axis performed. No deaths were reported in any of the three treatment groups.

In terms of infection, 10% of subjects in the mometasone group reported viral infection, while 7% and 12% of subjects reported viral infection in the budesonide and placebo group, respectively [206:70, 207:460]. One subject in the mometasone treatment group (subject I93-133-08, #018) and one subject in the placebo group reported herpes simplex labialis [207:409, 211:4003, 211:4283]. In this trial, one subject in the placebo treatment group (subject I93-133-18, #011) was noted by the examining physician to have moniliasis (i.e. oral candidiasis) on study Visit 9 [207:409, 460, 211:4296]. No subjects in either of the two active treatment groups were found to have moniliasis and no subjects in either of the three treatment groups were reported to have nasal candidiasis on any clinic visits [207:5141-5334].

A total of 10 subjects discontinued treatment because of adverse events but

none of these subjects were in the mometasone treatment group (5 in the budesonide group, and 5 placebo subjects) [206:77].

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the three treatment groups. One mometasone group subject was reported to have an elevated alkaline phosphatase at screening and Visit 9 which were not felt to be related to drug treatment (lab values: 343 U/L and 293 U/L, respectively at these visits) [207:479]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change with the exception of a significant decrease in the peripheral blood eosinophil count for subjects receiving either of the two active treatments [207:490, 519, 575,604, 661]. Adverse events did not appear to differ significantly based on age, sex, or race except that headache appeared to have a higher prevalence in male than female subjects for all three treatment groups, and in Caucasian subjects compared with other racial groups [207:429-471, 441, 449, 456, 465, 466, 468].

8.10.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of seasonal allergic rhinitis, as compared with placebo. Prophylaxis of subjects with mometasone 2-4 weeks prior to the onset of the pollen season resulted in a statistically significant increase in the proportion of minimal symptom days (total nasal symptom ≤ 2) compared with prophylaxis with placebo for the same period of time. Because the study was not designed to evaluate mometasone treatment at the time of onset of the allergy season as compared with prophylaxis with mometasone prior to onset of the allergy season and cross-study comparisons were not possible because of baseline differences in subject symptom scores for the respective studies, no comment can be made as to how mometasone treatment at the start of the allergy season would compare with mometasone prophylaxis in terms of clinical efficacy.
2. The other active treatment, budesonide also showed statistically greater efficacy in the treatment of symptoms of SAR, as compared with placebo.

8.11. Trial C92-280: Controlled, Pivotal Study of Mometasone for the Treatment of Perennial Allergic Rhinitis (PAR)

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Participating Centers: 19 U.S. centers

8.11.1. OBJECTIVE

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

8.11.2. STUDY DESIGN

The study was a phase III, randomized, multi-center, double-blind, active- and placebo-controlled study to determine the safety and efficacy of mometasone furoate 200 µg administered intranasally once daily (qd), vs. the active control, beclomethasone (Vancenase AQ) 168 µg administered twice daily (bid), and vs. placebo for a total of 12 weeks in the treatment of perennial allergic rhinitis. The study was also designed to examine HPA-axis suppression in mometasone treated subjects vs. placebo via roll-over of subjects into Study C93-014 (1 year follow-up of Study C92-280).

8.11.3. PROTOCOL

8.11.3.1.a. POPULATION: **Male or female subjects, ≥ 12 years of age, with PAR documented by a positive response to allergen skin prick tests [218:14, 220:848].**

(I) **Inclusion Criteria [218:14, 220:848-849]:**

1. **History of perennial allergic rhinitis of at least 2 years duration.**
2. **If not performed within 2 years of study entry, demonstration of a positive response to skin (via the prick method or intradermal) testing to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander). The wheal size must have been 3 millimeters (mm) greater than or equal to the diluent control with prick**

testing or 7 millimeters (mm) greater than or equal to the diluent control with intradermal testing. Subjects sensitive to animal dander must have had that animal as a constant (i.e. daily exposure) household pet [218:14, 220:848].

3. Clinical evidence of active symptoms at both screening and baseline. Nasal rhinorrhea and/or congestion symptom scores of at least moderate (score ≥ 2) severity at both screening and baseline. The combined score of nasal symptoms must total at least 5 at both the screening and baseline visit [218:26, 220:846]. The nasal rhinorrhea and/or congestion diary scores must be ≥ 2 during 4 of the 7 days (as assessed via a.m. or p.m. scores or via the rescue medication diary) just prior to the baseline visit.
4. Other than PAR, subjects must in good health and free of clinically significant disease that would interfere with the study schedule or evaluation of PAR.
5. Ability to adhere to dose and visit schedules and record symptom scores accurately and consistently twice daily in a diary.
6. Nonpregnant women of childbearing potential must have been using a medically acceptable form of birth control for at least 3 months prior to screening and were to continue its use for the duration of the study.

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

(II) Exclusion Criteria [218:15, 220:849-850]:

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 or evidence of posterior subcapsular cataracts.
6. History of allergy to corticosteroids, or a history of multiple drug allergies.
7. Subject dependency on nasal, oral, or ocular decongestants; as determined by the principal investigator, or diagnosis of rhinitis medicamentosa.
8. Subject use of any chronic medication which could affect the course of PAR.
9. Use of any investigational drug within the previous 90 days unless the investigational drug was a nasal corticosteroid or has a short (≤ 12 hours) duration of action, in which case the washout period was to be 30 days.
10. Presence of any clinically relevant abnormal vital signs, laboratory test results outside the normal range, or clinically significant abnormal ECG.
11. Subjects on immunotherapy, unless on maintenance therapy.
12. Pregnant or nursing women, pre-menarchal females or women of child-bearing potential not using a medically acceptable form of birth control.
13. Subjects with recurrent clinically significant sinusitis by history and/or chronic purulent postnasal drip, or subjects with an abnormal Water's view X-ray (opacification, mucosal thickening ≥ 6 mm, and/or air-fluid levels).
14. Subjects allergic to a seasonal aeroallergen (e.g. trees, grass, or weeds) with seasonal exacerbation anticipated to occur or occurring during the study.

(II) Concurrent Medication Restrictions [218:19, 220:851-853]

(A) General Considerations:

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

3. Subjects who developed an upper respiratory tract infection, including infectious rhinitis, sinusitis or otitis, could be treated with one course (up to 21 days) of antibiotics during the study.

(B) Medications restricted before screening (Visit 1) [218:20, 220:851-852]:

	Medication	Time Discontinued Prior to Visit 1
1.	Cromolyn sodium, all forms	2 weeks
2.	Corticosteroids, nasal or ocular	2 weeks
3.	Corticosteroids, inhaled, oral or intravenous	1 month
4.	Corticosteroids, intra-muscular or intra-articular	3 months
5.	High potency topical corticoids- Class 3 or higher in potency, For dermatological use [Stoughten/Cornell Scale]	1 month
6.	Antihistamines, short acting (e.g. chlorpheniramine)	12 hours
7.	Antihistamines, long acting (e.g. cetirizine, loratadine, atarax)	96 hours
8.	Terfenadine, clemastine, long-acting forms of chlorpheniramine	48 hours
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 [218:20-21, 220:852]:

1. Systemic, inhaled, topical nasal, and topical ocular corticosteroids.
2. High potency topical corticosteroids (≥ class 3).
3. Cromolyn sodium.
4. Antihistamines (except the short-acting antihistamine chlorpheniramine; given as a 'rescue' medication) allowed between screening and baseline as long as washout was 12

hours before baseline.

5. Topical (nasal and ocular decongestants).
6. Oral decongestants.
7. Immunotherapy 24 hours prior to any visit.
8. Systemic antibiotics (unless on a stable dose 1 month prior to the study with the dose remaining unchanged for the duration of the study).
9. Aspirin or nonsteroidal anti-inflammatory agents, except for chronic low dose (≤ 325 mg/day) aspirin for atherosclerosis prophylaxis.

(D) Medications allowed during the study duration [218:21, 220:852-853]:

1. Acetaminophen (for appropriate indications).
2. Inhaled or oral beta-agonists on an as needed basis, for asthma.
3. Theophylline, if on a stable dose before and during the study.
4. Topical antimicrobials.
5. Medium potency (≤ class 4) topical corticosteroids for dermatological use only if the patient had been on a stable dose for at least 2 weeks prior to the study.
6. Thyroid replacement therapy, if on a stable dosage before and during the study.
7. Saline eye drops, as needed.
8. Hormone replacement therapy for postmenopausal women, if on a stable dosage before and during the study.
9. Systemic antibiotics, if on a stable dose for the duration of the study.
10. Occasional use of ASA or NSAIDs (e.g. for menstrual cramps) was permitted.
11. Rescue medication consisting of chlorpheniramine 4 mg po q 4-6 hours, (not to exceed 6 tablets per 24 hours), for the relief of intolerable PAR symptoms.

8.11.3.1.b. PROCEDURE:

(I) Screening Visit (Visit 1) [218:22-23, 220:856-858]:

A complete medical history (including allergy history), physical examination (including a nasal exam and an ophthalmic exam with tonometry and slit lamp exam to assess glaucoma and cataracts), laboratory evaluation, 12-lead ECG, Water's view sinus film to rule out sinusitis and significant sinus mucosal thickening, and confirmation of the subject's perennial allergen hypersensitivity with skin prick testing (if not performed within the last 2 years) was performed at

the screening visit. Documentation of any seasonal allergy (trees, grasses, weeds relevant to the geographical vicinity of the study site) was to be performed at the screening visit. Subjects were to be symptomatic at both the screening and baseline visits with physical findings compatible with perennial allergic rhinitis. Subjects demonstrating a significant skin test response, by prick or intradermal test, to a seasonal allergen with a history of symptomatic exacerbation, would not be enrolled during the relevant season.

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

(A) **Perennial Allergic Rhinitis Symptom Categorization** [218:25, 220:864]:

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

(B) **Perennial Allergic Rhinitis Symptom Severity Scale** [218:25, 220:864-865]:

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

Reviewer's Note:

According to this symptom rating scale, any given study subject could achieve a: minimum score=0 or maximum score=12; for either nasal symptoms or non-nasal symptoms, respectively; and a minimum score =0, maximum score=24 for combined nasal and non-nasal symptoms.

Using this scale, study subjects were to have at least moderate rhinorrhea and/or nasal congestion (symptom score ≤ 2) at both screening and baseline and at least moderate rhinorrhea and/or nasal congestion (symptom score ≤ 2) on diary entries for 4 of the last 7 days of the run-in period to continue to qualify for study randomization. The combined score of total nasal symptoms was to be at least 5 [218:25-56, 220:865].

Subjects were given diary cards and rescue medication cards and were to be trained in the accurate recording of symptoms in the diary reflectively over the previous 12 hours (to be recorded twice daily at the same time of the day), and trained in the documentation of symptom scores for investigator review. From the screening visit onward, the amount and time of use of rescue medication (only chlorpheniramine allowed) was recorded in the rescue medication diary, in addition to the severity of symptoms prior to the dose. All concomitant medications, including any over-the-counter drugs, were recorded. The daily dose, route of administration, duration of treatment and reason for use were also recorded. The subject or parent/guardian (if subject ≤ 18 years of age) was instructed to return to the office within 7-14 days for the baseline visit (Visit 2).

(II) Baseline Visit (Visit 2= Day 1) [218:23-24, 220:858-861]:

Again, during the baseline visit, subjects were re-evaluated in terms of their perennial allergic rhinitis symptoms, physical exam (including nasal exam), vital signs, adverse events, concomitant medications taken, laboratory tests, and ECGs. Subjects were to continue to meet all inclusion and exclusion criteria at this visit in order to qualify to enroll in the study. For any laboratory abnormality, the subject could be included in the study if the abnormal result was expected in the disease setting and was considered unlikely to create an increased risk or the abnormal laboratory value was considered clinically insignificant and would not interfere with the conduct of the study or interpretation of results [218:23, 220:858]. Using the scoring scale described in Section 8.12.3.1.b., the subject's rhinorrhea and/or nasal congestion score (as per subject diary) must each have been at least moderate (score ≥ 2) in severity for 4 of the last 7 days of the run-in period in order to allow the subject to qualify for study enrollment. Subject rescue medication cards were examined to determine if the subject used rescue medication.

Following the performance of all medical and laboratory procedures, subjects who met entry criteria had a treatment number assigned and were randomized in a 1:1:1 ratio (using a SAS random number generator) to one of the following 3 treatment groups:

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

Subjects received 8 sprays per day (2 sprays in each nostril from the a.m. bottle

each morning and 2 sprays in each nostril from the p.m. bottle each evening).

Reviewer's Note: While the protocol and general study document state that study medication packages were identical in appearance for all 3 treatments, thus insuring blinding of both the subject and investigator to the treatment identity [218:16-17, 220:859, 866-868], the documents do not state how these **bottles were 'made identical' to ensure double-blinding. It appears from the protocol and general study document in the NDA submission that each active drug did not have a placebo control, i.e. a double-dummy design. Nonetheless, in speaking with Ms. Paula Rinaldi, Regulatory Affairs, of Schering Plough, Inc. [Telecon, Ms. Paula Rinaldi, Regulatory Affairs, Schering Plough, Inc. 08/28/97], all study medications were administered in Vancenase AQ bottles (including placebo), thus ensuring blinding.**

Subjects were instructed about dosing and received the first dose at the study center. Rescue medication (chlorpheniramine) was dispensed for the relief of intolerable symptoms of PAR during the study, not to exceed 6, 4 mg tablets of chlorpheniramine per 24 hour period. Additionally, subjects received new diary cards on which to record symptoms, rescue medication use, and other concomitant medications.

In summary, the study was designed to recruit at least 20 subjects with documented PAR in each of the 19 centers to ensure a total of at least 375 evaluable subjects. Subjects completing the initial 3 month double-blind phase (study C92-280) were given the option of entering the one year, open-label mometasone safety study (C93-014).

(III) Evaluation Visits [218:24-25, 220:861-864]:

Evaluation visits were defined as follows:
Visit 3=Day 8 ± 2 days,
Visit 4=Day 15 ± 2 days,
Visit 5=Day 29 ± 4 days,
Visit 6=Week 8 ± 4 days,
Visit 7=Week 12 ± 4 days.

Treatment days were numbered relative to the start of treatment which was designated as Day 1. During the follow-up visits, subjects had their diary cards checked for completeness and accuracy of recording and diary cards were reviewed to evaluate perennial allergic rhinitis symptoms. Of note, the evaluation included the entire time period since the last visit, up to and including the most current observation. Based on this data (diary review and symptom scoring), the overall condition of rhinitis was assessed by the principal investigator. Response to therapy was evaluated by the investigator 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 8.12.3.1.b. and using the following (C) therapeutic response scale:

(C) Therapeutic Response Scale [218:26, 220:866]:

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 8.12.4.3. Subjects underwent repeat clinical laboratory tests, 12 lead ECG, and nasal and ophthalmic examinations on Visit 7 (Week 12 of the study) .

Reviewer's Note: Given that response to perennial allergen(s) were assessed in Study C92-280, seasonal allergen pollen counts were not evaluated or maintained for this study.

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

Table I.

Table 1 Schedule of Study Procedures and Evaluations (Study No. C92-200).

		12-Week Treatment Period					
	Screening (Visit 1)	Baseline (Visit 2)	Day 8 (Visit 3)	Day 15 (Visit 4)	Day 29 (Visit 5)	Week 8 (Visit 6)	Week 12 (Visit 7)
Informed Consent, Medical and Allergy History	X						
Check Inclusion/ Exclusion Criteria	X	X					
Review Concomitant Medications	X	X	X	X	X	X	X
Physical and Ophthalmic Examination	X						X
Vital Signs	X	X	X	X	X	X	X
Body Weight	X						X
Height	X						
Skin Testing[a] and Water's View X-ray	X						
12 lead ECG	X						X
Nasal Examination	X	X					X
Laboratory Tests and Pregnancy Test[b]	X						X
Physician Assessment of Rhinitis Symptoms	X	X	X	X	X	X	X
Physician and Patient Assessment of Overall Condition	X	X	X	X	X	X	X
Physician and Patient Assessment of Response to Treatment			X	X	X	X	X
Dispense Study Medication		X			X	X	
Retrieve Study Medication					X	X	X
Study Drug Administered in Office		X			X	X	
Dispense Symptoms and Rescue Medication Diary	X	X	X	X	X	X	
Dispense Rescue Medication[c]	X	X	#	#	#	#	
Retrieve Rescue Medication[c]		X	X	X	X	X	X
Symptoms and Rescue Medication Diary Retrieval and Review		X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X

a: If not done in past 2 years.
b: All women.
#: As needed.
c: Chlorpheniramine

8.11.3.2. CLINICAL ENDPOINTS

(I) Primary Efficacy Variable [218:33-35, 38-39, 220:871-872]:
The mean change from baseline in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject diaries):

(1) Mean Change in Total nasal symptom score=

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

where the **total nasal symptom score=[discharge+ stuffiness+ sneezing+** itching], as previously defined in Section 8.12.3.1.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.

For subjects who used rescue medication between study visits, the last set of symptom scores recorded in the rescue medication diary prior to using rescue medication were considered the appropriate evaluation of symptoms for the next 12-hour period [218:34]. In other words, the subject symptom scores from the rescue medication diary replaced the corresponding scores in the (regular) diary for the appropriate 12-hour period in all analyses if rescue medication was used.

Additional analysis of the primary efficacy variable consisted of sub-analysis by week 1 (Day 1-7) and week 2 (Day 8-15) of total nasal symptom scores in order to assess onset of action of mometasone.

(II) Secondary Efficacy Variables:

(1) The mean change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30 (a.m. and p.m. combined), Days 31-45, Days 46-60, Days 61-75, and Days 76-90:

Mean Change in Total nasal symptom score$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$ =

Day 16-30 (or Day 31-45, Day 46-60, Day 61-75, Day 76-90) Interval Score[(Nasal a.m. average $_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$) + (Nasal p.m. average$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 3 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 3 Consecutive Days Prior to Baseline Visit}}$)]/2

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

(2) Endpoint total nasal symptom score (a.m. and p.m. combined): Endpoint score defined as the last available post-baseline value for each study subject, pooled across the 19 participating centers. The total nasal symptom score was determined as per the 0-3 point PAR symptom severity score [218:25, 220:864-865].

(3) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit). Again, nasal and non-nasal symptom scores were determined as per the 0-3 point PAR severity score [218:25, 220:864-865].

(4) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit). Total non-nasal scores were determined as per (2) and (3) above.

(5) Physician's evaluation of total nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8 , Week 12, and the endpoint visit). The total nasal symptom score was determined as per (2)-(4) above.

(6) Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit). The total symptom score was determined as per (2)-(5) above.

(7) Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit). Total non-nasal symptoms were determined as per (2)-(6) above.

(8) Subject's self-evaluation of overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, and the endpoint visit [218:26, 220:865].

(9) Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study day 8, 15, 29, Week 8, Week 12, and the endpoint visit [218:26, 220:865]. Again, the baseline score for physician-rated responses was based exclusively on the baseline visit (visit 2).

(10) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study day 8, 15, 29, Week 8, Week 12, and the endpoint visit [218:26, 220:866].

(11) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study day 8, 15, 29, Week 8, Week 12, and the endpoint visit [218:26, 220:866].

Reviewer's Note: For all physician rated responses, the baseline score was based on the baseline visit only (visit 2), whereas for all subject rated responses (including subject's evaluation of overall disease condition and therapeutic response), the baseline score was based on an average of the baseline visit and the 3 previous visits. Of note, secondary efficacy variables **(1) and (2)-(11) were listed in the general study document [218:39] but discussed in a superficial manner in the study protocol itself [220:872]. Therefore, listed as secondary efficacy variables (2)-(6) above are additional clinical parameters assessed by the sponsor and relevant to determination of treatment efficacy.**

8.11.3.3. STATISTICAL ANALYSIS [218:36-39, 220:870, 873]

A sample size of 125 valid subjects per treatment group or 375 valid subjects total was calculated to detect a treatment difference of approximately 1.43 units or more with respect to the primary efficacy variable--the mean change from baseline in the total nasal symptom score (diary scores averaged over the first 15 days of treatment) based on an estimated pooled standard deviation of 3.5 units with a power of 90% at an α=0.05 (2-tailed). A total of 491 subjects were randomized and 476 were considered evaluable by the sponsor.

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

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

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

The primary efficacy variable was analyzed for all efficacy evaluable and

intent-to-treat subjects (pooled across all centers) using a two-way analysis of variance (ANOVA) which extracted sources of variation due to treatment, center, and treatment by center interaction. The primary efficacy comparison of mometasone vs. placebo was then based on the least squares (LS) means from the ANOVA using a 5% two-sided significance level. The beclomethasone group was 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, asthma, seasonal allergic rhinitis and disease condition). Continuous variables (age, weight, duration of disease condition) 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 seasonal allergic rhinitis) were analyzed by categorical linear models (SAS CATMOD), race was analyzed by Fischer's exact test for Caucasians vs. non-Caucasians. Rescue medication use among the 3 treatment groups was not analyzed in any statistical manner, however a tabulation of the frequency of rescue medication use among the 3 treatment groups for each study interval (e.g. Day 1-15, 16-30, etc.) for both ITT and efficacy evaluable subjects was provided by the sponsor [218:250-253].

Reviewer's Note: For the purposes of efficacy and safety review of this and all studies in this submission, the intent-to-treat population was utilized rather than the sponsor's efficacy evaluable population, except where otherwise noted. Also of note, the sponsor lists perennial rhinitis rather than seasonal allergic rhinitis as a discrete variable which is incorrect and likely represents a typographical error [218:36, 37].

8.11.4. RESULTS

8.11.4.1. SUBJECT DEMOGRAPHICS

(A) Distribution of Subject Populations

A total of 491 subjects were randomized into the study, with 13 subjects excluded from the efficacy analysis because of protocol violations; thus resulting in 477 subjects comprising the efficacy evaluable population and 490 subjects comprising the intent-to-treat population. One subject in the placebo group (subject C92-280-04, #021) was excluded from all safety and efficacy evaluations as she received the first dose of medication at the study center and was an

immediate dropout from the study [218:42]. The distribution of subject populations is summarized in Table II. below:

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

	Mometasone (SCH 32088)	Beclomethasone (BDP)	Placebo	Total
Efficacy Population	160 (1 subject did not meet entry criteria, 2 subjects had insufficient efficacy data, and 1 subject had an unacceptable baseline)	157 (1 subject did not meet entry criteria, 1 subject had insufficient efficacy data, and 4 subjects had an unacceptable baseline)	160 (1 subject had insufficient efficacy data, 1 subject had insufficient efficacy data and insufficient medication, and 1 subject had an unacceptable baseline).	477
Safety Population (ITT)	164	163	163	490
Total # Randomized	164	163	164 (1 immediate dropout)	491

(B) Pooled demographic data with regard to subject characteristics in the safety population (ITT) is summarized in Table III. below [218:44].

Table III: Subject Demographics (Protocol C92-280): Intent-to-Treat Population

Table 7 Summary of Demographic Data[a] (Safety [Intent-to-Treat] Population) (Study No. C92-280).

	SCH 32088 (n=164)	BDP (n=163)	Placebo (n=163)	Overall Treatment P-Value
Age (years)				
Mean	35	34	33	0.57
Median	34	33	33	
Range (Min-Max)	12-68	12-74	12-66	
Sex				
Female	82	92	77	
Male	82	71	86	0.10
Race				
White	151	144	139	0.15
Black	4	7	14	
Other	9	12	10	
Weight (lbs)				
Mean	167	165	165	0.99
Median	163	157	162	
Range (Min-Max)	73-289	71-350	78-260	
Duration of Perennial Rhinitis (yrs)				
Mean	19	16	16	0.09
Median	17	13	14	
Range (Min-Max)	2-66	2-60	2-58	
Seasonal Allergic Rhinitis				
No	52	47	44	
Yes	112	116	119	0.67
History of Asthma				
No	136	136	137	
Yes	28	27	26	0.96

Sch 32088=Mometasone furoate

Reviewer's Note: With the exception of the duration of perennial allergic rhinitis (which was greatest in the mometasone treatment group, mean =19 years, median=17 years), all 3 treatment groups had comparable demographic and disease characteristics. The majority of subjects were Caucasian in all 3 treatment groups, as previously noted for the other 2 pivotal studies (SAR and prophylaxis of SAR) in the mometasone NDA submission. However, in contrast to these other studies, in study C92-280, approximately equal numbers of male and female subjects were enrolled in each treatment group. Finally, the majority (approximately 2/3 or greater than 2/3 (beclomethasone and placebo group, respectively)) of all subjects enrolled in this trial had a history or documentation via skin testing of seasonal allergic rhinitis. The majority of subjects in all 3 treatment groups (approximately 75%) did not have a history of asthma.

(C) Subject Distribution by Disease Severity at Baseline in Efficacy Evaluable Subjects [218:49]:

Table 18 Distribution of Patients by Disease Severity at Baseline -- Efficacy Population (Study No. C92-280).

Treatment Group	% Moderate	% Severe
SCH 32088	75%	25%
BDP	80%	18%
Placebo	81%	19%

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

(D) Subject Discontinuation

A total of 64 subjects (20 treated with Mometasone, 19 treated with Beclomethasone, 25 treated with placebo) discontinued the study prior to scheduled completion. This data is summarized in Table IV. [218:44-45].

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

	TREATMENT GROUP			
	Mometasone (n=164)[1]	Beclomethasone (n=163)	Placebo (n=164)	Total (n=491)
Number (%) Completed	144 (88%)	144 (88%)	139 (85%)	427 (87%)
Reason for Discontinuation				
--Adverse event	5 (3%)	9 (6%)	8 (5%)	22 (4%)
--Treatment Failure	5 (3%)	3 (2%)	5 (3%)	13 (3%)
--Did not meet entry requirements	1 (1%)	2 (1%)	1 (1%)	4 (1%)
--Administrative reasons	2 (1%)	0	2 (1%)	4 (1%)
--Noncompliance with Protocol	1 (1%)	0	1 (1%)	2 (<1%)
--Noncompliance with dosing regimen[2]	0	0	1 (1%)	1 (<1%)
--Subject did not Return	6 (4%)	5 (3%)	7 (4%)	18 (4%)
TOTAL # (%) DISCONTINUED	20 (12%)	19 (12%)	25 (15%)	64 (13%)

[1] n=number of randomized subjects at the time of study initiation.
[2] Patient C92-280-05, #018.

Reviewer's Note: In all 3 treatment arms, the total % of subject discontinuation was greater than 10% of the total enrolled--a relatively high discontinuation rate.

(E) Subject Validity

146 subjects (44 treated with mometasone, 46 treated with beclomethasone, and 56 treated with placebo) valid for efficacy had data invalidated for some visits. These subjects and the reasons for invalidation are summarized in Attachment 6 [218:213-248] and Table 9 [218:45-46] of the NDA. The most common reason for visit invalidation at most study visits was improper visit spacing, followed by concurrent illness [218:46-47].

Reviewer's Note: While the reason(s) for invalidation are reasonable, a relatively large number of subjects had data invalidated for some visits that could potentially influence results for the efficacy evaluable subjects. Interestingly, comparison of the ITT and efficacy evaluable subjects for the

primary efficacy variable (see below, Section 8.12.4.2) did not show a significant difference in results between these two subject populations in terms of total nasal symptom scores.

8.11.4.2. EFFICACY ENDPOINT OUTCOMES

(I) Primary Efficacy Variable (Mean change in the total nasal symptom score for days 1-15 post-initiation of treatment)

All efficacy analyses in this review were based on the intent-to-treat population (n=164 for mometasone, n=163 for beclomethasone, n=163 for placebo) for the primary efficacy variable--the average change from baseline in the total nasal symptom scores from patient diaries over the first 15 days of treatment. For the average change from baseline in total nasal symptom scores over the day 1-15 interval, both active treatment groups--mometasone and beclomethasone, respectively; were significantly more effective than placebo ($p=0.02$ for mometasone vs. placebo comparison of the mean change in the total nasal symptom score and $p<0.01$ for beclomethasone vs. placebo comparison of the mean change in the total nasal symptom score). Furthermore, the mometasone and beclomethasone treatment groups were not statistically significantly different from one another ($p=0.43$), although the beclomethasone group showed a numerical advantage with regard to response (mean change in the total nasal symptom score: a -1.5 point change for the mometasone group and a -1.7 point change for the beclomethasone group), compared with the mometasone group. Because of study design and underpowering to detect a difference between these 2 groups, no conclusion can be made regarding the true meaning of a p-value of 0.43 in this context. The mean % decrease in total nasal symptom scores (and raw total nasal symptom score) for subjects receiving mometasone (200 µg qd) was 20% (raw score=5.1), in comparison with a 23% (raw score=5.0) decrease in subjects receiving beclomethasone (168 µg bid) and a 13% (raw score=5.9) decrease in the placebo treatment group [218:318].

Reviewer's Note: Of note, the findings for the efficacy evaluable group were the same as that for the above intent-to-treat group with the exception of a 21% (rather than the ITT group's 20%) decrease in total nasal symptom scores for the mometasone group [218:255].

Regarding any potential difference of mometasone drug effect over the course of the day (i.e. a.m. vs. p.m.) and detection of waning of drug effect as demonstrated by a change in the primary efficacy variable, 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 numerical difference in symptom scores was found between any of these 3 mometasone groups (with the combined a.m. and p.m. total nasal $score_{DAY\ 1-15}$=5.1, a.m. total nasal $score_{DAY\ 1-15}$= 5.2, p.m. total nasal $score_{DAY\ 1-15}$= 4.9), nor

was any significant a.m. vs. p.m. difference noted in the beclomethasone and placebo treatment groups [218:318-320], however statistical comparisons of the a.m. vs. the p.m. total nasal symptom scores against one another was not performed. Statistical comparison of the change in a.m. and p.m. scores were compared to the change in the combined a.m. and p.m. total nasal score, and for this comparison, the change in p.m. total nasal symptom scores was found not to be statistically significantly lower during the day 1-15 interval than placebo [218:320].

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

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

A sub-analysis of the primary efficacy variable on a per week basis was performed using the SAS data files provided by the Sponsor (and generated by Dr. Jim Gebert, Biostatistics, Division of Pulmonary Drug Products, FDA, Attachment 1 for Study C92-280). A summary of the efficacy findings for week 1 and week 2 are summarized in Tables V.a. and V.b. Overall, a greater response in total nasal symptoms was noted for the 2 active treatment groups, mometasone and beclomethasone, during week 2 of treatment, however a statistically significant response in total nasal symptom scores for both active treatment groups was evident by week 1 of treatment (mometasone group vs. placebo: raw total nasal symptom score comparison, $p<.01$; mean change in total nasal symptom score, $p=0.02$; beclomethasone group vs. placebo: raw total nasal symptom score comparison, $p<.01$; mean change in total nasal symptom score, $p=0.01$) [Table V.a.].

Separate analysis of a.m. vs. p.m. differences in drug efficacy for week 1 vs. week 2 of the study (Table V.a., Table V.b. and Attachment 2) 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 (0.4 point difference between a.m. and p.m. scores). A post-hoc analysis of significance was not performed comparing the differences between these two symptom recording times. Both the a.m. and combined a.m. and p.m. (but not p.m. alone) scores for week 1 and week 2 of treatment demonstrated that mometasone had a clinically and statistically significant effect in reducing total nasal symptoms of PAR compared with placebo, but that this effect was greater by the second week of treatment. Based on this weekly analysis, one may conclude that clinical efficacy of mometasone (also beclomethasone) in reducing total nasal symptom scores was evident after 1 week of drug administration. These findings are consistent with the onset of action of mometasone, as discussed in study C93-184.

An analysis of the impact of rescue medication (chlorpheniramine) use in the ITT population during the day 1-15 interval was performed by the Sponsor and 37% (60/164) of subjects in the mometasone group, 33% (53/163) of subjects in the beclomethasone group, and 47% (76/163) of subjects in the placebo group were found to have used rescue medication during this study interval [218:251]. In most cases for all 3 treatment groups, rescue medications were used between 1-5 times during the 15 day interval. Findings for the day 1-15 interval in terms of rescue medication use are in contrast to findings for all 3 treatment groups during the screening to baseline period were each treatment group showed approximately equal frequency (50-56%) of rescue medication use [218:251].

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Table V.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of PAR:
Primary Efficacy Variable--Intent-to-Treat (ITT) POPULATION, [218:318-320]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARISONS A-B	A-C	B-C
DAYS	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**SD**	**TRT**	**INV**	**T X I**	**A-B**	**A-C**	**B-C**
BASELINE																
--am & pm nasal	163	6.6	2.2	163	6.7	2.0	162	6.9	2.0	2.0	0.34	0.01	0.06	0.69	0.16	0.31
--am nasal	163	6.8	2.2	163	6.8	2.1	162	7.0	2.1	2.1	0.4	0.03	0.07	0.73	0.34	0.19
--pm nasal	162	6.3	2.3	163	6.6	2.1	162	5.7	2.2	2.1	0.2	0.01	0.09	0.26	0.08	0.5
DAYS 1-15																
--am & pm nasal																
RAW	163	5.1	2.2	163	5.0	2.3	162	5.9	2.1	2.2	<.01	<.01	0.67	0.75	<.01	<.01
CHG	163	-1.5	2.0	163	-1.7	2.0	162	-1.0	1.6	1.9	0.01	0.07	0.6	0.43	0.02	<.01
%CHG	163	-20	32.2	163	-23	32.9	162	-13	26.1							
--am nasal																
RAW	163	5.2	2.3	163	5.0	2.3	162	6.0	2.2	2.2	<.01	<.01	0.56	0.46	<.01	<.01
CHG	163	-1.6	2.0	163	-1.7	2.1	162	-1.0	1.6	1.9	<.01	0.11	0.58	0.64	0.01	<.01
%CHG	163	-21	32.7	163	-23	33.0	162	-13	25.0							
--pm nasal																
RAW	162	4.9	2.2	163	5.0	2.3	162	5.7	2.2	2.2	<.01	<.01	0.59	0.89	<.01	<.01
CHG	162	-1.4	2.2	163	-1.7	2.0	162	-1.0	1.9	2.0	0.02	0.08	0.54	0.31	0.08	0.01
%CHG	162	-16	41.4	163	-20	57.6	162	-11	34.9							

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

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

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARISONS A-B	A-C	B-C
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE																
--am & pm nasal	163	6.6	2.2	163	6.7	2.0	162	6.9	2.0	2.0	0.34	0.01	0.06	0.59	0.18	0.31
--am nasal	163	6.8	2.2	163	6.8	2.1	162	7.0	2.1	2.1	0.4	0.03	0.07	0.62	<.01	<.01
--pm nasal	162	6.3	2.3	163	6.6	2.1	162	6.8	2.1	2.1	0.2	0.01	0.09	0.26	0.08	0.5
DAYS 1-7																
--am & pm nasal																
RAW	162	5.4	2.3	163	5.4	2.3	162	6.2	2.1	2.2	<.01	<.01	0.5	0.96	<.01	<.01
CHG	162	-1.2	1.8	163	-1.3	1.9	162	-0.7	1.6	1.8	0.01	0.07	0.35	0.71	0.02	0.01
%CHG	162	-15	30.9	163	-17	32.1	162	-7.4	31.2							
--am nasal																
RAW	162	5.6	2.4	163	5.5	2.4	162	6.4	2.2	2.3	<.01	0.02	0.44	0.62	<.01	<.01
CHG	162	-1.2	1.9	163	5.5	2.4	162	6.4	2.2	2.3	<.01	0.02	0.44	0.62	<.01	<.01
%CHG	162	-16	34.1	163	-17	33.4	162	-6.6	33.2							
--pm nasal																
RAW	161	5.2	2.3	163	5.4	2.4	162	6.0	2.2	2.2	<.01	<.01	0.43	0.55	<.01	0.01
CHG	161	-1.1	2.0	163	5.4	2.4	162	-0.8	1.9	1.9	0.06	0.07	0.17	0.6	0.08	0.02
%CHG	161	-13	36.3	163	-15	41.9	162	-6.3	38.2							

SD= Standard Deviation 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 PAR:
Weekly Analysis of the Primary Efficacy Variable: WEEK 2 (Intent-to-Treat (ITT) POPULATION), [SAS Datafiles]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Poolod	ANOVA P-Values			PAIRWISE COMPARISONS A-B	A-C	B-C
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE																
--am & pm nasal	163	6.6	2.2	163	6.7	2.0	162	6.9	2.0	2.0	0.34	0.01	0.06	0.69	0.16	0.31
--am nasal	163	6.8	2.2	163	6.8	2.1	162	7.0	2.1	2.1	0.4	0.03	0.07	0.62	<.01	<.01
--pm nasal	162	6.3	2.3	163	6.6	2.1	162	6.8	2.1	2.1	0.2	0.01	0.09	0.26	0.08	0.5
DAYS 8-15																
--am & pm nasal																
RAW	162	4.8	2.4	161	4.6	2.4	162	5.6	2.3	2.3	<.01	<.01	0.51	0.63	<.01	<.01
CHG	162	-1.8	2.3	161	-2.1	2.3	162	-1.3	1.9	2.2	0.01	0.02	0.64	0.43	0.03	<.01
%CHG	162	-24	35.5	161	-28	36.1	162	-17	28.3							
--am nasal																
RAW	162	4.9	2.4	161	4.7	2.5	162	5.7	2.4	2.3	<.01	<.01	0.47	0.45	<.01	<.01
CHG	162	-1.9	2.3	161	-2.1	2.4	162	-1.3	1.9	2.2	<.01	0.03	0.5	0.69	0.01	<.01
%CHG	162	-25	34.8	161	-27	37.5	162	-17	27.4							
--pm nasal																
RAW	159	4.6	2.3	160	4.6	2.5	161	5.5	2.4	2.3	<.01	<.01	0.63	>.99	<.01	<.01
CHG	159	-1.8	2.4	160	-2.0	2.4	161	-1.3	2.2	2.3	0.02	0.03	0.7	0.36	0.06	0.01
%CHG	159	-21	48.8	160	-23	77.0	161	-15	37.0							

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 (a.m. and p.m. combined, a.m. alone, p.m. alone): rhinorrhea, nasal congestion, nasal itching, sneezing on the determination of the final total nasal symptom score (a.m. and p.m. combined, a.m. alone, p.m. alone) for the day 1-15 interval in each of the 3 treatment groups was performed to rule out excessive contribution and therefore, skewing of the total nasal symptom score by any given one parameter [221:1092-1103]. Similar to findings noted in SAR study C93-013, the nasal congestion score [221:1095-1097], closely followed by the nasal discharge score [221:1092-1094], was found to contribute a slightly greater numerical weight in the determination of the final nasal symptom score than the other 3 parameters for all 3 treatment groups but this difference was consistent across all 3 groups. Regarding clinical response in terms of the each nasal symptom, statistical significance was achieved in the mometasone treatment group for days 1-15 of treatment for the nasal symptoms of nasal discharge [221:1092], sneezing [221:1098] and a numerically significant but marginally statistically significant response in nasal itching [221:1101], compared with placebo. In contrast to the pivotal SAR trial C93-013, a statistically significant response of nasal congestion scores in the mometasone treatment group was not demonstrated in this pivotal perennial rhinitis trial, C92-280.

In terms of categorizing treatment response by age and sex using the efficacy evaluable population (ITT population data not available), pooled data from all 19 centers for the primary efficacy variable revealed that female subjects overall had a similar response to mometasone as to beclomethasone [218:326-327] for the day 1-15 interval. Both active treatments demonstrated a greater response in both sexes than did placebo, as expected [218:326-327]. For male and female subjects combined, subjects < 34 years of age (n=78 for the mometasone group, n=81 for the beclomethasone group and n=81 for the placebo group) had a numerically (but not statistically significantly) greater response than the older age group (subjects ≥ 34 years of age) to mometasone in terms of total nasal symptom scores [218:323-324]. The older age subject group (n=82 for the mometasone group, n=75 for the beclomethasone group, and n=77 for the placebo group) conversely demonstrated a numerically greater response to beclomethasone treatment in terms of total nasal symptom scores, compared with the < 34 year age group [218:324]. While noted, the clinical significance of this small difference in age in this small number of subjects is unlikely to be relevant to the pathophysiology of PAR and furthermore, was not noted in other PAR studies in this NDA submission. Regarding racial differences, Caucasian subjects, who of note, comprised the majority of all study subjects (n=147 for the mometasone group, n=138 for the beclomethasone group, and n=135 for the placebo group) had a statistically significantly and numerically greater response in total nasal symptoms to mometasone than did non-Caucasian subjects (n=13 for the mometasone group, n=18 for the beclomethasone group, and n=23 for the placebo group) for the day 1-15 interval (-22% change in total nasal symptoms for Caucasian subjects treated with mometasone vs. -4.2% change in total nasal

symptoms for non-Caucasian subjects treated with mometasone) [218:329-330]. Because of severe underpowering of non-Caucasian subjects due to small subject numbers, no conclusions regarding racial differences in clinical response of perennial rhinitis can be made on the basis of this observation.

An analysis to assess the impact of treatment imbalance at baseline with respect to duration of disease condition (i.e. perennial rhinitis) and the primary efficacy variable was performed by the sponsor by incorporating the variable of duration of perennial rhinitis as an additional factor in the analysis of variance model used for the primary efficacy analysis. The duration of perennial rhinitis was not found to be significantly related to outcome (p=0.97), hence the potential treatment imbalance with respect to duration of perennial rhinitis did not bias the treatment comparisons. Thus, no adjustment on this score was made in the primary efficacy variable analysis or in any of the other analyses included in the NDA submission for study C92-280 [221:1976].

An assessment of data consistency across the 19 centers participating in protocol C92-280 showed that although the treatment by center interaction was not significant (p=0.10) [218:38] and mometasone was numerically favored over placebo at 16 of the 19 centers for the day 1-15 interval [218:255-274], mometasone treatment nonetheless demonstrated a statistically significant reduction in the total nasal symptom score at only one center (study center C92-280-01) [218:255]. Ten centers showed that numerically, beclomethasone reduced the mean nasal symptom score the most, followed in turn by mometasone, and then placebo. Four centers showed numerically, that mometasone reduced the mean nasal symptom score the most, followed by beclomethasone, and then placebo. With the exception of study center C92-280-16 [218:271], where significantly lower total nasal symptom scores were recorded for all 3 treatment groups for the day 1-15 interval, the 19 centers participating in the study did not show significant variability of efficacy results. Based on the overall findings of this study, and including the 3 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 day 16-30, day 31-45, day 46-60, day 61-75, day 76-90, and the endpoint interval were considered secondary efficacy variables. These time points were analyzed using the same model described for the primary efficacy variable. All other composite (total) and individual diary symptom scores and physician evaluated composite and individual symptom scores, as well as the subject's and physician's evaluation of overall disease condition and therapeutic response, were also considered secondary efficacy variables. All of these secondary variables were analyzed using the same two-way ANOVA as used for analysis of the primary efficacy variable. Summary tables of the secondary efficacy variables from the NDA submission are presented in Attachments 1 and 2.

(1) **Mean change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30, Days 31-45, Days 46-60, Days 61-75, and Days 76-90 (a.m. and p.m. combined) [218:318-320]:**

A review of the combined (a.m. and p.m.) mean change in the total nasal 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 5.1 (for days 1-15) to a mean of 4.4 (days 16-30) for the mometasone treatment group (10% difference). This symptom score decrease by day 16-30 of treatment was comparable to that of the beclomethasone treatment group which showed a decrease to a mean score of 4.2 (or 10 % difference) for the day 16-30 interval from a mean score of 5.0 (days 1-15). Similar to findings in the pivotal SAR study C93-013, most of the response in total nasal symptom scores for both mometasone and beclomethasone was found to occur within the first 2 weeks of treatment (Tables V. and VI.). No significant difference in a.m. and p.m. scores were noted for either of the active treatments during any of the 15 day study intervals, thus supporting evidence that mometasone appears to be effective over 24 hour dosing (mometasone group: day 16-30: 4.5=a.m. score vs. 4.3=p.m. score; day 31-45: 4.3=a.m. score vs. 4.0=p.m. score, day 46-60: 3.9=a.m. score vs. 3.7=p.m. score;; day 61-75: 3.8=a.m. score vs. 3.6=p.m. score; day 76-90: 3.8=a.m. score vs. 3.6=p.m. score) [218:319-320].

In summary, an overall greater numerical response to treatment by days 16-30 was seen in the beclomethasone group (33%) than in the mometasone group (30%), although both active treatments were found to have greater efficacy than placebo (18%). A similar trend for the beclomethasone treatment group to have numerically lower raw total nasal symptom scores and greater mean change in the total nasal symptom score than the mometasone treatment group (with greater efficacy of both active treatments compared with placebo) was likewise noted for all other 15 day study intervals [218:318]. For no 15 day interval were these numerical differences between the 2 active treatment groups statistically significant. A summary of total nasal symptom scores for all 3 treatment groups is provided in Tables VI. and VII.

(2) **Endpoint total nasal symptom score (a.m. and p.m.) [218:318-320]:**

Analysis of the endpoint total nasal symptom scores demonstrated a greater response of the mometasone treatment group than placebo. Using the last available post-baseline value for each study subject as the endpoint determination, endpoint nasal symptom score values were not found to be significantly different from nasal symptom scores for the day 46-60 interval. Again, distinction between the a.m. and p.m. scores revealed a small but clinically and statistically insignificant difference between a.m. and p.m. dosing with a slight decrease in total nasal symptoms during the p.m. measurement; a trend which has been noted in both the pivotal SAR study and pivotal prophylaxis of SAR study (4.0=a.m. score vs. 3.7=p.m. score). These results are summarized in Table VII.

Table VI.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Treatment of PAR:
Subject Evaluated Total Nasal Symptom Scores
Secondary Efficacy Variables--Intent-to-Treat (ITT) POPULATION [218:318-320]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARISONS A-B	A-C	B-C
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE																
--am & pm total	163	6.6	2.2	163	6.7	2.0	162	6.9	2.0	2.0	0.34	0.01	0.06	0.69	0.16	0.31
DAYS 16-30	am & pm total nasal symptom scores															
RAW	159	4.4	2.3	157	4.2	2.4	157	5.3	2.2	2.2	<.01	<.01	0.54	0.51	<.01	<.01
CHG	159	-2.2	2.3	157	-2.4	2.5	157	-1.6	2.1	2.2	<.01	<.01	0.37	0.37	0.02	<.01
%CHG	159	-30	34.9	157	-33	40.5	157	-18	59.4							
DAYS 31-45	am & pm total nasal symptom scores															
RAW	152	4.2	2.5	157	4.0	2.5	153	5.1	2.4	2.4	<.01	<.01	0.34	0.58	<.01	<.01
CHG	152	-2.5	2.7	157	-2.7	2.6	153	-1.8	2.3	2.5	<.01	0.01	0.22	0.52	0.01	<.01
%CHG	152	-33	41.6	157	-37	41.1	153	-19	85.9							
DAYS 46-60	am & pm total nasal symptom scores															
RAW	147	3.8	2.4	157	3.8	2.5	148	4.9	2.4	2.4	<.01	<.01	0.47	0.95	<.01	<.01
CHG	147	-2.8	2.7	157	-2.9	2.6	148	-2.0	2.4	2.5	0.01	0.02	0.52	0.86	0.01	<.01
%CHG	147	-38	40.5	157	-40	38.5	148	-22	86.9							

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 PAR:
Subject Evaluated Total Nasal Symptom Scores
Secondary Efficacy Variables--Intent-to-Treat (ITT) POPULATION, [218:318-320]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARISONS A-B	A-C	B-C
DAYS	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE																
--am & pm total	163	6.6	2.2	163	6.7	2.0	162	6.9	2.0	2.0	0.34	0.01	0.06	0.69	0.16	0.31
DAYS 61-75	am & pm total nasal symptom scores															
RAW	144	3.7	2.3	150	3.7	2.4	142	4.5	2.4	2.3	<.01	<.01	0.91	0.76	<.01	<.01
CHG	144	-2.9	2.5	150	-3.0	2.5	142	-2.3	2.5	2.4	0.06	<.01	0.05	0.87	0.05	0.03
%CHG	144	-41	35.3	150	-43	35.1	142	-26	90.4							
DAYS 76-90	am & pm total nasal symptom scores															
RAW	142	3.7	2.3	145	3.6	2.4	139	4.6	2.5	2.3	<.01	<.01	0.88	0.74	<.01	<.01
CHG	142	-2.9	2.5	145	-3.0	2.5	139	-2.3	2.7	2.5	0.04	<.01	0.36	0.75	0.05	0.02
%CHG	142	-42	36.0	145	-43	35.1	139	-25	95.1							
ENDPOINT VISIT	am & pm total nasal symptom scores															
RAW	163	3.9	2.5	163	3.9	2.6	162	4.8	2.7	2.5	<.01	<.01	0.96	0.92	<.01	<.01
CHG	163	-2.7	2.7	163	-2.8	2.5	162	-2.1	2.7	2.6	0.03	0.01	0.61	0.83	0.03	0.02
%CHG	163	-38	40.5	163	-41	35.6	162	-24	89.3							

SD= Standard Deviation 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)

(3) **Subject's self-evaluation of total symptom scores (nasal + non-nasal) for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit), [221:1086-1088]:**

Total symptom scores were not found to be statistically significantly decreased in the mometasone treatment group compared to placebo for any of the 15 day study intervals, although they were numerically lower at all time points compared to placebo treated subjects. This is in contrast to the beclomethasone treatment group which showed a significant response in total symptom scores compared to placebo for the day 1-15, day 16-30, day 31-45, and day 46-60 study intervals. As noted for the total nasal symptom scores, the greatest decrease in total symptom scores for all 3 treatment groups occurred during the first two weeks of study drug administration (day 1-15) [221:1086]. Separation of the day 1-15 interval into weekly intervals of day 1-7 and day 8-15, respectively, (Refer to Attachment 2) revealed a statistically significant decrease in total symptom scores (a.m. and p.m. combined) in the mometasone treated subjects by week 1, as compared with placebo ($p=0.04$) but not during week 2 of treatment ($p=0.14$). Separation of the day 1-15 interval revealed that the greatest change in the total symptom score occurred during week 1 of treatment with mometasone, a finding consistent with mometasone's onset of action. Analysis of the duration of effect of mometasone in terms of total symptom scores revealed a slight difference in the a.m. and p.m. total symptom scores for all 15 day intervals (range 0.3-0.4 difference) with higher total symptom scores recorded in the a.m. This insignificant difference is consistent with prior observations (Refer to discussion of the primary efficacy variable in Section 8.12.4.2. (I): Change in total nasal symptom scores) and supports once a day dosing of mometasone for the treatment of symptoms of PAR.

(4) **Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90 and the endpoint visit) [221:1089-1091, 1104-1115]:**

Total non-nasal symptom scores, as defined in Section 8.12.3.1.b., were not found to be significantly decreased in either the mometasone treatment group or the active comparator, beclomethasone treatment, as compared to placebo, for any of the 15-day intervals (p-value range for the mean change of total non-nasal symptom scores for the mometasone group compared to placebo: 0.45-0.91) [221:1089]. In terms of each individual non-nasal symptom, a review of the response of each respective symptom to mometasone [221:1104-1115] failed to show a statistically significant symptom score response. Furthermore, mometasone treated subjects failed to have numerically lower individual non-nasal symptom scores, as compared to placebo for all 4 non-nasal symptoms. A similar failure of beclomethasone treated subjects to demonstrate a statistically significant decrease in the individual non-nasal symptoms was likewise noted on review of

each respective individual non-nasal symptom score [221:1104-1115]. Analysis of drug effect by evaluation of a.m. and p.m. scores for total non-nasal symptoms and each individual non-nasal symptom for mometasone treated subjects, did not reveal a significant difference between a.m. and p.m. scores, again supporting once daily dosing of mometasone [221:1090-1091, 1105-1106, 1108-1109, 1111-1112, 1114-1115]. These results, along with a review of the clinical response for individual nasal symptoms are summarized in Table VIII. A summary of total symptoms, total nasal and total non-nasal responses for mometasone treated subjects at all study interval time points is presented in Table IX. below.

Table VIII. Change in Individual PAR Symptoms with Mometasone Treatment [221:1104-1115]

PAR SYMPTOM	*Clinical Response$_{DAY\ 1\text{-}15}$ (Yes=Y/No=N)	Clinical Response$_{DAY\ 16\text{-}30}$ (Y/N)	Clinical Response$_{DAY\ 31\text{-}45}$ (Y/N)	Clinical Response$_{DAY\ 46\text{-}60}$ (Y/N)	Clinical Response$_{DAY\ 61\text{-}75}$ (Y/N)	Clinical Response$_{DAY\ 76\text{-}90}$ (Y/N)	Clinical Response$_{E}$ (Y/N)
NASAL							
--Rhinorrhea	Yes	Yes	Yes	Yes	Yes	No (p^2=0.08)	
--Congestion	No (p=0.33)	No (p=0.06)	Yes	Yes	No (p=0.07)	No (p=0.19)	No (p=0.
--Itching	No (p=0.17)	No (p=0.39)	No (p=0.12)	No (p=0.18)	No (p=0.24)	No (p=0.12)	No (p=0.
--Sneezing	Yes	Yes	Yes	Yes	No (p=0.11)	Yes	Yes
NON-NASAL							
--Eye Itching	No (p=0.67)	No (p=0.89)	No (p=0.6)	No (p=0.5)	No (p=0.71)	No (p=0.99)	No (p=0.
--Eye Tearing	No (p=0.2)	No (p=0.49)	No (p=0.4)	No (p=0.27)	No (p=0.37)	No (p=0.75)	No (p=0
--Eye Redness	No (p=0.94)	No (p=0.96)	No (p=0.84)	No (p=0.79)	No (p=0.39)	No (p=0.25)	No (p=0
--Ear/palate itching	No (p=0.6)	No (p=0.9)	No (p=0.88)	No (p=0.7)	No (p=0.71)	No (p=0.61)	No (p=0.

* Clinical Response= Clinical response of mometasone treatment group, as compared with placebo (for am and pm scores combined).

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

Table IX. Summary of Change in PAR Symptoms (a.m. and p.m. combined) with Mometasone Treatment, [218:318, 221:1086, 1089]

PAR SYMPTOM	*Statistical Response$_{DAY\ 1\text{-}15}$ (Yes=Y/No=N)	Statistical Response$_{DAY\ 16\text{-}30}$ (Y/N)	Statistical Response$_{DAY\ 31\text{-}45}$ (Y/N)	Statistical Response$_{DAY\ 46\text{-}60}$ (Y/N)	Statistical Response$_{DAY\ 61\text{-}75}$ (Y/N)	Statistical Response$_{DAY\ 76\text{-}90}$ (Y/N)	Stati Resp (Y/N
Total symptoms	No (p^2=0.08)	No (p=0.12)	No (p=0.09)	No (p=0.06)	No (p=0.23)	No (p=0.32)	N
Total nasal symptoms	Yes	Yes	Yes	Yes	Yes	Yes	
Total non-nasal symptoms	No (p=0.45)	No (p=0.69)	No (p=0.59)	No (p=0.48)	No (p=0.89)	No (p=0.79)	N

* Statistical Response= Statistical response of the mometasone treatment group, as compared with placebo.
[2] p values were calculated based on the change in symptom score(s) from baseline.

(5) **Physician's evaluation of total nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8 , Week 12, and the endpoint visit)** [221:1116]:

Physician evaluations of subjects' total nasal symptoms demonstrated that at all study visits after initiation of drug treatment (i.e. Day 8, 15, 29, Week 8, Week 12, and the endpoint visit), subjects in the mometasone treatment group were found to have a statistically significant decrease in total nasal symptoms, as compared with placebo (p= 0.01-0.03 range for all visits except baseline). Again, beclomethasone was found to have a statistically significant and greater response than mometasone in decreasing total nasal symptoms at all study visits after the baseline visit.

(6) **Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit)** [221:1117]:

With the exception of Day 15 and Week 12, subjects in the mometasone treatment group were not found to have a statistically significant decrease in total symptoms compared with placebo, although numerically a decrease in symptom scores was noted with mometasone treatment (marginally statistically significant differences between mean change in total symptoms for the mometasone group vs. placebo, p=0.06-0.07) were noted for the Day 29, Week 8, and the endpoint visit) [221:1117]. The beclomethasone treatment group demonstrated a numerically greater response in total symptom scores at all study visits than the mometasone group. With beclomethasone treatment, a statistically significant decrease in total symptoms was noted on study Day 8, 15, and 29 with a marginally statistically significant decrease (p=0.06 for beclomethasone vs. placebo comparison) at Week 8 of the study.

(7) **Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit)** [221:1118]:

Subjects in the mometasone treatment group were not found to have a clinically and statistically significant decrease in total non-nasal symptoms compared with placebo, and again, no numerical decrease in symptom scores was noted with mometasone treatment as compared with placebo. Likewise, subjects in the beclomethasone treatment group were not noted to have a statistically significant improvement in total non-nasal symptoms at any visits, compared with placebo, although a greater numerical response in non-nasal symptom scores was demonstrable with beclomethasone treatment than with mometasone treatment [221:1118].

(8) **Subject's self-evaluation of overall disease condition using the PAR 0-3 point severity scale for study Day 8, 15, 29, Week 8, Week 12, and the endpoint visit** [221:1128]:

With the exception of Day 8 and Week 12, and the marginal exception of the endpoint visit (p=0.07), subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall condition compared with placebo. This clinical improvement in mometasone treated subjects was comparable numerically to the beclomethasone treatment group beginning Day 15 of the study till Week 12 of the study.

(9) **Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study Day 8, 15, 29, Week 8, Week 12, and the endpoint visit [221:1127]:**

Subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall condition compared with placebo at Day 29, Week 8, and the endpoint study visit ($p \leq 0.05$). Furthermore, responses for the mometasone and beclomethasone treatment groups were comparable at most study visits (Day 29, Week 12, endpoint visit) [221:1127].

(10) **Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study Day 8, 15, 29, Week 8, Week 12, and the endpoint visit [221:1130]:**

Subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall response to treatment, as compared to the placebo group only at Day 15 of the study (p=0.01), although mometasone treated subjects demonstrated a numerically greater overall response to treatment than placebo subjects. The beclomethasone treatment group demonstrated a statistically significant and numerically greater overall response to treatment than did the mometasone group per subject self-evaluation, as had been previously noted in several of the other secondary efficacy variables ($p \leq 0.02$ at all study visits) [221:1130].

(11) **Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study Day 8, 15, 29, Week 8, Week 12, and the endpoint visit [221:1129]:**

Subjects in the mometasone treatment group were found to have a statistically significant improvement in their overall response to treatment, as compared with placebo at all study visits ($p \leq 0.04$) with the exception of Day 8 (p=0.14). The beclomethasone treatment group demonstrated a statistically significant and a slightly greater response to treatment than did the mometasone

group ($p \leq 0.03$ at all study visits), again consistent with previous analyses of the primary efficacy variable and several secondary efficacy variables.

A summary of the secondary efficacy variable findings for mometasone is summarized in Table X. below and presented as primary data in Attachment 1 (for variables (3)-(11)):

Table X. Secondary Efficacy Variables of PAR and Treatment with Mometasone [218:318, 221:1086, 1089, 1116-1118, 1127-1130]

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1.	Subject evaluated mean Δ in Total Nasal Sx Score DAY16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90	Yes:	All study intervals.	
2.	Subject evaluated mean Δ in Endpoint Total Nasal Sx Score	Yes:	Endpoint visit.	
3.	Subject evaluated mean Δ in Total Sx Score DAY 1-15, DAY16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90, Endpoint Visit	No:	All study intervals.	
4.	Subject evaluated Total non-nasal Sx Score DAY 1-15, DAY16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90, Endpoint Visit	No:	All study intervals.	
5.	Physician Evaluated Total Nasal Sx Score	Yes:	All study visits:	Day 8, 15, 29, Week 8, Week 12, Endpoint visit
6.	Physician Evaluated Total Sx Score	Yes:	Study visits:	Day 15, Week 12
		No:	Study visits:	DAY 8, 29, Week 8, Endpoint visit
7.	Physician Evaluated Total non-nasal Sx Score	No:	All study visits	
8.	Subject overall condition evaluation	Yes:	Study visits:	Day 15, 29, Week 8
		No:	Study visits:	Day 8, Week 12, Endpoint visit
9.	Physician overall condition evaluation	Yes:	Study visits:	Day 29, Week 8, Endpoint visit
		No:	Study visits:	Day 8, 15, Week 12
10.	Subject overall Rx Response evaluation	Yes:	Study visit:	Day 15
		No:	Study visits:	Day 8, 29, Week 8, Week 12, Endpoint visit
11.	Physician overall Rx Response evaluation	Yes:	Study visits:	Day 15, 29, Week 8, Week 12, Endpoint visit
		No:	Study visit:	Day 8

Δ=Change, Sx=Symptom, Rx=Treatment

Reviewer's Note: Summary of Efficacy Findings

Overall, mometasone was found to be effective in reducing total nasal symptoms at a dose of 200 μg po qd, as related to perennial allergic rhinitis symptoms over the course of all study visits. Because of a lack of a clinically significant effect on non-nasal symptoms, mometasone did not demonstrate a significant effect on decreasing total symptoms of PAR, the total non-nasal symptoms or any of the individual non-nasal symptoms of PAR.

Rescue medication overall was used less frequently during the study by mometasone treated subjects, as compared to placebo or beclomethasone treated subjects. 59% of mometasone treated subjects (ITT population [218:250]) used the rescue antihistamine, chlorpheniramine, at some point during study C92-280, in contrast to 72% of placebo subjects and 67% of beclomethasone subjects.

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

In terms of the primary efficacy variable, mometasone treatment demonstrated a numerically greater but not statistically greater effect in individuals < 34 years of age . No commentary can be made regarding efficacy and racial differences as the majority of enrolled subjects were caucasian, however non-caucasian subjects were noted to have a statistically significantly and numerically smaller response to mometasone treatment for the day 1-15 interval than did caucasian subjects.

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

ATTACHMENT 2:

Secondary Efficacy Variables of PAR and Response to Mometasone Treatment:

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

(A) Subject a.m. and p.m. combined scores [221:1086]:

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

DAYS	(A) MOMETASONE N	MEAN	SD	(B) VANCENASE AQ N	MEAN	SD	(C) PLACEBO N	MEAN	SD	POOLED SD	ANOVA P-VALUES # TRT	INV	T X I	PAIRWISE COMPARISONS # A-B	A-C	B-C
BASELINE	163	10.8	4.6	163	10.5	4.1	162	11.1	4.1	4.1	0.36	0.01	0.04	0.37	0.61	0.16
1-15 RAW	163	8.5	4.4	163	7.9	4.2	162	9.4	4.2	4.1	0.01	<.01	0.39	0.18	0.06	<.01
CHG	163	-2.3	3.6	163	-2.6	3.6	162	-1.7	3.0	3.3	0.06	0.07	0.3	0.58	0.08	0.02
%CHG	163	-17	39.0	163	-21	37.4	162	-12	35.9							
16-30 RAW	159	7.5	4.5	157	6.7	4.4	157	8.3	4.3	4.2	<.01	<.01	0.43	0.09	0.1	<.01
CHG	159	-3.4	4.1	157	-3.8	4.3	157	-2.7	3.9	3.9	0.05	<.01	0.28	0.41	0.12	0.02
%CHG	159	-27	40.8	157	-32	47.0	157	-20	49.2							
31-45 RAW	152	7.1	4.8	157	6.3	4.5	153	7.9	4.6	4.4	<.01	<.01	0.38	0.15	0.06	<.01
CHG	152	-3.9	4.7	157	-4.2	4.4	153	-3.1	4.2	4.3	0.07	0.01	0.2	0.62	0.09	0.03
%CHG	152	-31	48.0	157	-36	47.2	153	-22	65.8							
46-60 RAW	147	6.6	4.6	157	6.1	4.5	148	7.5	4.6	4.4	<.01	<.01	0.19	0.32	0.03	<.01
CHG	147	-4.4	4.8	157	-4.5	4.4	148	-3.5	4.2	4.4	0.08	0.04	0.44	0.93	0.06	0.04
%CHG	147	-36	44.8	157	-40	42.0	148	-26	65.6							
61-75 RAW	144	6.3	4.3	150	5.9	4.4	142	6.9	4.4	4.2	0.07	<.01	0.58	0.31	0.21	0.02
CHG	144	-4.7	4.4	150	-4.6	4.2	142	-4.0	4.4	4.2	0.41	<.01	0.5	0.9	0.23	0.27
%CHG	144	-40	39.0	150	-43	36.5	142	-30	71.2							
76-90 RAW	142	6.4	4.4	145	5.8	4.4	139	7.0	4.6	4.3	0.05	<.01	0.74	0.25	0.2	0.02
CHG	142	-4.6	4.5	145	-4.7	4.3	139	-4.0	4.7	4.4	0.45	<.01	0.2	0.86	0.32	0.24
%CHG	142	-39	40.7	145	-43	37.0	139	-29	72.8							
LVOPT RAW	163	6.6	4.6	163	6.1	4.5	162	7.4	5.0	4.6	0.03	<.01	0.76	0.39	0.08	0.01
CHG	163	-4.3	4.8	163	-4.4	4.3	162	-3.7	4.7	4.6	0.32	0.02	0.54	0.97	0.2	0.18
%CHG	163	-35	46.4	163	-40	38.9	162	-28	69.5							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LEVENES PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 8 SYMPTOMS FROM AVERAGED AM AND PM DIARIES
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM AND PM BASELINE VALUES
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
LVOPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT
SYMPTOMS ADJUSTED FOR RESCUE MEDICATION

ATTACHMENT 2--continued

(B) Subject a.m. scores [221:1087]

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

	(A) FORCHROME			(B) VANCENASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	163	11.1	4.6	163	10.6	4.1	162	11.2	4.2	4.2	0.26	0.01	0.03	0.10	0.91	0.14
1-15 RAW	163	8.8	4.4	163	8.0	4.3	162	9.6	4.3	4.2	<.01	<.01	0.35	0.06	0.1	<.01
CHG	163	-2.3	3.6	163	-2.6	3.5	162	-1.6	3.0	3.3	0.03	0.09	0.34	0.58	0.05	0.01
%CHG	163	-17	39.9	163	-21	36.6	162	-12	31.1							
16-30 RAW	159	7.7	4.5	157	6.8	4.4	157	8.5	4.3	4.2	<.01	<.01	0.53	0.06	0.1	<.01
CHG	159	-3.5	4.1	157	-3.8	4.3	157	-2.6	3.9	4.0	0.03	<.01	0.21	0.59	0.05	0.01
%CHG	159	-28	39.1	157	-31	42.9	157	-19	43.3							
31-45 RAW	152	7.2	4.8	157	6.6	4.5	153	8.1	4.6	4.4	<.01	<.01	0.23	0.12	0.06	<.01
CHG	152	-4.0	4.7	157	-4.1	4.5	153	-3.0	4.2	4.4	0.04	<.01	0.31	0.84	0.04	0.02
%CHG	152	-32	45.9	157	-35	46.5	153	-22	57.4							
46-60 RAW	147	6.7	4.6	157	6.2	4.6	148	7.7	4.6	4.4	<.01	<.01	0.15	0.31	0.02	<.01
CHG	147	-4.6	4.7	157	-4.4	4.5	148	-3.4	4.3	4.4	0.05	0.03	0.38	0.73	0.02	0.05
%CHG	147	-37	42.2	157	-38	45.1	148	-25	64.3							
61-75 RAW	144	6.4	4.3	150	5.9	4.5	142	7.1	4.3	4.2	0.05	<.01	0.58	0.23	0.21	0.01
CHG	144	-4.8	4.4	150	-4.6	4.3	142	-4.0	4.5	4.3	0.27	<.01	0.52	0.69	0.12	0.24
%CHG	144	-40	39.6	150	-41	40.4	142	-28	66.9							
76-90 RAW	142	6.5	4.4	145	5.8	4.4	139	7.2	4.6	4.3	0.03	<.01	0.8	0.2	0.18	0.01
CHG	142	-4.7	4.4	145	-4.7	4.4	139	-4.0	4.8	4.4	0.34	<.01	0.3	0.88	0.18	0.23
%CHG	142	-39	40.6	145	-41	41.0	139	-30	62.4							
ENDPT RAW	163	6.7	4.6	163	6.2	4.5	162	7.5	5.0	4.6	0.02	<.01	0.77	0.33	0.08	0.01
CHG	163	-4.4	4.8	163	-4.4	4.4	162	-3.7	4.7	4.6	0.21	0.01	0.53	0.8	0.1	0.17
%CHG	163	-36	45.7	163	-39	41.4	162	-28	60.4							

(C) Subject p.m. scores [221:1088]:

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

	(A) VANCENASE			(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	162	10.6	4.7	163	10.4	4.2	162	11.0	4.3	4.3	0.42	<.01	0.09	0.68	0.38	0.19
1-15 RAW	162	8.3	4.4	163	7.8	4.2	162	9.2	4.2	4.1	0.01	<.01	0.43	0.41	0.04	<.01
CHG	162	-2.3	3.7	163	-2.5	3.5	162	-1.6	3.4	3.5	0.13	0.08	0.31	0.63	0.15	0.05
%CHG	162	-14	48.9	163	-16	77.7	162	-9.8	47.5							
16-30 RAW	158	7.3	4.5	157	6.6	4.4	157	8.0	4.3	4.2	0.01	<.01	0.4	0.15	0.1	<.01
CHG	158	-3.3	4.2	157	-3.9	4.4	157	-2.8	4.3	4.3	0.3	<.01	0.43	0.32	0.26	0.03
%CHG	158	-24	53.1	157	-20	103	157	-19	60.4							
31-45 RAW	150	6.8	4.8	157	6.2	4.6	153	7.7	4.6	4.4	0.01	<.01	0.38	0.26	0.05	<.01
CHG	150	-3.9	4.7	157	-4.2	4.5	153	-3.2	4.3	4.4	0.1	0.01	0.13	0.58	0.13	0.04
%CHG	150	-29	61.1	157	-27	138	153	-21	79.3							
46-60 RAW	146	6.4	4.6	157	5.9	4.6	148	7.4	4.6	4.4	0.01	<.01	0.26	0.34	0.03	<.01
CHG	146	-4.2	5.0	157	-4.5	4.4	148	-3.5	4.3	4.5	0.12	0.08	0.35	0.62	0.14	0.05
%CHG	146	-32	55.0	157	-36	60.0	148	-25	88.2							
61-75 RAW	143	6.1	4.4	149	5.8	4.5	142	6.8	4.5	4.2	0.11	<.01	0.58	0.42	0.21	0.04
CHG	143	-4.6	4.6	149	-4.7	4.3	142	-4.1	4.5	4.3	0.85	<.01	0.53	0.88	0.38	0.31
%CHG	143	-38	43.6	149	-40	96.0	142	-30	78.5							
76-90 RAW	141	6.2	4.4	145	5.8	4.5	139	6.8	4.7	4.3	0.08	<.01	0.7	0.34	0.22	0.03
CHG	141	-4.4	4.6	145	-4.7	4.4	139	-4.0	4.9	4.5	0.53	0.02	0.38	0.66	0.31	0.27
%CHG	141	-36	48.3	145	-41	45.2	139	-27	88.2							
ENDPT RAW	162	6.4	4.5	163	6.1	4.5	162	7.3	5.1	4.6	0.04	<.01	0.76	0.56	0.07	0.01
CHG	162	-4.2	4.8	163	-4.4	4.5	162	-3.7	4.9	4.7	0.43	0.04	0.5	0.84	0.31	0.22
%CHG	162	-33	51.0	163	-36	47.6	162	-26	84.5							

ATTACHMENT 2--continued

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

(A) Subject a.m. and p.m. combined scores [221:1089]:

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

DAYS	(A) MOMETASONE N	MEAN	SD	(B) VANCENASE AQ N	MEAN	SD	(C) PLACEBO N	MEAN	SD	POOLED SD	ANOVA P-VALUES # TRT	INV	T X I	PAIRWISE COMPARISONS # A-B	A-C	B-C
BASELINE	163	6.3	2.8	163	3.8	2.5	162	4.2	2.6	2.5	0.16	0.01	0.04	0.08	0.77	0.13
1-15 RAW	163	3.5	2.5	163	3.0	2.3	162	3.5	2.4	2.3	0.03	<.01	0.16	0.04	0.81	0.02
CHG	163	-0.8	1.8	163	-0.9	1.7	162	-0.7	1.7	1.7	0.6	0.03	0.08	0.84	0.45	0.34
%CHG	158	16.1	319	158	-3.8	105	161	1.9	95.6							
16-30 RAW	159	3.1	2.5	157	2.5	2.3	157	3.0	2.4	2.3	0.03	<.01	0.3	0.01	0.68	0.04
CHG	159	-1.2	2.2	157	-1.4	2.1	157	-1.1	2.1	2.1	0.61	<.03	0.22	0.55	0.69	0.32
%CHG	154	-15	106	152	-16	151	156	-17	78.6							
31-45 RAW	152	2.9	2.5	157	2.6	2.3	153	2.8	2.5	2.3	0.05	<.01	0.13	0.03	0.88	0.04
CHG	152	-1.4	2.3	157	-1.5	2.3	153	-1.3	2.3	2.2	0.72	0.01	0.16	0.8	0.59	0.43
%CHG	147	-24	107	152	-19	136	152	-17	125							
46-60 RAW	147	2.7	2.4	157	2.2	2.4	148	2.7	2.5	2.3	0.1	<.01	0.09	0.07	0.94	0.06
CHG	147	-1.6	2.4	157	-1.6	2.2	148	-1.5	2.2	2.3	0.73	0.09	0.36	0.97	0.48	0.5
%CHG	142	-29	92.9	152	-33	89.4	147	-27	112							
61-75 RAW	144	2.6	2.3	150	2.2	2.3	142	2.4	2.3	2.2	0.27	<.01	0.21	0.11	0.54	0.33
CHG	144	-1.8	2.3	150	-1.6	2.1	142	-1.7	2.4	2.2	0.91	0.02	0.41	0.68	0.89	0.78
%CHG	139	-30	61.6	145	-34	115	141	-32	84.6							
76-90 RAW	142	2.7	2.4	145	2.2	2.3	139	2.4	2.5	2.3	0.19	<.01	0.61	0.07	0.45	0.3
CHG	142	-1.7	2.4	145	-1.7	2.2	139	-1.7	2.4	2.3	0.95	0.06	0.37	0.98	0.79	0.77
%CHG	137	-30	77.6	140	-29	148	136	-31	93.7							
ENDPT RAW	163	2.7	2.4	163	2.3	2.3	162	2.7	2.6	2.4	0.17	<.01	0.42	0.09	0.85	0.12
CHG	163	-1.6	2.5	163	-1.6	2.2	162	-1.6	2.5	2.4	0.99	0.05	0.39	0.87	0.91	0.96
%CHG	158	-5.2	319	158	-27	144	161	-28	91.0							

ATTACHMENT 2--continued

(B) Subject a.m. non-nasal scores [221:1090]:

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

	(A) FLUTICASONE			(B) VANCERAIE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	163	4.3	2.8	163	3.8	2.5	162	4.2	2.6	2.6	0.14	0.01	0.02	0.06	0.56	0.18
2-15 RAW	163	3.6	2.5	163	3.0	2.3	162	3.6	2.4	2.3	0.02	<.01	0.14	0.01	0.92	0.02
CHG	163	-0.8	1.9	163	-0.9	1.7	162	-0.6	1.7	1.8	0.45	0.04	0.1	0.59	0.48	0.21
%CHG	155	-5.4	96.6	156	-12	73.2	159	-1.8	68.9							
16-30 RAW	159	3.1	2.5	157	2.5	2.3	157	3.0	2.4	2.3	0.02	<.01	0.32	0.01	0.61	0.04
CHG	159	-1.2	2.2	157	-1.4	2.2	157	-1.1	2.2	2.1	0.51	<.01	0.18	0.64	0.5	0.25
%CHG	153	-12	109	150	-24	96.5	154	-10	64.1							
31-45 RAW	152	3.0	2.5	157	2.4	2.4	153	2.9	2.5	2.3	0.05	<.01	0.16	0.03	0.68	0.04
CHG	152	-1.5	2.4	157	-1.5	2.3	153	-1.2	2.4	2.3	0.57	0.01	0.2	0.93	0.39	0.34
%CHG	146	-23	107	150	-21	138	150	-22	70.6							
46-60 RAW	147	2.7	2.4	157	2.3	2.4	148	2.7	2.5	2.3	0.11	<.01	0.07	0.08	0.91	0.07
CHG	147	-1.7	2.5	157	-1.6	2.3	148	-1.4	2.3	2.3	0.94	0.08	0.36	0.72	0.28	0.45
%CHG	141	-28	98.7	150	-31	114	145	-32	58.1							
61-75 RAW	144	2.6	2.3	150	2.2	2.4	142	2.6	2.3	2.2	0.22	<.01	0.18	0.08	0.46	0.32
CHG	144	-1.8	2.4	150	-1.7	2.2	142	-1.7	2.4	2.3	0.88	0.01	0.43	0.62	0.7	0.92
%CHG	138	-36	66.9	143	-38	107	139	-36	61.6							
76-90 RAW	142	2.7	2.4	145	2.2	2.3	139	2.5	2.5	2.3	0.2	<.01	0.65	0.07	0.44	0.31
CHG	142	-1.7	2.4	145	-1.7	2.2	139	-1.7	2.5	2.3	0.97	0.02	0.24	0.81	0.95	0.86
%CHG	136	-31	74.4	138	-35	109	136	-36	61.0							
EXPT RAW	163	2.7	2.5	163	2.3	2.3	162	2.7	2.7	2.4	0.19	<.01	0.43	0.09	0.79	0.15
CHG	163	-1.6	2.5	163	-1.5	2.3	162	-1.5	2.5	2.4	0.92	0.03	0.36	0.72	0.72	0.99
%CHG	155	-31	74.0	156	-33	106	159	-33	63.1							

(C) Subject p.m. non-nasal scores [221:1091]:

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

	(A) FLUTICASONE			(B) VANCERAIE 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	162	4.2	2.8	163	3.8	2.5	162	4.2	2.7	2.6	0.10	<.01	0.00	0.11	0.99	0.11
1-15 RAW	162	3.3	2.4	163	2.9	2.3	162	3.5	2.4	2.3	0.06	<.01	0.2	0.1	0.54	0.02
CHG	162	-0.9	1.8	163	-0.9	1.8	162	-0.7	1.9	1.8	0.71	0.05	0.12	0.83	0.42	0.56
%CHG	152	0.4	161	155	2.5	192	161	5.5	112							
16-30 RAW	158	3.0	2.5	157	2.4	2.3	157	2.9	2.4	2.3	0.04	<.01	0.32	0.02	0.81	0.04
CHG	158	-1.2	2.2	157	-1.4	2.2	157	-1.2	2.2	2.1	0.72	<.01	0.3	0.56	0.84	0.43
%CHG	148	-25	107	149	-27	196	156	-26	82.5							
31-45 RAW	150	2.8	2.5	157	2.3	2.3	153	2.8	2.5	2.3	0.07	<.01	0.15	0.05	0.98	0.05
CHG	150	-1.5	2.3	157	-1.5	2.3	153	-1.4	2.4	2.3	0.83	0.02	0.11	0.87	0.67	0.55
%CHG	140	-24	110	149	-26	197	152	-22	80.5							
46-60 RAW	146	2.7	2.5	157	2.2	2.4	148	2.6	2.5	2.3	0.08	<.01	0.34	0.06	0.97	0.06
CHG	146	-1.6	2.4	157	-1.6	2.3	148	-1.5	2.3	2.3	0.85	0.12	0.42	0.8	0.75	0.57
%CHG	137	-28	91.6	149	-30	76.8	147	-31	70.8							
61-75 RAW	143	2.5	2.3	148	2.2	2.3	142	2.6	2.6	2.2	0.37	<.01	0.28	0.17	0.67	0.35
CHG	143	-1.8	2.3	148	-1.6	2.2	142	-1.7	2.6	2.3	0.88	0.02	0.47	0.88	0.97	0.86
%CHG	134	-37	63.6	141	-42	82.8	141	-32	77.4							
76-90 RAW	141	2.8	2.4	145	2.2	2.3	138	2.6	2.5	2.3	0.22	<.01	0.28	0.06	0.49	0.3
CHG	141	-1.6	2.4	145	-1.7	2.2	139	-1.7	2.5	2.3	0.87	0.14	0.36	0.89	0.61	0.7
%CHG	132	-31	85.2	137	-37	73.5	138	-30	93.9							
EXPT RAW	162	2.7	2.6	163	2.2	2.3	162	2.7	2.7	2.6	0.28	<.01	0.68	0.11	0.98	0.11
CHG	162	-1.6	2.6	163	-1.6	2.3	162	-1.6	2.6	2.6	0.99	0.09	0.43	0.93	0.99	0.92
%CHG	152	-28	163	155	-30	108	161	-26	93.6							

ATTACHMENT 2--continued

(5) Physician's evaluation of total nasal symptoms [221:1116]:

VISIT NASAL SYMPTOM SCORE @ - POOLED VISIT DATA

	(A) MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	164	7.3	1.9	163	7.4	1.8	163	7.6	1.9	1.8	0.51	0.06	0.11	0.86	0.28	0.36
DAY 8 RAW	164	5.4	2.3	161	5.3	2.5	163	6.2	2.5	2.4	<.01	<.01	0.95	0.68	<.01	<.01
CHG	164	-1.9	2.5	161	-2.1	2.5	163	-1.4	2.5	2.5	0.02	0.02	0.95	0.59	0.03	0.01
%CHG	164	-24	32.2	161	-28	32.8	163	-17	32.6							
DAY15 RAW	160	5.0	2.4	159	4.6	2.7	159	5.9	2.4	2.4	<.01	0.01	0.27	0.3	<.01	<.01
CHG	160	-2.4	2.7	159	-2.7	2.8	159	-1.7	2.6	2.7	<.01	<.01	0.77	0.41	0.02	<.01
%CHG	160	-30	33.7	159	-35	35.9	159	-19	36.0							
DAY29 RAW	159	4.5	2.3	157	4.3	2.7	157	5.3	2.3	2.4	<.01	0.01	0.58	0.63	<.01	<.01
CHG	159	-2.9	2.6	157	-3.0	2.9	157	-2.2	2.7	2.7	0.03	0.01	0.85	0.85	0.03	0.02
%CHG	159	-37	31.5	157	-40	36.0	157	-26	34.0							
WK 8 RAW	151	4.2	2.7	157	4.1	2.6	151	5.1	2.7	2.6	<.01	<.01	0.9	0.99	<.01	<.01
CHG	151	-3.2	3.0	157	-3.3	2.8	151	-2.4	2.7	2.8	0.02	<.01	0.96	0.81	0.01	0.02
%CHG	151	-41	37.0	157	-43	36.8	151	-31	33.7							
WK 12 RAW	147	3.8	2.3	148	3.8	2.5	143	4.7	2.4	2.4	<.01	0.01	0.89	0.96	<.01	<.01
CHG	147	-3.6	2.8	148	-3.5	2.8	143	-2.9	2.5	2.7	0.07	0.01	0.85	0.55	0.03	0.1
%CHG	147	-46	33.6	148	-46	36.1	143	-37	32.3							
ENDPT RAW	164	4.0	2.4	163	4.1	2.7	163	4.9	2.7	2.6	<.01	<.01	0.85	0.61	<.01	<.01
CHG	164	-3.6	2.9	163	-3.3	2.9	163	-2.7	2.7	2.8	0.03	0.01	0.83	0.72	0.01	0.03
%CHG	164	-43	35.3	163	-43	38.0	163	-34	35.5							

(6) Physician's evaluation of total symptoms [221:1117]:

VISIT TOTAL SYMPTOM SCORE @ - POOLED VISIT DATA

	(A) MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	164	11.9	4.1	163	11.6	3.8	163	11.8	3.9	3.8	0.67	0.01	0.02	0.36	0.76	0.57
DAY 8 RAW	164	9.0	4.4	161	8.4	4.4	163	9.6	4.5	4.3	0.03	<.01	0.53	0.19	0.2	0.01
CHG	164	-2.9	4.3	161	-3.2	4.1	163	-2.2	3.9	4.1	0.07	0.00	0.06	0.54	0.1	0.02
%CHG	164	-20	42.4	161	-25	35.8	163	-17	34.3							
DAY15 RAW	160	8.5	4.6	159	7.6	4.7	159	9.3	4.5	4.5	0.01	<.01	0.35	0.1	0.13	<.01
CHG	160	-3.5	4.4	159	-3.9	4.5	159	-2.4	4.6	4.4	0.01	<.01	0.05	0.44	0.04	<.01
%CHG	160	-26	36.9	159	-32	41.0	159	-17	39.5							
DAY29 RAW	159	7.7	4.3	157	7.0	4.7	157	8.4	4.1	4.3	0.02	<.01	0.44	0.13	0.18	<.01
CHG	159	-4.3	4.5	157	-4.6	4.8	157	-3.3	4.4	4.5	0.06	0.02	0.63	0.67	0.07	0.03
%CHG	159	-33	35.3	157	-38	39.4	157	-25	35.4							
WK 8 RAW	151	7.1	4.8	157	6.5	4.5	151	7.7	4.7	4.5	0.06	<.01	0.81	0.3	0.2	0.02
CHG	151	-4.9	5.0	157	-5.0	4.8	151	-3.9	4.9	4.8	0.00	<.01	0.53	0.96	0.06	0.06
%CHG	151	-39	40.0	157	-41	40.6	151	-31	38.4							
WK 12 RAW	147	6.4	4.8	148	6.2	4.2	143	7.1	4.1	4.8	0.14	<.01	0.67	0.52	0.2	0.05
CHG	147	-5.7	4.7	148	-5.3	4.5	143	-4.6	4.6	4.5	0.15	0.01	0.59	0.5	0.05	0.21
%CHG	147	-44	36.8	148	-44	37.6	143	-37	35.6							
ENDPT RAW	164	6.8	4.2	163	6.7	4.6	163	7.6	4.7	4.6	0.00	<.01	0.47	0.75	0.09	0.04
CHG	164	-5.1	5.0	163	-4.9	4.7	163	-4.2	4.9	4.8	0.17	0.04	0.38	0.69	0.07	0.16
%CHG	164	-39	44.8	163	-40	40.6	163	-34	39.9							

ATTACHMENT 2--continued

(7) Physician's evaluation of total non-nasal symptoms [221:1118]:

VISIT NON-NASAL SYMPTOM SCORE @ - POOLED VISIT DATA

	(A) FEXOFENADINE			(B) PSEUDOEPHEDRINE HCl			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	164	4.6	2.9	163	4.2	2.5	163	4.2	2.6	2.6	0.31	<.01	0.07	0.16	0.22	0.85
DAY 8 RAW	164	3.6	2.6	161	3.2	2.4	163	3.4	2.6	2.4	0.15	<.01	0.09	0.05	0.5	0.21
CHG	164	-1.0	2.5	161	-1.1	2.2	163	-0.8	2.2	2.3	0.52	0.53	0.48	0.62	0.52	0.25
%CHG	153	-18	62.8	150	-18	66.0	155	-12	66.3							
DAY15 RAW	160	3.5	2.7	159	3.0	2.5	159	3.4	2.7	2.6	0.14	<.01	0.48	0.06	0.64	0.15
CHG	160	-1.1	2.4	159	-1.3	2.3	159	-0.7	2.7	2.5	0.28	0.02	0.87	0.62	0.3	0.12
%CHG	150	-19	65.1	148	-27	67.8	151	-4.3	80.3							
DAY29 RAW	159	3.2	2.5	157	2.6	2.6	157	3.0	2.4	2.4	0.08	<.01	0.46	0.03	0.5	0.13
CHG	159	-1.4	2.7	157	-1.6	2.6	157	-1.1	2.6	2.6	0.34	0.06	0.78	0.59	0.37	0.15
%CHG	149	-26	61.0	146	-37	66.3	149	-15	78.0							
WK 8 RAW	151	3.0	2.6	157	2.5	2.4	151	2.6	2.6	2.5	0.37	<.01	0.79	0.06	0.27	0.44
CHG	151	-1.7	2.7	157	-1.8	2.6	151	-1.5	2.9	2.7	0.66	0.01	0.69	0.88	0.49	0.39
%CHG	141	-34	59.5	146	-37	62.8	143	-26	65.5							
WK 12 RAW	147	2.6	2.2	148	2.4	2.2	143	2.4	2.3	2.2	0.44	<.01	0.3	0.21	0.36	0.75
CHG	147	-2.1	2.7	148	-1.9	2.4	143	-1.7	2.9	2.6	0.58	0.12	0.38	0.57	0.3	0.62
%CHG	139	-41	54.0	137	-42	57.9	135	-34	66.0							
ENDPT RAW	164	2.8	2.4	163	2.6	2.4	163	2.7	2.6	2.3	0.51	<.01	0.12	0.25	0.54	0.59
CHG	164	-1.8	2.8	163	-1.6	2.5	163	-1.6	2.9	2.8	0.83	0.28	0.13	0.74	0.54	0.78
%CHG	153	-36	56.0	152	-31	62.8	155	-29	78.5							

(8) Subject's self-evaluation of overall condition [221:1128]:

SUBJECT'S EVALUATION OF SUBJECT'S OVERALL CONDITION (POOLED)

	(A) FEXOFENADINE			(B) PSEUDOEPHEDRINE HCl			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	164	2.3	0.5	162	2.2	0.5	163	2.3	0.4	0.5	0.35	0.14	0.5	0.2	0.86	0.22
DAY 8 RAW	164	1.8	0.6	160	1.7	0.7	163	1.9	0.6	0.7	<.01	0.43	0.9	0.02	0.26	<.01
CHG	164	-0.4	0.7	160	-0.6	0.7	163	-0.4	0.6	0.7	0.06	0.28	0.94	0.2	0.28	0.02
DAY15 RAW	159	1.6	0.7	158	1.6	0.7	159	1.8	0.6	0.7	<.01	0.28	0.97	0.77	0.01	<.01
CHG	159	-0.6	0.8	158	-0.6	0.8	159	-0.4	0.7	0.7	0.03	0.18	0.95	0.58	0.01	0.05
DAY29 RAW	159	1.6	0.7	157	1.6	0.7	157	1.8	0.7	0.7	0.01	0.46	0.91	0.02	<.01	0.01
CHG	159	-0.7	0.8	157	-0.7	0.9	157	-0.5	0.7	0.8	0.03	0.45	0.79	0.31	0.01	0.1
WK 8 RAW	151	1.6	0.7	157	1.6	0.7	151	1.7	0.8	0.7	<.01	<.01	0.97	0.88	<.01	<.01
CHG	151	-0.8	0.8	157	-0.8	0.8	151	-0.6	0.8	0.8	0.02	0.88	0.81	0.54	0.01	0.04
WK 12 RAW	147	1.4	0.7	148	1.4	0.7	143	1.5	0.7	0.7	0.15	<.01	0.79	0.88	0.11	0.88
CHG	147	-0.8	0.8	148	-0.8	0.8	143	-0.7	0.7	0.8	0.34	<.01	0.43	0.62	0.34	0.5
ENDPT RAW	164	1.5	0.7	162	1.5	0.7	163	1.6	0.7	0.7	0.88	0.01	0.76	0.85	0.85	0.86
CHG	164	-0.8	0.8	162	-0.8	0.8	163	-0.7	0.8	0.8	0.2	0.85	0.49	0.62	0.87	0.32

ATTACHMENT 2--continued

(9) Physician's evaluation of subject's overall condition [221:1127]:

PHYSICIAN'S EVALUATION OF SUBJECT'S OVERALL CONDITION (POOLED)

	(A) MINOCYCLINE			(B) VANCOMYCIN AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	164	2.2	0.4	163	2.2	0.4	163	2.2	0.4	0.4	0.62	<.01	0.57	0.36	0.88	0.44
DAY 8 RAW	164	1.8	0.6	161	1.7	0.6	163	1.9	0.6	0.6	0.01	0.15	0.57	0.36	0.08	<.01
CHG	164	-0.4	0.7	161	-0.5	0.7	163	-0.3	0.6	0.7	0.05	0.48	0.96	0.47	0.1	0.02
DAY15 RAW	160	1.7	0.6	159	1.5	0.6	159	1.8	0.6	0.6	<.01	0.06	0.15	0.01	0.18	<.01
CHG	160	-0.5	0.7	159	-0.7	0.7	159	-0.4	0.7	0.7	0.02	0.07	0.56	0.14	0.19	0.01
DAY29 RAW	159	1.5	0.6	157	1.5	0.7	157	1.7	0.6	0.6	0.01	0.2	0.22	0.75	0.01	<.01
CHG	159	-0.7	0.7	157	-0.7	0.8	157	-0.5	0.7	0.7	0.03	0.03	0.5	0.68	0.01	0.04
WK 8 RAW	151	1.5	0.7	157	1.4	0.7	151	1.6	0.7	0.7	0.06	0.03	0.96	0.92	0.04	0.04
CHG	151	-0.8	0.8	157	-0.7	0.8	151	-0.6	0.7	0.8	0.13	<.01	0.99	0.47	0.05	0.19
WK 12 RAW	147	1.4	0.7	148	1.4	0.7	143	1.5	0.7	0.7	0.15	<.01	0.91	0.77	0.13	0.07
CHG	147	-0.8	0.8	148	-0.8	0.8	143	-0.7	0.7	0.7	0.36	0.01	0.8	0.51	0.16	0.44
ENDPT RAW	164	1.4	0.7	163	1.4	0.7	163	1.6	0.7	0.7	0.05	<.01	0.8	0.71	0.02	0.05
CHG	164	-0.8	0.8	163	-0.7	0.8	163	-0.6	0.7	0.8	0.09	0.03	0.66	0.4	0.03	0.18

(10) Subject's self-evaluation of overall response to treatment [221:1130]:

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

	(A) MINOCYCLINE			(B) VANCOMYCIN AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
DAY 8 RAW	164	3.4	1.0	161	3.2	1.1	163	3.6	0.9	1.0	<.01	0.21	0.99	0.1	0.06	<.01
DAY15 RAW	159	3.2	1.0	159	3.0	1.1	159	3.5	1.0	1.0	<.01	0.04	0.69	0.09	0.01	<.01
DAY29 RAW	159	3.1	1.1	157	2.9	1.0	157	3.3	1.1	1.1	0.01	0.01	0.65	0.16	0.06	<.01
WK 8 RAW	151	3.0	1.2	157	2.8	1.1	151	3.2	1.1	1.1	0.03	0.03	0.93	0.28	0.12	0.01
WK 12 RAW	147	2.9	1.1	148	2.8	1.1	143	3.1	1.1	1.1	0.05	0.01	0.82	0.47	0.09	0.02
ENDPT RAW	164	3.0	1.2	163	2.9	1.2	163	3.2	1.2	1.1	0.03	0.06	0.57	0.47	0.06	0.01

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (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 [221:1129]:

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

	(A) MINOCYCLINE			(B) VANCOMYCIN AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
DAY 8 RAW	164	3.5	0.9	161	3.4	1.0	163	3.7	0.9	1.0	0.08	0.11	0.89	0.5	0.14	0.03
DAY15 RAW	160	3.3	1.0	159	3.1	1.0	159	3.5	1.0	1.0	<.01	0.1	0.92	0.09	0.04	<.01
DAY29 RAW	159	3.1	1.1	157	2.9	1.1	157	3.4	1.0	1.1	<.01	0.01	0.97	0.43	<.01	<.01
WK 8 RAW	151	3.0	1.1	157	2.8	1.1	151	3.3	1.1	1.1	<.01	0.04	0.89	0.29	<.01	<.01
WK 12 RAW	147	2.8	1.1	148	2.8	1.2	143	3.2	1.1	1.1	0.02	<.01	0.71	0.09	0.02	0.01
ENDPT RAW	164	2.9	1.1	163	2.9	1.2	163	3.3	1.2	1.1	<.01	0.01	0.55	0.79	0.01	<.01

8.11.4.3. SAFETY ANALYSIS

A review of safety data was performed on the safety (intent-to-treat) population which consisted of all randomized subjects who received at least one post-baseline evaluation. For the safety population, 164 subjects were treated with mometasone and 163 subjects each were treated with beclomethasone or placebo.

Safety data consisted of clinical adverse events (further characterized as treatment emergent [218:71-74, 219:415-424] and treatment related (severe and non-severe) [218:78-80, 76-77], laboratory test values, ECGs, vital signs, and pertinent physical exam findings such as: the presence of nasal septal perforation, nasal ulceration(s) or nasal candidiasis, and/or presence of abnormally elevated (i.e. >22 mm Hg, as defined by the Sponsor) intraocular pressure measurements or cataract formation. A review of all safety parameters submitted by the sponsor by line listings was performed and those laboratory results, vital sign abnormalities, physical exam findings, and adverse events deemed by the medical reviewer to be clinically significant or pertinent negative results, are discussed in the sections below.

Overall, analysis of the safety data for protocol C92-280 indicates that mometasone was safe and well tolerated by subjects. Adverse events were similar to those observed with beclomethasone and in general, similar to those seen with nasal corticosteroid use. The incidence of adverse events was found, as expected, to be highest in the placebo treatment group. No significant difference in adverse event rates was found based on age, gender, or race.

Adverse events were reported by 81% of subjects treated with mometasone, compared to 81% of subjects treated with beclomethasone, and 77% of subjects treated with placebo. The most frequently reported adverse events are summarized in Table 20 of the NDA submission (see below) [218:71]. For a complete listing of adverse events, please refer to [NDA 20-762: Volumes 225, 226, 227, and 228].

Table 20 Incidence of Patients Reporting Frequent[a] Treatment Emergent Adverse Events[b] -- Safety (Intent-to-Treat) Population (Study No. C92-280).

	Number[c] (%) of Patients		
	SCH 32088 (n = 164)	BDP (n = 163)	Placebo (n = 163)
Any Adverse Event	133 (81)	132 (81)	126 (77)
Body As A Whole - General Disorders			
fever	3 (2)	0	8 (5)
headache	55 (34)	56 (34)	51 (31)
influenza-like symptoms	17 (10)	19 (12)	20 (12)
Central and Peripheral Nervous System Disorders			
dizziness	1 (1)	8 (5)	4 (2)
Gastrointestinal System Disorders			
abdominal pain	0	7 (4)	3 (2)
nausea	7 (4)	4 (2)	2 (1)
vomiting	1 (1)	5 (3)	1 (1)
Hearing and Vestibular Disorders			
earache	9 (5)	9 (6)	9 (6)
Musculoskeletal System Disorders			
musculoskeletal pain	14 (9)	12 (7)	5 (3)
myalgia	6 (4)	6 (4)	10 (6)
Reproductive Disorders, Female[d]			
dysmenorrhea	2 (2)	1 (1)	7 (9)
Resistance Mechanism Disorders			
infection viral	35 (21)	30 (18)	27 (17)
Respiratory System Disorders			
cough, nonproductive	5 (3)	0	2 (1)
coughing	13 (8)	17 (10)	18 (11)
epistaxis	31 (19)	37 (23)	10 (6)
nasal burning	5 (3)	7 (4)	11 (7)
nasal irritation	4 (2)	6 (4)	3 (2)
pharyngitis	28 (17)	23 (14)	31 (19)
rhinitis	6 (4)	11 (7)	2 (1)
sinusitis	10 (6)	12 (7)	21 (13)
sneezing	1 (1)	9 (6)	6 (4)
upper respiratory infection	11 (7)	9 (6)	12 (7)
Vision Disorders			
conjunctivitis	7 (4)	7 (4)	0

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

Headache was reported as the most frequent adverse event and was found to be present in 34% of subjects treated with mometasone, 34% of subjects treated with beclomethasone, and 31% of subjects treated with placebo [226:5465-5523, 227:5717-5762]. The second most frequent adverse event was epistaxis (present in 19% of mometasone subjects, 23% of beclomethasone subjects, and 6% of placebo subjects), followed by pharyngitis (present in 17% of mometasone subjects, 14% of beclomethasone subjects, and 19% of placebo subjects). In general, epistaxis was mild or moderate in severity, intermittent, and of short duration in all treatment groups. In summary, the most frequent adverse events cited were symptoms known to be associated with perennial allergic rhinitis itself, and not necessarily related to drug use, per se.

Nasal examinations performed at each visit generally revealed nasal

mucosal findings consistent with allergic rhinitis such as boggy or erythematous mucosa indicative of nasal turbinate swelling. No cases of nasal septal perforation were reported in any of the three treatment groups, although one case each of nasal ulceration in the both the mometasone (study subject C92-280-015, #013 [228:6791]) and placebo group (study subject C92-29-80-009, #014, [228:6746]) and 4 cases of nasal ulceration in the beclomethasone group (study subjects C92-280-009, #028 [228:6744], -010, #019 [228:6752], -015, #017 [228:6794], and -017, #013 [228:6808]) were noted after initiation of study drug. Only one case of cataract formation was noted in a placebo group subject--subject C92-280-009, #003 during week 12 of treatment [227:5915] (none noted in either active treatment group). One additional placebo treated subject (C92-280-05, #008 [218:85] had a trace posterior subcapsular cataract in the left eye at both screening and week 12 of the study. In terms of study subject intraocular pressure monitoring to rule out glaucoma, mean and median intraocular pressures the right and left eyes for all 3 treatment groups at screening and week 12 of the study failed to show any significant difference in measurements with all 3 treatments [220:839]. Evaluation of individual study subject intraocular pressures revealed only 1 subject in the mometasone treatment group who at week 12 had a 3 mm Hg increase in intraocular pressure (to a total pressure of 24 mm Hg) in the right eye [228:6597]. This difference was not felt to represent a significant change from baseline (daily fluctuations of 4 mm Hg felt to be acceptable) per the ophthalmology consultant for study center C92-280-006. Another mometasone treated subject, while not detected to have increased intraocular pressures by week 12 of treatment, was noted to have developed several scattered punctate cortical opacities in the right eye > left eye [228:6609]. The clinical significance of these opacities were deemed unknown by the principal investigator. One beclomethasone treated subject (C92-280-008, #027 [228:6604]) likewise developed a borderline increased intraocular pressure to 22 mm Hg in the right eye after 12 weeks of treatment with beclomethasone. The other several beclomethasone and placebo subjects who had borderline elevated intraocular pressures had these values at screening (with no significant increase post-initiation of study drug), hence these results could not be attributed to administration of the study drug.

In terms of infections, overall 11/164 or 7% of mometasone treated subjects reported upper respiratory infections, compared with 9/163 or 6% of beclomethasone treated subjects and 1/163 or 1% of placebo treated subjects. 10/164 or 6% of mometasone treated subjects reported sinusitis, compared with 12/164 or 7% of beclomethasone treated subjects and 21/163 or 13% of placebo treated subjects. Interestingly, 2 cases of pneumonia (incidence 1%) were reported solely in mometasone treated subjects on weeks 8 and 12 (subject C92-280-004, #002 and subject C92-280-013, #008) [226:5406]-a 39 year old male and 33 year old female subject, respectively. In neither case was the pneumonia felt related to mometasone treatment by the principal investigator. Two cases of cystitis were reported in mometasone treated subjects (1% incidence) [226:5436],

compared to 1 case of cystitis reported in a beclomethasone treated subject (1% incidence) and no cases in placebo treated subjects (0% incidence) [218:74]. No cases of herpes simplex or candidiasis were reported in any mometasone treated subjects during any study visit [218:79].

Regarding laboratory test results, one serious[2] adverse event consisting of elevated liver enzymes (SGOT (AST)=1144, SGPT (ALT)=1119, LDH=522, and alkaline phosphatase=291) at the last study visit was reported for one subject (34 year old female) treated with beclomethasone who was later confirmed to have active hepatitis B. The subject was treated conservatively by her personal physician and recovered without clinical sequelae. Aside from this finding, no other clinically relevant abnormal laboratory test results were reported in this study. Although there were scattered laboratory test values outside the normal ranges for several subjects, as assessed by shift tables, none were remarkable.

No clinically relevant changes in mean values from pretreatment were in noted in any of the subjects' vital signs or body weight. Shift tables were similar among all 3 treatment groups. ECGs performed pretreatment and at endpoint failed to reveal any relevant abnormal findings.

Gender, race and age subgroup analyses of vital signs, body weight, laboratory data, ECGs, and adverse events failed to reveal any significant differences between any of these subgroups and the overall subject population, with the exception of the following minor observations. In non-Caucasian subjects (n=53 total), mometasone treatment group subjects (n=12) were noted to have a greater mean weight (n=12, mean weight=177.4 lbs.) than the beclomethasone treated non-Caucasian subjects (n=18, mean weight=154.7 lbs.) and placebo group non-Caucasian subjects (n=23, mean weight=166.6 lbs.) [220:776]. Adverse event profiles for all subgroups based on age, gender and race were similar with the exception of the following instances: (1) a slightly higher incidence of epistaxis in mometasone treated subjects < 18 years of age (2 cases, 18% incidence based on n=11 subjects) compared with beclomethasone treated subjects < 18 years of age (n=16, 1 case (6% incidence)) and placebo treated subjects < 18 years of age (n=17, 0 cases (0% incidence)) [219:364], (2) a significantly higher incidence of headache in mometasone treated subjects ≥ 65 years of age (n=2, 1 case (50% incidence), compared with beclomethasone treated subjects ≥ 65 years of age (n=1, 0 cases (0% incidence)) and placebo treated subjects ≥ 65 years of age (n=1, 0 cases (0% incidence)) [219:375], (3) a higher incidence of headache in Black subjects treated with mometasone (n=4, 2 cases (50% incidence)), compared with beclomethasone treated Black subjects (n=7, 2 cases (29% incidence)) and placebo treated Black subjects (n=14, 0 cases (0% incidence)) [219:405], and (4) a higher incidence of viral infections in Hispanic subjects treated with mometasone (n=8, 3 cases (38% incidence)), compared with beclomethasone treated Hispanic subjects

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[2]Serious is defined as any adverse event which resulted in death, hospitalization, or prolongation of an existing hospitalization, a permanent or significant disability, or was considered life-threatening. Reports of malignancy, overdose, congenital anomaly, and end-organ toxicity are likewise categorized as 'serious' events.

(n=10, 1 case (10% incidence)) and placebo treated Hispanic subjects (n=8, 0 cases (0% incidence)) [219:411]. Because of the small number of subjects analyzed in these subgroups of study subjects no meaningful conclusions can be made based on these observations.

Regarding subject drop-outs due to adverse events, a total of 22 subjects (5 treated with mometasone, 9 treated with beclomethasone, and 8 treated with placebo) discontinued treatment because of adverse events. Only 6/22 of these subjects had discontinued treatment 'possibly' due to adverse events incurred by the treatment given (all other cases were unrelated to treatment with the exception of the cataract present in a placebo group subject which was classified as 'probably' related to treatment) and 3 of these 6 drop-outs had 'mild' symptoms (subject C92-280-13, #015: hyperesthesia, subject C92-280-10, #009: epistaxis, and subject C92-280-12, #029: nausea [218:81]). No subject deaths were reported in any of the 3 treatment arms for Protocol C92-280.

8.11.5. Reviewer's Conclusion of Study Results:

In this PAR trial 164 subjects received mometasone treatment, 163 subjects received the active comparator beclomethasone, and 163 subjects received placebo treatment.

With the exception of a greater percentage of subjects in the mometasone group consisting of subjects with a 'severe' rating of PAR (subject self-rated 0-3 score) and longer duration of disease, all 3 treatment arms were otherwise similar in demographic and clinical characteristics.

Results that Support Approval:

Mometasone administered at a dose of 200 μg qd was statistically better than placebo in decreasing the average change from baseline in the subject self-rated total nasal symptom score (rhinorrhea, nasal congestion, nasal itching, and sneezing) for days 1-15 of treatment--the primary efficacy variable ($p=0.02$). Mometasone provided an approximately 20% decrease in the total nasal symptom score as compared to a 13% decrease achieved with placebo treatment [Table V.]. Separation of the subject self-rated total nasal symptom score by week 1 and week 2 of treatment indicates that mometasone was effective in decreasing total nasal symptoms during both weeks, with a clinically and statistically significant improvement in symptoms achieved by week 1 of treatment ($p=0.02$). Of the 4 nasal symptoms, mometasone appeared to exert its greatest effect on decreasing the severity of rhinorrhea (nasal discharge), closely followed by sneezing.

Mometasone was likewise statistically better than placebo in decreasing the average change from baseline in the subject self-rated total nasal symptom score for days 16-30, days 31-45, days 46-60, days 61-75, and days 76-90 of treatment ($p\leq 0.05$), and the subject self-rated total nasal symptom score at the endpoint visit ($p=0.03$). In terms of study sub-analysis, mometasone was statistically better than

placebo in decreasing the average change from baseline in the subject self-rated total symptom score for week 1 of treatment. Physician-rated subject total nasal symptom scores taken during all study visits were likewise significantly reduced with mometasone treatment, as compared with placebo [Attachment 1 (5)]. Additional treatment response was gained during the third to twelfth weeks of treatment with mometasone, in addition to efficacy achieved by the second week of mometasone treatment.

Finally, physician rated total PAR subject symptom scores, along with both subject and physician overall PAR evaluation, and both subject and physician treatment response evaluations [Attachment 1 (8)-(11)] support greater efficacy of mometasone in reducing the symptoms of PAR for at least some study visits, as compared with placebo.

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8.12. Trial C93-014. Long-term Safety of Mometasone Furoate Nasal Spray in the Treatment of Perennial Allergic Rhinitis (PAR).

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

Participating Centers: 19 U.S. centers.

8.12.1. OBJECTIVES:

1. To characterize the long-term safety profile (including assessment of glaucoma/cataract formation) of a fixed dose of mometasone furoate nasal spray (200 µg qd) and a variable dose of mometasone furoate nasal spray (200 µg qd initially, titrated between 100-400 µg qd depending on the subject's therapeutic response), compared with beclomethasone (Vancenase) 168 µg bid.
2. To evaluate long-term efficacy of mometasone aqueous nasal spray in the treatment of symptoms of PAR (efficacy assessment was not the primary objective of this study).

8.12.2. STUDY DESIGN:

This was a randomized, multi-center, open-label, active-controlled, parallel group trial in adult subjects with perennial allergic rhinitis which was an extension of the 3 month double-blind PAR study C92-280. Study enrollable subjects consisted of those who successfully completed the double-blind study C92-280 or who were dropped from C92-280 due to treatment failure or intercurrent illness. A variable mometasone dose group was included in this study in order to obtain additional efficacy and safety information on doses of mometasone which were above or below the 200 µg qd dose and also to gain information regarding the individualization of mometasone dosing for PAR. Study medications were given to PAR subjects for a total duration of 52 weeks (1 year).

8.12.3. PROTOCOL:

8.12.3.1.a. POPULATION:

Entry criteria for this study after completion of a washout period (up to 7 days) were essentially the same as those for study C92-280, namely: (1) age ≥ 12 years [253:10], (2) presence of IgE-mediated hypersensitivity to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 1 year of study entry via the prick testing method, and (3) successful completion of study C92-280, or discontinuation secondary to treatment failure or intercurrent illness [253:12, 256:1010, 1014].

8.12.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the sponsor in Table 1. of Trial C93-014 in the NDA submission [253:11, 256:1042] and is similar to

study design of PAR study C92-280. Subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Week 4 (Visit 3), 8 (Visit 4), 12 (Visit 5), 24 (Visit 6), 36 (Visit 7), and 52 (Visit 8) of therapy. Subjects entered a washout phase (up to 7 days) between the screening and baseline visit, during which they took no medications except for rescue medication (note: no restrictions outlined in the protocol with regard to the type of rescue medication that could be used by a subject with the exception of corticosteroid use), as prescribed by the principal investigator for relief of intolerable PAR symptoms prior to initiation of the open-label treatment [253:15, 256:1019]. Of note, for C92-280 roll-over subjects, the final visit determination (Visit 7 of study C92-280) served as the screening (Visit 1) determination for study C93-014. Following the washout period, subjects who met all inclusion criteria were randomly assigned to one of the following 3 treatment groups, received diary cards to record symptoms and began therapy with mometasone (fixed and variable doses) administered in the a.m. and beclomethasone administered in the a.m. and p.m. (bid):

(A)	**Mometasone aqueous nasal spray 200 µg qd** (FIXED DOSE)
(B)	**Mometasone aqueous nasal spray 100, 200 or 400 µg qd** (VARIABLE DOSE)
(C)	**Beclomethasone 168 µg bid (336 µg qd total)**

Subjects underwent clinical efficacy and safety evaluation (including nasal exam on Visits 3-8) during each study visit [256:1016-1020, 1023-1030]. Eye examinations to assess glaucoma and cataract formation were performed during the screening and final (Visit 8) study visit [253:20-21, 256:1009]. Efficacy evaluation was again based on a 0-3 severity scale [253:21-22, 256:1026] and a 1-5 scale of therapeutic response [253:22, 256:1027].

In concordance with the supervising physician, subjects randomized to the mometasone 'variable dose' group were allowed to lower the medication dose to 100 µg qd if nasal symptoms (specifically rhinorrhea and nasal congestion) were well controlled or to increase the dose to 400 µg qd in order to improve control of nasal symptoms [256:1015, 1021, 1023]. Rescue medication use was allowed throughout the study duration for all 3 treatment groups, excluding steroid formulations (nasal, inhaled, etc.)

A primary efficacy variable was not defined in this study. Supplementary efficacy variables consisted of: (1) physician and (2) subject evaluations of overall condition and (3) physician and (4) subject evaluations of therapeutic response [253:29] in the ITT population [253:29, 256:1031]. Pollen counts were not collected in this study. Rescue medication use between the 3 treatment groups was not analyzed in any systematic manner in this study, thus making it difficult to reach any solid conclusions about clinical efficacy of the different treatments evaluated in this study.

8.12.4. RESULTS

A total of 296 subjects with PAR were randomized into study C93-014, with 3 immediate drop-outs (subjects did not receive any study drug)[253:81-83], leaving 293 subjects for the ITT population [253:32]. One hundred (100) subjects in the ITT population received mometasone 200 µg qd, 95 subjects received variable dose (100-400 µg qd) mometasone, and 98 subjects received beclomethasone [253:32]. Of note, the attrition rates for study subjects by Week 52 of the study were quite high with 14.2% (14/98) of mometasone 200 µg qd subjects, 18.9% (18/95) of variable dose mometasone subjects, and 14.4% (14/97) of beclomethasone subjects discontinuing treatment by this study endpoint.

The treatment groups in this study were comparable with regard to demographic and disease characteristics with the exception of a marginally statistically significant difference among the treatment groups in age (mean age of the mometasone 200 µg group=37 years vs. mean age of the mometasone variable dose group=33 years vs. mean age of the beclomethasone group=35 years; p=0.06) [253:33, 86-87]. Again, for all 3 treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the treatment groups was approximately equal. The majority of subjects (64-77% range) had SAR in addition to PAR. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a statistically significant difference among the 3 treatment groups although the mometasone 200 µg group had a numerically greater % of subjects with 'severe' PAR (18%) in comparison with the other 2 groups (mometasone variable group; 'severe' subjects=11%, vs. beclomethasone group, 'severe' subjects=13%) [253:35-36]. Therefore, at baseline, the majority of subjects in all 3 treatment groups were assessed as having 'mild' or 'moderate' PAR.

Analysis of the efficacy variables for the ITT population showed that overall, subjects in all 3 active treatment groups demonstrated an improvement in symptoms which was maintained for the study duration. For the physician's evaluation of the overall condition of PAR, subjects in all 3 treatment groups demonstrated an improvement by Week 4 of the study (as supported by the majority of subjects having 'mild' PAR symptoms) and this improvement was maintained through the Week 52 visit [253:37, 247, 268-269]. Subject self-evaluation of the overall condition of PAR paralleled that of the physician evaluation; namely that improvement in symptoms was noted by Week 4 of the study (supported by the majority of subjects rating their overall PAR condition as 'mild') and was maintained throughout the study duration [253:39-40, 254:296, 317-318]. Both of these findings support maintenance of a therapeutic effect for mometasone (fixed and variable dose) and beclomethasone throughout the open-treatment period. Physician evaluation of subjects' therapeutic response to treatment (1-5 scale) indicated that all 3 treatment groups experienced moderate-marked relief in PAR symptoms starting at Week 4 of the study and continuing throughout the open-treatment period, again providing evidence of maintenance of a therapeutic effect throughout the study duration [253:42, 254:345-346, 367]

Subject evaluation of therapeutic response paralleled the physician evaluation of subjects' therapeutic response with the majority of study subjects reporting moderate-marked relief in PAR symptoms by Week 4 of treatment [253:44, 254:388-389, 410]. Again, this response was maintained for the study duration.

Regarding the 'variable dose' mometasone group, 10/95 (10.5%) of subjects received mometasone 100 µg qd, 57/95 (60.0%) of subjects received mometasone 200 µg qd, and 28/95 (29.5%) of subjects received mometasone 400 µg qd [253:45]. Within the variable mometasone group, the majority of subjects either maintained the 200 µg qd dose throughout the study (54%) or changed the dose level only once and maintained that dose level for the remainder of the study (28% of subjects titrated their dose to 400 µg qd and 10% of subjects in this subgroup titrated their mometasone dose downwards to 100 µg qd). The remaining 8% of subjects had their mometasone dose changed > 1 times during the study. In summary, these data for the 'variable dose' mometasone group suggest that the most effective dose of mometasone for the control of PAR symptoms was 200 µg qd. Gradual increase in dose of mometasone over the course of the study was not observed.

While this trial was not blinded and not designed to provide enough power to conduct inferences on efficacy, results of these supplementary analyses nonetheless provide supportive information that mometasone is effective in the treatment of symptoms of PAR. Results of the 4 efficacy variables for the 2 mometasone treatment groups are summarized in Table I. below.

Table I. Efficacy Variables of PAR and Treatment with Mometasone 200 µg qd and 'Variable Dose' Mometasone (100, 200, or 400 µg qd) (ITT Population), [253:36-45, 247, 268-269, 254:296, 317-318, 345-346, 367, 388-389, 410]

EFFICACY VARIABLE		Improvement in PAR symptoms throughout study duration: Mometasone 200 µg qd: (Yes/No)	Improvement in PAR symptoms throughout study duration: 'Variable dose' Mometasone: (Yes/No)
1.	Physician's evaluation of subject overall PAR condition compared to baseline	Yes	Yes
2.	Subject self evaluation of overall PAR condition compared to baseline	Yes	Yes
3.	Physician evaluated response to Rx compared to baseline	Yes	Yes
4.	Subject self-evaluated response to Rx compared to baseline	Yes	Yes

sx=Symptom, Rx=Treatment, ITT=Intent-to-treat
Statistical analysis for between group differences performed using 2-way ANOVA.

8.12.4.3. ADVERSE EVENTS:

The safety analysis was based on 293 subjects in the ITT population; 100 subjects were treated with mometasone 200 μg qd, 95 subjects were treated with variable dose mometasone (100, 200, or 400 μg qd), and 95 subjects were treated with beclomethasone [253:46, 254:431]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, nasal, and ophthalmologic examinations, and clinical laboratory tests relative to baseline [256:1023-1030].

Adverse events were similar for all three treatment groups, with headache being the most frequently reported treatment-related adverse event. Overall, adverse events were reported in 86% of subjects in the mometasone 200 μg qd treatment group, 81% of subjects in the variable dose mometasone treatment group, and 85% of subjects in the beclomethasone group [253:50, 254:431]. Headache was reported in 36% of subjects in the mometasone 200 μg qd group, 37% of subjects in the variable dose mometasone group, and 32% of subjects in the beclomethasone group [253:48, 254:432, 259:2258-2311, 2518-2554, 2740-2792]. Interestingly, for this long-term study headache was followed by sinusitis as the second most frequently reported adverse event; reported in 24% of mometasone 200 μg qd subjects compared to 16% of variable dose mometasone subjects and 16% of beclomethasone treated subjects [253:49, 254:438, 259:2446-2459, 2686-2693, 2920-2931]. Reported next in frequency was pharyngitis; with 15% of subjects in the mometasone 200 μg qd group, 18% of subjects in the variable dose mometasone group, and 21% of subjects in the beclomethasone group recording this adverse event [253:49, 254:438]. Other relatively frequent ADRs reported in this follow-up study included coughing (15% of mometasone 200 μg qd subjects, 9% of variable dose mometasone subjects, and 12% of beclomethasone subjects [253:49, 254:438]), viral infection (18% of mometasone 200 μg qd subjects, 16% of variable dose mometasone and beclomethasone subjects [253:48, 254:437]), upper respiratory tract infection (13% of mometasone 200 μg and variable dose mometasone subjects, and 15% of beclomethasone subjects [253:4, 254:438]), musculoskeletal pain (13% of mometasone 200 μg qd subjects, 7% of variable dose mometasone subjects, and 17% of beclomethasone subjects [253:51, 254:435]), and epistaxis (12% of mometasone 200 μg qd and variable dose mometasone subjects, and 9% of beclomethasone subjects [253:49, 254:438]). Furthermore, there was no apparent dose relationship in the overall incidence of ADRs in the mometasone variable dose group noted for the study duration (incidence of ADRs for mometasone 100 μg qd group=65%, incidence of ADRs for mometasone 200 μg qd group=71%, incidence of ADRs for mometasone 400 μg qd group=62% [253:69]) or for specific ADRs with the exception of a small proportional increase in the incidence of headache [254:502], earache [254:505], and pharyngitis [254:509] with increasing doses of mometasone [254:501-514].

There were no reports of nasal septal perforation in either the of the 2 mometasone treatment groups or the beclomethasone active comparator group

Nasal ulcers were however reported in all 3 treatment groups as follows:

(1) mometasone 200 µg qd group: reports in 4 subjects (1 at Visit 3, 1 at Visit 4, 1 at Visit 5, and 1 at Visit 6) [261:4098, 4111, 4176, 4178].

(2) mometasone variable (100-400 µg qd) group: reports in 3 subjects (1 at Visit 3, 1 at Visit 5, and 1 at Visit 6) [261:4114, 4161, 4171], and

(3) beclomethasone group 168 µg bid group: reports in 8 subjects (1 at Visit 3, 1 at Visit 4, 2 at Visit 5, 1 at Visit 6, 2 at Visit 7, and 1 at Visit 8 [2260:2906, 2907, 2932, 61:4079, 4106, 4107, 4142, 4154, 4182, 4191, 4201]. In 2 of these 8 beclomethasone subjects, the nasal ulcers were noted to be nasal septal ulcerations [253:53, 260:2907].

Evaluation for glaucoma by tonometry indicated that the mean (right and left) intraocular pressures for the screening and Week 52 visits were similar for the 3 treatment groups and ranged from 14.8 mm Hg-15.7 mm Hg with no significant mean increase in intraocular pressure noted for any of the 3 groups between screening and the Week 52 visit [254:533]. For individual study subjects, 1 subject in the variable mometasone dose group and 1 subject in the beclomethasone group demonstrated a significant elevation in intraocular pressures in both eyes post-screening [260: 2728, 261:3968, 3985]. One subject in the beclomethasone group also developed a mild anterior subcapsular cataract of the right lens by day 397 of the study [261:3965]. No subjects in either mometasone treatment group were noted have cataract formation as determined via slit lamp eye examination. Again, no assessments of HPA-axis were performed in this follow-up study. No deaths were reported in any of the three treatment groups.

In terms of infection, 18% of subjects in the mometasone 200 µg qd group reported viral infections, while 16% of subjects in both the variable dose mometasone and the beclomethasone group, respectively, reported viral infections [253:52]. One subject in the mometasone 200 µg qd treatment group and one subject in the beclomethasone group reported herpes simplex labialis [253:52]. One subject in the in the mometasone 200 µg qd group (subject C93-014-09, #005) and one subject in the variable dose mometasone treatment group (subject C93-014-16, #011, patient was receiving 200 µg qd of mometasone) were noted by the examining physician to have moniliasis (i.e. oral candidiasis) on study Visit 7 and Visit 6, respectively [254:507, 259:2403, 2634]. One subject in the variable dose mometasone group (subject C93-014-19, #002, patient was receiving mometasone 200 µg qd) also reported pneumonia which was felt by the principal investigator to be unrelated to study medication [254:509, 259:2678]. No subjects in either of the three treatment groups were reported to have nasal candidiasis on any clinic visits.

A total of 15 subjects discontinued treatment because of adverse events (7 subjects in the mometasone 200 µg qd group, 4 subjects in the variable dose mometasone group, and 4 subjects in the beclomethasone group) [253:62, 228-238]. The most common reason for discontinuation that was considered 'possibly related' to study medication involved nasal irritation. One subject in the variable-

dose mometasone group (subject C93-014-06, #003; the subject was receiving mometasone 200 µg qd at the time of the adverse event) discontinued treatment on the day of hospitalization for meningitis which was considered not to be related to study drug administration but rather secondary to a local outbreak of meningitis in the community [254:601, 259:2564]. One subject in the beclomethasone group (C93-014-09, #001) discontinued treatment because of 'moderate' nasal septum ulceration that was considered to be related to study medication. Otherwise, most subject discontinuations due to ADRs were considered unrelated to treatment by the principal investigator.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the three treatment groups. Three subjects in the variable dose mometasone group were reported to have minor or transient decreases in their white blood cell count (WBC) [255:606]. Of note, in all 3 cases, the pre-baseline WBC for each subject was already below or at the lower limit of normal (WBC lower limit of normal = 4.36 x 10^3/mL) [255:606]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change. Adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects between 12-17 years and > 64 years of age was too small to draw meaningful conclusions.

8.12.5. CONCLUSIONS:

1. The results of this study support the safety of mometasone 100 µg, 200 µg and 400 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 52 weeks (1 year) in subjects with PAR.
2. While not specifically designed to evaluate efficacy, assessment of subject overall condition and response to treatment with mometasone over 52 weeks (by study subjects and their respective physicians), supports the efficacy of mometasone in doses of 100-400 µg qd for the treatment and maintenance treatment of symptoms of PAR. For the majority of study subjects, 'moderate-marked' relief of PAR symptoms and an overall rating of PAR symptoms as 'mild' in severity was demonstrable by week 4 of mometasone treatment and was maintained though week 52 of the study.

Results that did not Support Approval:

Overall, mometasone did not demonstrate a statistically significant effect in decreasing any of the subject self-rated or physician rated non-nasal symptoms of PAR (eye itching, eye tearing, eye redness, ear or palatal itching), at any of the study intervals (day 1-15, day 16-30, day 31-45, day 46-60, day 61-75, day 76-90, or the endpoint visit), as compared with placebo. Because of this lack of significant effect on the non-nasal symptoms of PAR, mometasone likewise did not have a statistically significant effect on decreasing the [illegible]

score in treated subjects, as compared with placebo. As the non-nasal symptoms of PAR represent a group of secondary efficacy measurements which clinically are less important symptoms of PAR, lack of significant efficacy of mometasone on these parameters does not change the overall conclusion about efficacy of mometasone in the treatment of PAR. Furthermore, non-nasal symptoms are generally less likely to be affected by medications administered intranasally, therefore a lack of significant response with intranasal corticosteroid administration (also seen with beclomethasone) is not unexpected.

Mometasone treatment likewise did not demonstrate a statistically significant effect in decreasing total subject self-rated PAR symptom scores at any of the study intervals. As mentioned previously, mometasone treatment did not uniformly decrease the subject or physician rated overall condition or overall treatment response evaluation for all study visits, as compared with placebo.

Other Results:

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

Safety:

Overall, mometasone was safe and well-tolerated administered as a once a day, 200 µg dose. No serious adverse events occurred in subjects treated with mometasone, nor were any deaths reported. Similar to placebo, headache was the most common adverse event associated with mometasone use, followed by epistaxis and then, pharyngitis. No nasal septal perforations or cases of nasal candidiasis were reported. While no cases of cataracts were reported with mometasone treatment this study did not evaluate (because of study duration) hypothalamic-pituitary-adrenal (HPA) axis suppression. A 1 year follow-up study of C92-280, study C93-014, evaluated the potential long term effects of steroid use and specifically addressed glaucoma and cataract formation in mometasone treated subjects (Refer to Section 8.13: Study C93-014).

Summary:

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