8.13. Trial I92-293. Efficacy and Safety of Mometasone Furoate Nasal Spray vs. Beconase and vs. Placebo in the Treatment of Perennial Allergic Rhinitis (PAR).

Principal Investigator: Peter Clement, M.D.

Participating Centers: 24 centers in Europe (Belgium, Finland, Germany, The Netherlands, Norway, Sweden, Switzerland, and the U.K.) and Canada.

8.13.1. OBJECTIVES:

1. To investigate the safety and efficacy of mometasone furoate aqueous nasal spray 200 µg qd in the treatment of symptoms of perennial allergic rhinitis (PAR).

8.13.2. STUDY DESIGN:

The study was a phase III, randomized, multi center, double-blind, double-dummy, active- and placebo-controlled parallel group study to determine the safety and efficacy of mometasone furoate 200 µg administered intranasally once daily (qd), vs. the active control, beclomethasone (Beconase AQ) 200 µg administered twice daily (bid), and vs. placebo for a total of 12 weeks in the treatment of perennial allergic rhinitis. The study was also designed to examine long-term safety in mometasone treated subjects vs. placebo via roll-over of subjects into Study I93-018 (1 year follow-up of Study I92-293).

8.13.3. PROTOCOL:

8.13.3.1.a. POPULATION:

Entry criteria for this study were very similar to those for all other PAR studies, namely: (1) age ≥ 12 years [235:16, 238:997, 999], (2) presence of IgE-mediated hypersensitivity to a relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 1 year of study entry via the prick testing or intradermal method [235:16, 238:999], and (3) presence of PAR symptoms of sufficient severity (nasal rhinorrhea and/or congestion scores at least moderate in severity (≥ 2), a total symptom score ≥ 5 at both screening and baseline, and rhinorrhea and/or congestion scores ≥ 2 during 4 of the last 7 days prior to the baseline visit), in order to begin study drug treatment [235:16, 29, 238:997, 999, 1015-1016].

8.13.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1. of Trial I92-293 in the NDA submission [235:15, 238:1028] and is similar to the study design of PAR study C92-280. Subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Day 8 (Visit 3), 15 (Visit 4), 29 (Visit 5), and Weeks 8 (=Day 57, Visit 6), and 12 (=Day 85, Visit 7) of therapy [235:35-36]. Day 1 was designated as the start of treatment date [235:35]. Medication restrictions consisted of those previously discussed for mometasone SAR and PAR studies [235:22-24, 238:1001-1003], although subjects were allowed to use a rescue medication (loratadine, up to 10 mg po qd maximum dose) for intolerable PAR symptoms starting with the screening visit (the 'run-in' phase) and continuing for the duration of the study [235:20, 238:998, 1018]. Subjects who met all inclusion criteria were randomized to one of the following 3 treatment groups, received diary cards to record symptoms reflectively over the previous 12 hours and began therapy with study drug every a.m. and p.m. (4 bottles utilized for this double dummy design--each active drug had a matching placebo) [235:18, 25-27, 238:9981017-1018]:

(A) Mometasone aqueous nasal spray 200 µg qd		
a.m. dosing:	Bottle 1: Mometasone 200 µg	Bottle 2: Beconase Placebo
p.m. dosing	Bottle 3: Mometasone Placebo	Bottle 4: Beconase Placebo
(B) Beclomethasone nasal spray (Beconase) 200 µg bid		
a.m. dosing:	Bottle 1: Mometasone Placebo	Bottle 2: Beconase 200 µg
p.m. dosing:	Bottle 3: Mometasone Placebo	Bottle 4: Beconase 200 µg
(C) Placebo (0 µg qd)		
a.m. dosing:	Bottle 1: Mometasone placebo	Bottle 2: Beconase Placebo
p.m. dosing:	Bottle 3: Mometasone placebo	Bottle 4: Beconase Placebo

Subjects underwent clinical efficacy and safety evaluation (including nasal exam on Visits 2 (baseline) and 7 (Week 12)) during each study visit [235:15, 27-33, 238:998, 1006-1016]. Efficacy evaluation was again based on a 0-3 severity scale [235:29, 238:1015], a 0-3 scale of the overall condition of PAR [235:29, 238:1015], and a 1-5 scale of therapeutic response [235:30, 238:1016].

The primary efficacy variable [358:42-43, 238:998] was defined as: the mean change from baseline (the mean of the a.m. and p.m. baseline scores and the a.m. and p.m. scores from the 7 prior consecutive days) in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject diaries) where the:

Mean Change in Total nasal symptom score= 15 Day Interval Score[(Nasal a.m. average $_{\text{Day 1-15}}$) + (Nasal p.m. average$_{\text{Day 1-15}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

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

Secondary efficacy variables consisted of the following [235:43-44, 238:1023]:

(1) The mean change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30 (a.m. and p.m. combined), Days 31-45, Days 46-60, Days 61-75, and Days 76-90 [235:43]:

Mean Change in Total nasal symptom score$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$**=Day 16-30 (or Day 31-45, Day 46-60, Day 61-75, Day 76-90) Interval Score**[(Nasal a.m. average $_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$) + (Nasal p.m. average$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

(2) Endpoint total nasal symptom score (a.m. and p.m. combined)[235:44]: Endpoint score defined as the last available post-baseline value for each study subject, pooled across the 24 participating centers.

(3) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit) [235:44].

(4) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit) [235:44].

(5) Physician's evaluation of total nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8 , Week 12, and the endpoint visit) [235:44].

(6) Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit) [235:44].

(7) Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit) [235:44].

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

(9) Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study day 8, 15, 29, Week 8, Week 12, and the endpoint visit.

(10) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study day 8, 15, 29, Week 8, Week 12, and

(11) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study day 8, 15, 29, Week 8, Week 12, and the endpoint visit [235:44].

Pollen counts were not collected in this study. Rescue medication use between the 3 treatment groups was not analyzed statistically but a frequency of rescue medication for all 3 treatment groups was tabulated, thus providing a general overview of differences in rescue medication use.

8.13.4. RESULTS

A total of 430 subjects with PAR were randomized into study I92-293, with 3 immediate drop-outs from the placebo group (subjects did not receive any double-blind medication and were excluded from all analyses) [235:46], leaving 427 subjects evaluable in the ITT population [235:46]. One hundred and forty three (143) subjects in the ITT population received mometasone treatment, 146 subjects received beclomethasone, and 138 subjects received placebo [235:46]. An additional 40 subjects were excluded from efficacy analyses because of various protocol violations, leaving 387 subjects in the efficacy evaluable population [235:46].

The treatment groups in this study were comparable with regard to demographic and disease characteristics. Again, for all 3 treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the treatment groups was approximately equal. Approximately half of the subjects had SAR in addition to PAR and the majority did not have asthma (68-77%) [235:48]. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a statistically significant difference among the 3 treatment groups with the majority of subjects in all 3 groups having 'moderate' PAR symptoms [235:53].

Analysis of the primary efficacy variable for the ITT population demonstrated greater efficacy of both active treatment groups in decreasing total nasal symptoms for the day 1-15 interval, compared with placebo. The raw total nasal symptom score for the mometasone treatment group was 4.5 (with a -1.7 unit decrease in total nasal symptoms from baseline or a -26% change), compared with a raw total nasal symptom score of 5.0 (-1.0 unit decrease in total nasal symptoms or -13% change) for the placebo group ($p<.01$) [235:350], and a raw total nasal symptom score of 4.1 (-1.9 unit decrease in total nasal symptoms or -.29% change) for the beclomethasone treatment group ($p<.01$ for beclomethasone vs. placebo). No statistically significant difference was noted between the mometasone and beclomethasone treatment groups. Furthermore, no significant difference was noted between the a.m. and p.m. total nasal symptom scores in the mometasone treatment group for the day 1-15 interval, once again supporting once daily dosing of mometasone [235:352-353]. Additionally, no significant difference

population [235:284, 350]. A summary of results for the primary and secondary efficacy variables is summarized in Table I. and Table II. below and overall support the efficacy of mometasone in decreasing the symptoms of PAR. No significant difference in clinical efficacy was noted based on age, sex, or racial group however some sub-groups were too small in number (i.e. age 12-17, age >64 or non-Caucasian subjects) to make any generalized conclusions.

Sub-analysis of subject and physician-rated individual nasal and non-nasal symptoms are summarized in Table III. below. Based on these data and in support of previous findings of mometasone administration for the control of SAR or PAR symptoms, mometasone treatment was noted to have a greater effect on decreasing the symptoms of rhinorrhea and sneezing, with a statistically insignificant effect on nasal congestion and nasal itch, and little effect on the non-nasal symptoms of PAR (Table III.), as compared with placebo.

Analysis of rescue medication use (efficacy evaluable population) in the 3 treatment groups revealed similar overall rates of rescue medication use with slightly lower rates in the two active drug groups (48% of mometasone subjects, 46% of beclomethasone subjects, and 55% of placebo subjects used rescue medication > 1 time during the study) [236:584-585].

Table I. Primary Efficacy Variable of PAR and Treatment with Mometasone (ITT Population) [235:350]

1° EFFICACY VARIABLE	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1. Subject evaluated mean Δ in Total Nasal Sx Score$_{DAY\ 1\text{-}15}$	*Yes

sx=Symptom

* Note: Statistically significant response for 1° efficacy variable in the efficacy evaluable population (ITT data not provided) carried by 2 of the 20 distinct study centers (i.e. 18/20 centers had a statistically non-significant response) [235:284-304].

Table II. Secondary Efficacy Variables of PAR and Treatment with Mometasone (Efficacy Evaluable Population, except where *otherwise noted), [235:349, 350, 236:357-376, 378-380, 382-385, 387, 424, 451, 478, 499]

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1.	*Subject evaluated mean Δ in Total Nasal Sx Score 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.	Yes:	Day 31-45, 61-75, 76-90, Endpoint visit.	
		No:	Day 1-15, 16-30, 46-60.	
4.	Subject evaluated Total non-nasal Sx Score DAY 1-15, 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:	Study visits:	Day 8, 15, 29, Week 12, Endpoint visit.
		No:	Week 8	
6.	*Physician Evaluated Total Sx Score	Yes:	Study visit:	Day 8.
		No:	Study visits:	Day 15, 29, Week 8, Week 12, Endpoint visit.
7.	Physician Evaluated Total non-nasal Sx Score	No:	All study visits	
8.	Subject overall condition evaluation	Yes:	Study visits:	Day 8.
		No:	Study visits:	Day 15, Day 29, Week 8, Week 12, Endpoint visit.
9.	Physician overall condition evaluation	Yes:	Study visits:	Day 8.
		No:	Study visits:	Day 15, 29, Week 8, Week 12, Endpoint visit
10.	Subject overall Rx Response evaluation	Yes:	Study visit:	Day 8, 15, 29, Endpoint visit.
		No:	Study visits:	Week 8, Week 12.
11.	Physician overall Rx Response evaluation	Yes:	Study visits:	Day 8, 15, Week 12, Endpoint visit.
		No:	Study visit:	Day 29, Week 8.

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

Note: Analyses are for a.m. and p.m. combined symptom scores.

Table III. Change in Individual PAR Symptoms (Subject and Physician Evaluated, a.m. and p.m. combined) with Mometasone Treatment (Efficacy Evaluable Population), [236:390-397, 399-422]

PAR SYMPTOM	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
Subject Evaluated Individual Nasal Sx Score	Yes:	Rhinorrhea:	All study visits.
		Sneezing:	Day 16-30, 31-45, 46-60, 61-75, 76-90, Endpoint visit.
		Nasal Itch:	Day 61-75.
	No:	Congestion:	All study visits.
		Sneezing:	Day 1-15.
		Nasal Itch:	Day 1-15, 16-30, 31-45, 46-60, 76-90, Endpoint visit.
Physician Evaluated Individual Nasal Sx Score	Yes:	Rhinorrhea:	Day 8, 15, Week 8, 12, Endpoint visit.
		Sneezing:	Endpoint visit.
		Nasal Itch:	Day 8, 15, Endpoint visit.
	No:	Rhinorrhea:	Day 29.
		Congestion:	All study visits.
		Sneezing:	Day 8, 15, 29, Week 8 and 12.
		Nasal Itch:	Day 29, Week 8 and 12.
Subject Evaluated individual non-nasal Sx Score	Yes:	Eye redness:	Day 76-90.
	No:	Eye tear:	All study visits.
		Eye redness:	Day 1-15, 16-30, 31-45, 46-60, 61-75, Endpoint visit.
		Eye Itch:	All study visits.
		Ear/palate Itch:	All study visits.
Physician Evaluated individual non-nasal Sx Score	No:	For each non-nasal sx: All study visits.	

Sx=Symptom

8.13.4.3. ADVERSE EVENTS:

The safety analysis was based on 427 subjects in the ITT population; 143 subjects were treated with mometasone 200 µg qd, 146 subjects were treated with with beclomethasone, and 138 subjects were treated with placebo [235:77, 236:520]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, and nasal examinations, and clinical laboratory tests relative to baseline [235:30-33, 77, 238:1006-1016].

Adverse events were again similar for all three treatment groups, with viral infection being the most frequently reported treatment-related adverse event. Overall, adverse events were reported in 71% of subjects in the mometasone and beclomethasone treatment groups, and 65% of subjects in the placebo group [235:78, 79, 236:520-527]. Viral infection was reported in 29% of subjects in the mometasone group, 25% of subjects in the beclomethasone group, and 26% of subjects in the placebo group [235:78, 82, 236:524, 240:2120-2137, 2274-2289, 241:2419-2435]. Headache was the second most common adverse event; reported in 22% of mometasone subjects compared to 16% of beclomethasone treated subjects, and 19% of placebo subjects [235:78,79, 236:520, 240:2060-2079, 2214-2229, 241:2373-2388]. Reported next in frequency was epistaxis; with 21% of subjects in the mometasone group, 24% of subjects in the beclomethasone group, and 13% of placebo subjects reporting this ADR [235:78, 79, 236:525]. As in other rhinitis studies in this NDA submission, episodes of epistaxis were generally mild and self-limited (but not always) in duration. And finally, pharyngitis was reported by 12% of subjects in all 3 treatment groups [235:78, 79, 236:525].

There were no reports of nasal septal perforation in any of the 3 treatment groups but nasal ulcers were reported in the 3 subjects in the beclomethasone group (1 report on Day 29, 2 reports on Week 12) [242:5855, 5856, 5994] and 2 subjects in the placebo groups (1 report on Day 15, 1 report on Week 12) [242:5861, 5867]. There were no reports of nasal ulceration in mometasone treated subjects. No assessment of glaucoma/cataract formation or suppression of the HPA-axis were performed in this PAR study. No deaths were reported in any of the 3 treatment groups.

In terms of infection, viral infection (see above) was reported as the most frequent ADR in all 3 treatment groups in this study. One subject in the placebo treatment group reported herpes simplex labialis on Day 15 of the study (subject I92-293-19, #001)[235:82, 241:2417] and additionally one subject in the placebo group (subject I92-293-04, #008) reported bronchial pneumonia during Week 8 of the study which was felt by the principal investigator to be unrelated to study medication [241:2466]. No subjects in either of the three treatment groups were reported to have nasal or oral candidiasis on any clinic visits.

A total of 16 subjects discontinued treatment because of adverse events (8 subjects in the mometasone group, 6 subjects in the beclomethasone group, and 2 subjects in the placebo group) [235:90]. Common reasons for discontinuation of treatment that were considered 'possibly related' to study medication primarily

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 3 treatment groups. Flag shift distributions of laboratory values failed to reveal any significant patterns of change. Adverse events did not appear to differ significantly based on age, sex, or race, although again, the number of non-Caucasian subjects and subjects between 12-17 years and > 64 years of age was too small to draw meaningful conclusions.

8.13.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 12 weeks in subjects with PAR.
2. In terms of individual PAR symptoms and as noted in previous studies in this NDA submission, mometasone treatment demonstrated a greater effect in decreasing the nasal PAR symptoms of rhinorrhea and sneezing, as compared with placebo. Mometasone did not show a statistically significant response in decreasing nasal congestion or any of the non-nasal symptoms and showed a mixed response on nasal itch symptom scores.
3. Mometasone treatment demonstrated adequate duration of effect in treating PAR symptoms over 24 hours, supportive of once a day dosing.

APPEARS THIS WAY
ON ORIGINAL

8.14. Trial I93-018. Efficacy and Safety of Mometasone Furoate Nasal Spray vs. Beconase and vs. Placebo in the Treatment of Perennial Allergic Rhinitis (PAR).

Principal Investigator: Peter Clement, M.D.

Participating Centers: 24 centers in Europe (Belgium, Finland, Germany, the Netherlands, Norway, Sweden, Switzerland, and the U.K.) and Canada.

8.14.1. OBJECTIVES:

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

8.14.2. STUDY DESIGN:

This was a randomized, multi-center, open-label, active-controlled, parallel group trial in adult subjects with perennial allergic rhinitis which was an extension of the 3 month double-blind PAR study I92-293. Study enrollable subjects consisted of those who successfully completed the double-blind study I92-293 or who were dropped from I92-293 due to treatment failure or intercurrent illness (with exception of the Netherlands, where subjects who dropped out due to treatment failure were not enrolled in I93-018) [273:12, 277:983-984]. For study subjects at the U.K. centers, total exposure to mometasone, which included any exposure that subjects received in study I92-293, was limited to 12 months total; hence subjects who received a total of 3 months of mometasone treatment in study I92-293 could only receive mometasone for 9 months in study I93-018 [273:12, 277:971]. A variable mometasone dose group was included in this study in order to obtain additional efficacy and safety information on doses of mometasone which were above or below the 200 µg qd dose and also to gain information regarding the individualization of mometasone dosing for PAR. Study medications were given to PAR subjects for a total duration of 52 weeks (1 year) (with the above noted exception of U.K. subjects).

8.14.3. PROTOCOL:

8.14.3.1.a. POPULATION:

Entry criteria for this study after completion of a washout period (up to 7 days) were essentially the same as those for study I92-293, namely (1) [illegible]

years [273:15], (2) presence of IgE-mediated hypersensitivity to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 1 year of study entry via the prick testing or intradermal method [273:15, 277:965], and (3) successful completion of study I92-293, or discontinuation secondary to treatment failure or intercurrent illness (exception: the Netherlands) [273:15].

8.14.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1. of Trial I93-018 in the NDA submission [273:14, 277:1005] and is similar to the study design of PAR study C93-014. Subjects were assessed at pre-baseline (Visit 1), baseline (Visit 2), and at Week 4 (Visit 3), 8 (Visit 4), 12 (Visit 5), 24 (Visit 6), 36 (Visit 7), and 52 (Visit 8) of therapy [277:985]. Subjects enrolled at U.K. centers completed the study by Visit 7 (Week 36)[273:14,277:992-999]. For 'roll-over' subjects, the final visit in I92-293 (Visit 7) served as the pre-baseline visit for study I93-018 [273:14, 277:971].

Subjects entered a washout phase (up to 7 days) between the pre-baseline and baseline visit, during which they took no medications except for rescue medication (note: no restrictions outlined in the protocol with regard to the type of rescue medication that could be used by a subject with the exception of corticosteroid use), as prescribed by the principal investigator for relief of intolerable PAR symptoms prior to initiation of the open-label treatment [273:18, 277:984]. Following the washout period, subjects who met all inclusion criteria were randomly assigned to one of the following 3 treatment groups, received diary cards to record symptoms reflectively over the previous 12 hours and began therapy with mometasone (fixed and variable doses) administered in the a.m. and beclomethasone administered in the a.m. and p.m. (bid) [277:984-985]:

(A)	**Mometasone aqueous nasal spray 200 µg qd** (FIXED DOSE)
(B)	**Mometasone aqueous nasal spray 100, 200 or 400 µg qd** (VARIABLE DOSE)-subjects started treatment with mometasone 200 µg qd
(C)	**Beclomethasone 200 µg bid (400 µg qd total)**

Subjects underwent clinical efficacy and safety evaluation (including nasal exam) during each study visit [273:23-29, 277:992-1001]. Of note, eye examinations to assess glaucoma/cataract formation and assessments of HPA-axis suppression were not performed in this study. Efficacy evaluation was again based on a 0-3 severity scale [273:25, 277:998] and a 1-5 scale of therapeutic response [273:25-26, 277:998-999].

Subjects randomized to the mometasone 'variable dose' group started treatment at 200 µg qd but were allowed to lower the medication dose to 100 µg qd if nasal symptoms were well controlled or to increase the dose to 400 µg qd in

were not to be done more frequently that once every 2 weeks, and an intermediate dose of 300 µg qd was not allowed [273:17, 277:990]. Rescue medication use was allowed throughout the study duration for all 3 treatment groups, excluding steroid formulations (nasal, inhaled, etc.).

A primary efficacy variable was not defined in this study. Supplementary efficacy variables consisted of: (1) physician and (2) subject evaluations of overall condition and (3) physician and (4) subject evaluations of therapeutic response in the ITT population [273:33, 277:1002]. Centers 3, 7, 9, 12, 14, 28, 22, and 24 were combined for efficacy analysis since each of these sites had ≤ 7 subjects randomized [273:33]. Pollen counts were not collected in this study. Rescue medication use between the 3 treatment groups was not analyzed in any systematic manner in this study, thus making it difficult to reach any solid conclusions about clinical efficacy of the different treatments evaluated in this study.

8.14.4. RESULTS

A total of 229 subjects with PAR were randomized into study I93-018, with 1 immediate drop-out (the subject did not receive any study drug)[273:36], leaving 228 subjects for the ITT population [273:36]. Seventy-seven (77) subjects in the ITT population received mometasone 200 µg qd, 80 subjects received variable dose (100-400 µg qd) mometasone, and 72 subjects received beclomethasone [273:36]. Similar to study C93-014, the attrition rates for study subjects by Week 52 of study I93-018 were quite high with 30.3% (23/76) of mometasone 200 µg qd subjects, 23.4% (19/80) of variable dose mometasone subjects, and 29.6% (21/71) of beclomethasone subjects discontinuing treatment by this study endpoint [274:277].

The treatment groups in this study were comparable with regard to demographic and disease characteristics with the exception of a marginally statistically significant difference among the treatment groups with respect to weight (mean weight of the mometasone 200 µg group subjects=76 kg vs. mean weight of the mometasone variable dose group subjects=72 kg vs. mean weight of the beclomethasone group subjects=72 kg; p=0.15) [273:36]. Given the minimal-absent systemic bioavailability of intranasally administered mometasone and therefore, unlikely relevance of weight in determining dosing requirements for individual subjects, the small weight difference between treatment groups in this study was not likely to be clinically significant. Again, for all 3 treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the treatment groups was approximately equal. Approximately 50% study subjects in all 3 treatment groups had SAR in addition to PAR. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a statistically significant difference among the 3 treatment groups although the mometasone variable group had a numerically greater % of subjects with 'severe' PAR (11%) in comparison with the other 2 groups (mometasone variable group; 'severe' subjects=6%, vs. beclomethasone group; 'severe'

groups were assessed as having 'moderate' or 'severe' PAR, indicating little carry-over effect from treatment in I92-293 to I93-018.

Analysis of the efficacy variables for the ITT population showed that overall, subjects in all 3 active treatment groups demonstrated an improvement in symptoms which was maintained for the study duration. For the physician's evaluation of the overall condition of PAR, subjects in the 2 (fixed and variable) mometasone treatment groups demonstrated an improvement by Week 4 of the study (as supported by the majority of subjects having 'mild' PAR symptoms) and this improvement was maintained through the Week 52 visit [273:40-41, 225, 248-249]. While beclomethasone treated subjects also demonstrated an improvement in the overall condition of PAR, this improvement was numerically lower than that of the mometasone treated subjects. Subjects' self-evaluation of the overall condition of PAR paralleled that of the physician evaluation; namely that improvement in symptoms was noted by Week 4 of the study (supported by the majority of subjects rating their overall PAR condition as 'mild') and was maintained throughout the study duration [274:277, 300-301]. Both of these findings support maintenance of a therapeutic effect for mometasone (fixed and variable dose) and beclomethasone throughout the open-treatment period. Physician evaluation of subjects' therapeutic response to treatment (1-5 scale) indicated that all 3 treatment groups experienced moderate-marked relief in PAR symptoms starting at Week 4 of the study and continuing throughout the open-treatment period, again providing evidence of maintenance of a therapeutic effect throughout the study duration [273:44-45, 329-330]. Subjects' evaluation of therapeutic response paralleled the physician evaluation of subjects' therapeutic response with the majority of study subjects reporting moderate-marked relief in PAR symptoms by Week 4 of treatment [273:48, 274:375-376]. Again, this response was maintained for the study duration.

Regarding the 'variable dose' mometasone group, 8/80 (10%) of subjects received mometasone 100 μg qd, 48/80 (60.0%) of subjects received mometasone 200 μg qd, and 24/80 (30%) of subjects received mometasone 400 μg qd at the time of the final study visit [253:45, 275:506]. Within the variable mometasone group, 35/80 (44%) of subjects maintained the 200 μg qd dose throughout the study, 22/80 (28%) increased their dose to 400 μg qd, and 8/80(10%) decreased their dose to 100 μg qd. Fifteen subjects (19%) varied their mometasone dose more than once during the study [275:507]. Again, these 'variable dose' mometasone group data suggest that the most effective dose of mometasone for the control of PAR symptoms was 200 μg qd. As noted in study C93-014, gradual increase in dose of mometasone over the course of study I93-018 was not observed.

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

Table I. Efficacy Variables of PAR and Treatment with Mometasone 200 µg qd and 'Variable Dose' Mometasone (100, 200, or 400 µg qd) (ITT Population), [273:225, 248-249, 329-330, 274:277, 300-301, 375-376]

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

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

8.14.4.3. ADVERSE EVENTS:

The safety analysis was based on 228 subjects in the ITT population; 77 subjects were treated with mometasone 200 µg qd, 80 subjects were treated with variable dose mometasone (100, 200, or 400 µg qd), and 71 subjects were treated with beclomethasone [273:50]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, nasal, and clinical laboratory tests relative to baseline [273:26-29].

Adverse events were similar for all 3 treatment groups, with viral infection being the most frequently reported adverse event. Overall, adverse events were reported in 68% of subjects in the mometasone 200 µg qd treatment group, 76% of subjects in the variable dose mometasone treatment group, and 77% of subjects in the beclomethasone group [273:50].

Viral infection was reported in 35% of subjects in the mometasone 200 µg qd group, 30% of subjects in the variable dose mometasone group, and 28% of subjects in the beclomethasone group [273:50,52, 279:1797-1808, 280:1942-1952, 2084-2094]. Viral infection was followed by headache as the second most frequently reported adverse event; reported in 19% of mometasone 200 µg qd subjects, compared to 30% of variable dose mometasone subjects and 25% of beclomethasone treated subjects [273:50, 52, 279:1738-1750, 1875-1896, 280:2015-2037]. Reported next in frequency was pharyngitis; with 17% of subjects in the mometasone 200 µg qd group, 13% of subjects in the variable dose mometasone group, and 11% of subjects in the beclomethasone group recording this adverse event [273:51, 53, 279:1839, 280:1975-1978, 2111-2114]. Other relatively frequent ADRs reported in this follow-up study included epistaxis (8% of

mometasone 200 µg qd subjects, 13% of variable dose mometasone subjects, and 14% of beclomethasone subjects [273:51, 53, 279:1818-1830, 280:1959-1969, 2099-2106]), coughing (8% of mometasone 200 µg qd subjects, 8% of variable dose mometasone subjects, and 14% of beclomethasone subjects [273:51, 53, 279:1814-1817, 280:1957-1958, 2096-2098]), and sinusitis (5% of mometasone 200 µg qd subjects, 9% of variable dose mometasone subjects and 10% of beclomethasone subjects [273:51, 53, 279:1852-1853, 280:1982-1985, 2117-2118]).

Unlike study C93-014, for study I93-018 there did appear to be a dose relationship in the overall incidence of ADRs in the mometasone variable dose group noted for the study duration (incidence of ADRs for mometasone 100 µg qd group=42%, incidence of ADRs for mometasone 200 µg qd group=59%, incidence of ADRs for mometasone 400 µg qd group=71% [273:71]). ADRs which primarily exhibited a dose response for the varying doses of mometasone were coughing (0%, 4%, and 9% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose, respectively), epistaxis (0%, 8%, and 11% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose, respectively), and sinusitis (0%, 5%, and 9% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose of, respectively) [273:51]. Nonetheless, the small number of study subjects in the variable dose mometasone groups, especially the 100 µg group, precludes any definitive conclusion regarding the mometasone dose-relationship of adverse events.

There was one report of a distal nasal septal perforation at screening and at the one year follow-up visit (Visit 8) in a subject in the variable dose mometasone group (subject I93-018-05, #017) [281:2927]. Nasal ulcers were reported in all 3 treatment groups as follows:

(1) mometasone 200 µg qd group: a report in 1 subject (at Visit 3 (Week 4), [281:3034]),

(2) mometasone variable (100-400 µg qd) group: reports in 6 subjects (1 at Visit 3, 1 at Visit 5, 1 at Visit 6, 2 at Visit 7, and 1 at Visit 8) [281:3045, 3047, 3049, 3051, 3090, 3124], and

(3) beclomethasone group 200 µg bid group: reports in 7 subjects (1 at Visit 3, 3 at Visit 4, 1 at Visit 6, 1 at Visit 7, and 1 at Visit 8 [281:3055, 3056, 3061, 3063, 282:3082, 3134, 3222].

Again, no assessments of HPA-axis suppression or glaucoma/cataract formation were performed in this follow-up study. No deaths were reported in any of the three treatment groups.

In terms of infection, viral infection was the most frequently reported ADR in the study for all 3 treatment groups with a reported incidence of 35% in mometasone 200 µg qd subjects, 30% in variable dose mometasone subjects, and 28% in beclomethasone treated subjects [273:50]. In this study there were no reports of herpes simplex labialis, nasal or oral candidiasis for any of the 3 treatment groups.

A total of 15 subjects discontinued treatment because of adverse events (5

mometasone group, and 4 subjects in the beclomethasone group) [273:63]. The most common reason for discontinuation that was considered 'possibly or probably related' to study medication involved headache, epistaxis, or nasal irritation. Otherwise, most subject discontinuations due to ADRs were considered unrelated to treatment by the principal investigator.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 3 treatment groups with the exception of several reports of elevated LFTs and several reports of a decrease in the WBC. Three subjects total developed elevated LFTs; in 1 case this was felt to be possibly related to study medication (subject I93-018-08, #14 who received mometasone 200 µg qd and developed an increase in the SGOT from 40 IU/L at screening to 114 IU/L at Visit 5 and an increase in the SGPT from 88 IU/L at screening to 277 IU/L at Visit 5) [273:66, 67, 279:1780]. One additional subject in the mometasone 200 µg qd group (subject I93-018-20, #12) developed an elevated SGOT on the final study visit (111 IU/L from 24 IU/L at screening)[273:64, 66, 275:504, 279:1780] which was considered 'unaccessible' in terms of relation to study medication although no other etiology for this elevation was determined and one subject in the variable dose mometasone group (subject I93-018-02, #08) developed an elevated bilirubin (4.0 mg/dL at Week 23 from 3.6 mg/dL at screening) which was reported to be secondary to hepatitis (although hepatitis serology was negative) and not considered related to study medication [273:65-66, 275:502, 280:1921]. Two subjects in the variable dose mometasone group were reported to have minor or transient decreases in their white blood cell count (WBC) [273:66]. Of note, in both cases, the pre-baseline WBC for each subject was already below or at the lower limit of normal ($3.26 \times 10^3/mm^3$ and $4.03 \times 10^3/mm^3$) [273:66]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change. Adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects <18 or > 65 years of age was too small to draw meaningful conclusions.

8.14.5. CONCLUSIONS:

1. **The results of this study support the safety of mometasone 100 µg, 200 µg and 400 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 52 weeks (1 year) in subjects with PAR.**

8.15. Trial I94-079. Efficacy and Safety of Mometasone Furoate Nasal Spray vs. Fluticasone Proprionate Nasal Spray and vs. Placebo in the Treatment of Perennial Allergic Rhinitis (PAR).

Principal Investigator: None (Multi-center study)

Participating Centers: 25 centers in Canada, Latin America (Argentina, Chile, Venezuela, Mexico, Columbia, Guatemala), and Europe (Austria, Portugal, and the U.K.).

8.15.1. OBJECTIVES:

1. To investigate the safety and efficacy of mometasone furoate aqueous nasal spray 200 µg qd in the treatment of symptoms of perennial allergic rhinitis (PAR).

8.15.2. STUDY DESIGN:

The study was a phase III, randomized, multi center, double-blind, double-dummy, active- and placebo-controlled, parallel group study to determine the safety and efficacy of mometasone furoate 200 µg administered intranasally once daily (qd), vs. the active control, fluticasone (Flonase) 200 µg administered once daily (qd), and vs. placebo for a total of 12 weeks for the treatment of perennial allergic rhinitis (plus 1 additional week of observation at the end of the double-blind treatment period (the 'offset' or Week 13 visit) [243:37]).

8.15.3. PROTOCOL:

8.15.3.1.a. POPULATION:

Entry criteria for this study were very similar to those for all other PAR studies, namely: (1) age ≥ 12 years [243:16, 246:1137, 1140], (2) presence of IgE-mediated hypersensitivity to a relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 2 years of study entry via the prick testing or intradermal method; or in the absence of a positive skin test, a diagnosed or suspected history of non-allergic rhinitis with eosinophilia syndrome (NARES) which had been corroborated by nasal cytology demonstrating eosinophilia [243:16, 26, 246:1138, 1140], and (3) presence of PAR symptoms of sufficient severity (nasal rhinorrhea and/or congestion scores at least moderate in severity (≥ 2), a total symptom score ≥ 5 at both screening and baseline, and rhinorrhea and/or congestion scores ≥ 2 during 4 of the last 7 days prior to the baseline visit), in order to begin study drug treatment [243:30, 36, 246:1138].

8.15.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1. of Trial I94-079 in the NDA submission [243:15, 246:1173] and is similar to the study design of PAR study I92-293. Subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Day 8 (Visit 3), 15 (Visit 4), 29 (Visit 5), and Weeks 8 (=Day 57, Visit 6), and 12 (=Day 85, Visit 7) of therapy [243:14-15, 25-29, 246:1146-1147, 1148-1159]. Subjects were also evaluated at Week 13 at the end of the 'off-set' period (Visit 8) when subjects were no longer receiving double-blind medication in order to assess duration of effect of each treatment in decreasing PAR symptoms [243:14, 246:1158]. Day 1 was designated as the start of treatment date [243:37]. Medication restrictions consisted of those previously discussed for the mometasone SAR and PAR studies [243:22-24, 246:1142-1145], although subjects were allowed to use a rescue medication (loratadine, up to 10 mg po qd maximum dose) for intolerable PAR symptoms starting with the screening visit (the 'run-in' phase) and continuing for the duration of the study, including the offset period [243:20, 21, 26-27, 246:1145, 1148, 1163].

Subjects who met all inclusion criteria were randomized to one of the following 3 treatment groups, received diary cards to record symptoms reflectively over the previous 12 hours (upon awakening, before the a.m. medication dose and before retiring (p.m. recording)) and began therapy with study drug every a.m. and p.m. (4 bottles utilized for this double dummy design--each active drug had a matching placebo) [243:18, 21, 27-28, 246:1138-1139, 1146-1147]:

(A) Mometasone aqueous nasal spray 200 µg qd		
a.m. dosing:	Bottle 1: Mometasone 200 µg	Bottle 2: Fluticasone Placebo
p.m. dosing	NONE	
(B) Fluticasone nasal spray (Beconase) 200 µg qd		
a.m. dosing:	Bottle 1: Mometasone Placebo	Bottle 2: Fluticasone 200 µg
p.m. dosing:	NONE	
(C) Placebo (0 µg qd)		
a.m. dosing:	Bottle 1: Mometasone placebo	Bottle 2: Fluticasone Placebo
p.m. dosing:	NONE	

Subjects underwent clinical efficacy and safety evaluation (including nasal exam on Visits 2 (baseline) and 7 (Week 12) during each study visit [243:28-34, 246:1148-1165]. Efficacy evaluation was again based on a 0-3 severity scale [243:30, 246:1159], a 0-3 scale of the overall condition of PAR [243:30, 246:1160], and a 1-5 scale of therapeutic response [243:31, 246:1160].

The primary efficacy variable [243:43-44, 246:1168-1169] was defined as: the mean change from baseline (the mean of the a.m. and p.m. baseline scores and

the a.m. and p.m. scores from the 7 prior consecutive days) in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject diaries) where the:

Mean Change in Total nasal symptom score= 15 Day Interval Score[(Nasal a.m. average $_{\text{Day 1-15}}$) + (Nasal p.m. average$_{\text{Day 1-15}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

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

Secondary efficacy variables consisted of the following [243:44, 246:1169]:

(1) The mean change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30 (a.m. and p.m. combined), Days 31-45, Days 46-60, Days 61-75, and Days 76-90 [243:44]:

Mean Change in Total nasal symptom score$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$**=Day 16-30 (or Day 31-45, Day 46-60, Day 61-75, Day 76-90) Interval Score**[(Nasal a.m. average $_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$) + (Nasal p.m. average$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

(2) Endpoint total nasal symptom score (a.m. and p.m. combined): Endpoint score defined as the last available post-baseline value for each study subject, pooled across the 24 participating centers [243:38].
(3) Mean change in the total nasal symptom score for the 'offset' (Week 13) visit [243:40].
(4) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, endpoint visit, and the offset visit) [243:44].
(5) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, endpoint visit, and the offset visit) [243:44].
(6) Physician's evaluation of total nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8 , Week 12, endpoint visit, and the offset visit) [243:44].
(7) Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit) [243:44].
(8) Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit) [243:44].
(9) Subject's self-evaluation of overall disease condition using the PAR 0-3

visit, and the offset visit [243:44].

(10) Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [243:44].

(11) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit and the offset visit [243:44].

(12) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [243:44].

(13) The proportion of 'symptom-free' days (i.e. total nasal symptom=0) during the entire treatment period (i.e. excluding baseline visit) [243:44].

Pollen counts were not collected in this study. Rescue medication use between the 3 treatment groups was not analyzed statistically but a frequency of rescue medication for all 3 treatment groups was tabulated, thus providing a general overview of differences in rescue medication use [244:317].

8.15.4. RESULTS

A total of 550 subjects with PAR were randomized into study I94-079, with 2 immediate drop-outs (1 subject in the mometasone group and 1 subject in the fluticasone group, respectively who did not receive any double-blind medication and were excluded from all analyses) [243:47], leaving 548 subjects evaluable in the ITT population [243:47]. One hundred and eighty one (181) subjects in the ITT population received mometasone treatment, 183 subjects received fluticasone, and 184 subjects received placebo [243:47]. An additional 89 subjects were excluded from efficacy analyses because of various protocol violations, leaving 459 subjects in the efficacy evaluable population [243:47].

The treatment groups in this study were comparable with regard to demographic and disease characteristics [243:49]. Again, for all 3 treatment groups, the majority of subjects were Caucasian, although approximately 28-30% of all subjects in each of the 3 treatment groups were Hispanic [243:49]. The distribution of male and female subjects in each of the treatment groups was approximately equal, with slightly more female than male subjects enrolled in all 3 treatment groups. Approximately 35-40% of the subjects had SAR in addition to PAR and the majority did not have the NARES syndrome (7 subjects total, 1 subject in the mometasone treatment group) [243:219-221]. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a statistically significant difference among the 3 treatment groups with the majority of subjects in all 3 groups having 'moderate' PAR symptoms at baseline [243:51].

Analysis of the primary efficacy variable for the ITT population demonstrated greater efficacy of both active treatment groups in decreasing total

nasal symptom score/unit change for the mometasone treatment group was 3.8 (with a -2.3 unit decrease in total nasal symptoms from baseline or a -37% change), compared with a raw total nasal symptom score of 4.5 (-1.3 unit decrease in total nasal symptoms or -17% change) for the placebo group ($p<.01$) [244:403], and a raw total nasal symptom score of 3.9 (-2.2 unit decrease in total nasal symptoms or -35% change) for the fluticasone treatment group ($p<.01$ for fluticasone vs. placebo) [244:403]. No statistically significant difference was noted between the mometasone and fluticasone treatment groups. Furthermore, no significant difference was noted between the a.m. and p.m. total nasal symptom scores or change in scores in the mometasone treatment group for the day 1-15 interval (mometasone group a.m. raw total nasal symptom score/change in raw score=3.9/-2.3 unit change vs. mometasone group p.m. raw total nasal symptom score/change in raw score=3.7/-2.3 unit change), once again supporting once daily dosing of mometasone [244:404-405]. Additionally, no significant difference in the primary efficacy variable was noted between the ITT and efficacy evaluable population [244:373, 403].

Sub-analysis of the primary efficacy variable (total nasal symptom scores) on a weekly basis for the efficacy evaluable population revealed a statistically significant response in the mometasone treatment group compared to placebo by week 1 of treatment ($p<0.01$) [244:442] and a continued decrement in the raw total nasal symptom score by week 2 of treatment which was statistically greater than that of the placebo group ($p<.01$) [244:442]. No statistically significant difference was noted between the 2 active drugs although fluticasone treated subjects had a slightly greater numerical response during weeks 1 and 2 of treatment, compared to the mometasone treatment group [244:442]. Again no significant difference between the a.m. and p.m. total nasal symptom scores (raw and change in raw scores) was noted for weeks 1 and 2 for the mometasone treatment group [244:443-444]. A summary of results for the primary and secondary efficacy variables is summarized in Table I. and Table II. below and overall, support the efficacy of mometasone in decreasing the symptoms of PAR. No significant difference in clinical efficacy was noted based on age, sex, or racial group with the exception that efficacy evaluable female subjects in the 2 active treatment groups showed a greater mean reduction in the total nasal symptom scores from baseline than did efficacy evaluable male subjects, and male subjects in the placebo group showed a greater mean reduction in total nasal symptom scores from baseline than did placebo group female subjects [243:53, 244:409]. In general, however, the number of subjects comprising the sub-groups were too small (i.e. age 12-17, age >64 or non-Caucasian subjects) to make any generalized conclusions [244:409] regarding possible differences in efficacy.

Analysis of subject and physician-rated individual nasal and non-nasal symptoms are summarized in Table III. below. Interestingly, in this PAR study mometasone treatment was noted to have an statistically significant effect on decreasing each individual nasal symptom, in particular nasal congestion--a

the other studies reviewed in this NDA submission. Mometasone treatment likewise demonstrated a very small numerical response in decreasing the individual non-nasal symptoms of PAR (Table III.), however these changes were not found to be statistically significant as compared with placebo. Analysis of the 'offset' visit indicates that for both the nasal and non-nasal, while not generally statistically significant, the mometasone treatment group did demonstrate a greater decrease in PAR symptoms than did placebo treated subjects one week after discontinuation of treatment. These findings suggest that mometasone (also fluticasone) continues to provide some relief of PAR symptoms 1 week after discontinuation of medication use and suggests that mometasone has a somewhat prolonged duration of action once subjects reach steady state dosing. Also, while numerically small, mometasone treatment increased the mean proportion of 'symptom-free' days for the entire study duration to 9.5 days, compared to 4.4 'symptom-free' days for placebo treated subjects ($p<.01$, no significant difference noted between the mometasone and fluticasone treatment groups) [244:400].

Analysis of rescue medication use (efficacy evaluable population) in the 3 treatment groups revealed lower rates of rescue medication use in the two active drug groups (53.9% of mometasone subjects, 57.3% of fluticasone subjects, and 71.0% of placebo subjects used rescue medication > 1 time during the study) [244:317-318]. A greater percentage of placebo group subjects tended to use rescue medication 11-15 times or more for the study duration than did subjects in either of the 2 active drug groups [244:317].

Table I. Primary Efficacy Variable of PAR and Treatment with Mometasone (ITT Population) [243:403]

1° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1.	Subject evaluated mean Δ in Total Nasal Sx Score$_{DAY\ 1\text{-}15}$	*Yes

sx=Symptom

* Note: Statistically significant response for 1° efficacy variable in the efficacy evaluable population (ITT data not provided) carried by 3 of the 21 distinct study centers (i.e. 18/20 centers had a statistically non-significant response) [244:374-396]. 4 study centers (-009, -012, -013, and -022 had ≤ 10 efficacy evaluable subjects hence were combined as 1 single large center [243:41]).

Table II. Secondary Efficacy Variables of PAR and Treatment with Mometasone (ITT Population, except where *otherwise noted), [244:400, 403, 407, 246:1495, 1498, 1527, 1528, 1537-1540]

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1.	Subject evaluated mean Δ in Total Nasal Sx Score 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 Offset Total Nasal Sx Score	Yes:	Offset visit.	
4.	Subject evaluated mean Δ in Total Sx Score DAY 1-15, DAY16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90, Endpoint Visit, Offset Visit.	Yes:	All study intervals and visits.	
5.	Subject evaluated mean Δ in Total non-nasal Sx Score DAY 1-15, DAY16-30, DAY 31-45, DAY 46-60, DAY 61-75, DAY 76-90, Endpoint Visit, Offset Visit.	Yes:	Day 31-45, 61-75, Endpoint visit, Offset visit.	
		No:	Day 1-15, 16-30, 46-60, 76-90.	
6.	Physician Evaluated Total Nasal Sx Score	Yes:	Study visits:	Day 8, 15, 29, Week 8, Week 12, Endpoint visit.
		No:	Offset visit.	
7.	Physician Evaluated Total Sx Score	Yes:	Study visit:	Day 8, 15, Week 8, Week 12, Endpoint visit.
		No:	Study visits:	Day 29, Offset visit.
8.	Physician Evaluated Total non-nasal Sx Score	No:	All study visits	
9.	Subject overall condition evaluation	Yes:	Study visits:	Day 8, 15, 29, Week 8, Week 12, Endpoint visit.
		No:	Study visits:	Offset visit.
10.	Physician overall condition evaluation	Yes:	Study visits:	Day 8, 15, 29, Week 8, Week 12, Endpoint visit.
		No:	Study visits:	Offset visit.
11.	Subject overall Rx Response evaluation	Yes:	Study visit:	All study visits.
12.	Physician overall Rx Response evaluation	Yes:	Study visits:	All study visits.
13.	*Proportion of symptom-free days for the entire treatment period (Total nasal sx score=0)	Yes		

Δ=Change, Sx=Symptom, Rx=Treatment Note: Analyses are for a.m. and p.m. combined symptom scores.

ITT=Intent-to-Treat Population.
*Otherwise noted=efficacy evaluable population.

Table III. Change in Individual PAR Symptoms (Subject and Physician Evaluated, a.m. and p.m. combined) with Mometasone Treatment (ITT Population), [246:1501-1524, 1526-1528, 1529-1536]

PAR SYMPTOM	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
Subject Evaluated Individual Nasal Sx Score	Yes:	For all 4 nasal sxs: All study visits.	
Physician Evaluated Individual Nasal Sx Score	Yes:	Rhinorrhea:	Day 8, 15, 29, Week 8, 12, Endpoint visit.
		Congestion:	Day 8, 15, 29, Week 8, 12, Endpoint visit.
		Sneezing:	Day 8, 15, 29, Endpoint visit.
		Nasal Itch:	Week 8, Endpoint visit.
	No:	Rhinorrhea:	Offset visit.
		Congestion:	Offset visit.
		Sneezing:	Week 8 , Week 12, Offset visit.
		Nasal Itch:	Day 8, 15, 29, Week 12, Offset visit.
Subject Evaluated individual non-nasal Sx Score	Yes:	Eye tear:	Day 31-45, Endpoint visit.
		Eye itch:	Day 31-45, Endpoint visit.
		Ear/palate itch:	Day 1-15, 31-45, 46-60, 61-75, Endpoint visit, Offset visit.
	No:	Eye tear:	Day 1-15, 16-30, 46-60, 61-75, 76-90, Offset visit.
		Eye redness:	All study visits..
		Eye Itch:	Day 1-15, 16-30, 46-60, 61-75, 76-90, Offset visit.
		Ear/palate itch:	Day 16-30, 76-90.
Physician Evaluated individual non-nasal Sx Score	No:	All 4 non-nasal Sxs:	All study visits.

Sx=Symptom

8.15.4.3. ADVERSE EVENTS:

The safety analysis was based on 548 subjects in the ITT population; 181 subjects were treated with mometasone 200 µg qd, 183 subjects were treated with with fluticasone 200 µg qd, and 184 subjects were treated with placebo [243:76, 245:615]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, and nasal examinations, and clinical laboratory tests relative to baseline [243:31-34, 246:1148-1165].

Adverse events were again similar for all three treatment groups, with viral infection and headache being the most frequently reported treatment-related adverse event. Overall, adverse events were reported in 75% of subjects in the mometasone group, 71% of subjects in the fluticasone treatment group, and 65% of subjects in the placebo group [243:77, 78, 245:615]. Viral infection was reported in 28% of subjects in the mometasone group, 19% of subjects in the fluticasone group, and 27% of subjects in the placebo group [243:78, 245:621, 249:5957-5980, 250:6253-6267, 6518-6538]. Headache was reported in 27% of mometasone and fluticasone subjects, compared to 24% of placebo subjects [243:78, 245:616, 249:5829-5873, 6135-6171, 250:6419-6457]. Reported next in frequency were pharyngitis and epistaxis; with 19% of subjects in the mometasone group, 21% of subjects in the fluticasone group, and 17% of placebo subjects reporting pharyngitis [243:78, 79, 245:622, 249: 6038-6052, 250:6334-6349, 6590-6605], and 19% of subjects in the mometasone group, 21% of subjects in the fluticasone group, and 13% of placebo subjects reporting epistaxis, respectively [243:78, 79, 245:621, 249:6003-6028, 250:6298-6321, 6559-6573]. As in other rhinitis studies in this NDA submission, episodes of epistaxis were generally mild and self-limited in duration. The third most frequent ADR was coughing, reported in 15% of mometasone subjects, 11% of fluticasone subjects, and 12% of placebo subjects [243:79, 245:621, 249:5985-6000, 250:6283-6295, 6546-6555]. Compared to the other PAR studies in this NDA submission, sinusitis was less frequent in study I94-079, being reported in 5% of mometasone treated subjects, 7% of fluticasone subjects, and 3% of placebo subjects [243:79, 245:621, 249:6064-6068, 250:6360-6365, 6622-6625].

There were no reports of nasal septal perforation in any of the 3 treatment groups but one mometasone treated subject was noted to have a left septal ulcer on Visit 7 (Week 12) of the study which was absent on screening (subject I94-079-06, #008) [251:7883] and one fluticasone treated subject was found to have a right nasal septal ulcer on Visit 7 (Week 12) of the study which was absent on screening (subject I94-079-06, #006) [251:7885]. Nasal ulcers were reported in 4 subjects in the mometasone group on Visit 7 of the study (subjects I94-079-04, #001, -05, #003, -06, #007, -011, #022) [252:7973, 7993, 8013, 8094], 2 subjects in the fluticasone group (1 report on Visit 6 and 1 report on Visit 7, subjects I94-079-25, #010 and -11, #018) [252:8101, 8290], and 2 subjects in the placebo group (1 report on Visit 3, subject I94-079-05, #020,[250:6634] and 1 report on Visit 7, subject I94-079-05, #011) [251:7881]. No assessment of glaucoma/cataract

deaths were reported in any of the 3 treatment groups.

In terms of infection, viral infection (see above) was reported as the most frequent ADR in all 3 treatment groups in this study. Herpes simplex infection was more prevalent in this PAR study with 2 subjects in the mometasone group (1% incidence), 5 subjects in the fluticasone group (3% incidence), and 2 subjects in the placebo group (1% incidence) reporting this adverse event [243:78, 245:621, 249:5954, 250:6250, 6517]. One subject in the fluticasone treatment group (subject I94-079-02, #026) was reported to have pneumonia during Visit 6 and Visit 7 of the study which was felt by the principal investigator to be unrelated to study medication [245:622, 250:6350]. One subject in the fluticasone treatment group was reported to have nasal candidiasis (right nares) on Visit 7 of the study (subject I94-079-17, #023) [252:8184]. No subjects in either of the three treatment groups were reported to have oral candidiasis on any clinic visits [245:621].

A total of 9 subjects discontinued treatment because of adverse events (3 subjects in the mometasone group, 4 subjects in the fluticasone group, and 2 subjects in the placebo group) [243:93]. Of the 3 subjects who discontinued treatment in the mometasone group (due to eczema, an upper respiratory infection (URI), and hyperglycemia from diabetes, respectively), none of these discontinuations were felt to be related to the study medication [243:93, 309, 311, 312].

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 3 treatment groups with the exception of several reports of a decrease in the WBC in mometasone treated subjects. Three subjects in the mometasone treatment group were noted to have a significant decrease in their WBC count on Visit 7 (Week 12) of the study to 2.46, 2.54, and 2.5 x 10^3/mL from a screening value of 5.33, 3.16, and 4.0 x 10^3/mL, respectively (subject I94-079-08, #024, I94-079-22, #001, and I94-079-23, #013) [243:95, 245:714-715]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change with the exception of a mild shift to the low normal range for the % neutrophil count in subjects of the 2 active drug groups, mometasone and fluticasone [245:988]. Adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects between 12-17 years and > 64 years of age was too small to draw meaningful conclusions.

8.15.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 12 weeks (plus 1 week off medication) in subjects with

2. In terms of individual PAR symptoms, mometasone treatment demonstrated a statistically significant effect in decreasing the PAR symptoms of rhinorrhea, nasal congestion, sneezing, and nasal itch: as compared with placebo. Mometasone did not show a statistically significant response in decreasing any of the non-nasal symptoms although a small degree of improvement was demonstrated in mometasone treated subjects, as compared with placebo for all 4 non-nasal symptoms.
3. Mometasone treatment demonstrated adequate duration of effect in treating PAR symptoms over 24 hours, supportive of once a day dosing.
2. While not specifically designed to evaluate efficacy, assessment of subject overall condition and response to treatment with mometasone over 52 weeks (by study subjects and their respective physicians), supports the efficacy of mometasone in doses of 100-400 μg qd for the treatment and maintenance treatment of symptoms of PAR.
3. A proportional increase incidence in overall adverse events with increasing mometasone dose (100, 200, and 400 μg qd); in particular, coughing, epistaxis, and sinusitis, was reported in study I93-018.

8.16. Trial I93-180. Assessment by Nasal Biopsy of Long-term Safety of Mometasone Furoate Aqueous Nasal Spray vs. Fluticasone Proprionate (Flixonase) in Perennial Rhinitis Patients (PAR).

Investigators: Stephen R. Durham, M.D., Robert J. Davies, M.D., and Valerie J. Lund, M.D.

Participating Centers: 3 Centers in the U.K.

8.16.1. OBJECTIVES:

1. To assess the effects of long-term treatment with mometasone furoate nasal spray (200 μg qd) vs. fluticasone propionate nasal spray (200 μg qd), on the nasal mucosa of PAR subjects, using nasal biopsy results.
2. To evaluate long-term efficacy of mometasone aqueous nasal spray in the treatment of symptoms of PAR (efficacy assessment was not the primary objective of this study).

8.16.2. STUDY DESIGN:

This was a randomized, multi center, open-label, active-controlled, parallel group trial in adult subjects with perennial allergic rhinitis to investigate the effect of mometasone 200 μg qd administered for 12 months on nasal mucosa. Nasal biopsies were performed pre- and post-treatment for both treatment groups; for each treatment subject one nostril was biopsied at baseline and the other was biopsied at the final visit. A separate group of healthy (i.e. non-allergic) subjects did not receive any treatment, but underwent nasal biopsy at baseline and after 12 months to assess biopsy sampling technique artifacts [283:10, 284:595].

8.16.3. PROTOCOL:

8.16.3.1.a. POPULATION:

Entry criteria for this study were the following: (1) age ≥ 18 years [283:14, 284:595, 597], (2) presence of IgE-mediated hypersensitivity to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 1 year of study entry via the prick testing or intradermal method [283:14, 284:597], and (3) a history of mild to moderate PAR for at least 1 year with sufficient symptoms at screening and baseline (i.e. a total nasal symptom score ≥ 4)[283:21-22, 284:596, 597]. Normal subjects must have been non-allergic by history in order to be study enrollable, with nasal mucosa of normal appearance on physical examination [283:12-13, 284:598].

8.16.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Tables 1.a. (for active treatment subjects) and 1.b. (for normal controls) of Trial I93-180

treatment subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Week 5 (Visit 3), 9 (Visit 4), 13 (Visit 5), 25 (Visit 6), 37 (Visit 7), and 53 (Visit 8) of therapy [283:11, 284:596, 601]. Normal control subjects were assessed at screening (Visit 1), baseline (Visit 2), and Week 53 (Visit 8) [283:10-11]. The discrepancy of the 1 week extension of this study compared with previous PAR studies was in order to account for the 1 additional week between the baseline nasal biopsy and the initiation of treatment (to allow time for healing of the nasal biopsy site) [283:11].

All subjects (active drug and normal control subjects) underwent routine screening during Visit 1 where a history and physical examination (including nasal exam), an assessment of the severity of subject PAR symptoms (according to a 0-3 severity scale, as per subject and physician evaluations), lab tests, and a screening ECG was performed [283:20-21, 284:603-604]. On the second study visit (baseline visit) approximately one week later, subject PAR symptom scores were re-evaluated, along with adverse events and concomitant medications. Study enrollable subjects were randomized to one of the following 4 treatment sequences, and along with normal control subjects, underwent a baseline nasal biopsy [283:21, 284:585, 605-607]:

		BIOPSY SITE SEQUENCE	
		BASELINE	FINAL VISIT
(A)	**Mometasone nasal spray 200 µg qd**	LEFT	RIGHT
(B)	**Mometasone nasal spray 200 µg qd**	RIGHT	LEFT
(C)	**Fluticasone nasal spray 200 µg qd**	LEFT	RIGHT
(D)	**Fluticasone nasal spray 200 µg qd**	RIGHT	LEFT

Subjects in the mometasone and fluticasone treatment groups began therapy, administered once daily each a.m., one week (7 days) following the baseline visit [283:22, 284:606]. The normal control subjects did not undergo any further testing or follow-up except for a follow-up nasal biopsy 12 months later [283:22, 284:606]. Subjects in the 2 active treatment groups were allowed use of rescue medication (not specified in protocol but to exclude all steroids) for relief of intolerable PAR symptoms [284:606]. Of note, eye examinations to assess glaucoma/cataract formation and assessments of HPA-axis suppression were not performed in this study. For study Visits 3-8, active treatment group subjects underwent routine re-assessment of their PAR status and any adverse events, along with a follow-up nasal exam, and on Visits 5-8, had follow-up lab tests [283:22-26, 284:607-609, 614-616]. Efficacy evaluation and overall condition of PAR was again based on a 0-3 severity scale [283:24, 284:610] and a 1-5 scale of therapeutic response [283:24, 284:610-611].

efficacy variables consisted of: (1) physician and (2) subject evaluations of overall condition and (3) physician and (4) subject evaluations of therapeutic response in the ITT population, as compared to baseline [283:35-36, 284:617]. Pollen counts were not collected in this study. Rescue medication use between the 2 treatment groups was not analyzed in any manner in this study (data not provided in the submission), thus making it difficult to reach any solid conclusions about clinical efficacy of the different treatments evaluated in this study.

A comparative (qualitative) study evaluating differences in nasal mucosal histology between steroid treated allergic subjects (mometasone and fluticasone subjects) and normal 'non-allergic' controls was performed in order to assess any long-term effects of mometasone treatment on nasal epithelium and the degree of study artifact (reason for normal control subjects). Using paraffin embedded, blinded, nasal biopsy specimens obtained from mometasone, fluticasone, and normal control subjects at baseline and at 12 months of the study, a number of histologic parameters were evaluated via light microscopy: (1) epithelial thickness, (2) cross-sectional area/mm of basement membrane, (3) epithelial phenotype: the percentage (%) of epithelium that was composed of basement membrane (BM) only, BM plus basal cells, BM plus columnar cells, and intact epithelium (including cilia), (4) degree of epithelial integrity, atrophy, and presence/absence of metaplasia, (5) extent of eosinophilia, and (6) extent of inflammatory cell infiltration (note: 'inflammatory' cells were defined in this study as comprising lymphocytes, monocytes, plasma cells, and neutrophils, in addition to eosinophils) [283:31-32, 35, 284:576-579, 611-612, 638-639]. For these parameters, a 2-way ANOVA extracting sources of variation due to treatment, center, and treatment by center interaction was used to compare treatment groups.

8.16.4. RESULTS

8.16.4.1.a. Efficacy

A total of 145 subjects with PAR were randomized into study I93-180, with 4 immediate dropouts after the baseline visit (3 subjects in the mometasone group and 1 subject in the fluticasone group; these subjects did not receive any study drug [283:38]), leaving 141 subjects in the ITT population [283:38]. Sixty-nine (69) subjects in the ITT population received mometasone and 72 subjects received fluticasone [283:38]. Six of the 30 normal control subjects were excluded from the study because they dropped out of the study immediately after the baseline visit [283:38-39]. The attrition rates for study subjects by Week 53 of study I93-180 were quite high, with 21.7% (15/69) of mometasone subjects, 19.7% (14/71) of fluticasone subjects, and 20% (6/30) of normal control subjects discontinuing treatment by this study endpoint [283:163, 170].

The treatment groups in this study were comparable with regard to demographic and disease characteristics with the exception of a statistically

with respect to age which nonetheless, did not affect treatment inferences (mean age of the mometasone subjects=30 years vs. mean age of the fluticasone subjects=34 years; p=0.02) [283:36, 40]. Again, for both active treatment groups, the majority of subjects were Caucasian. The distribution of male and female subjects in each of the 2 treatment groups was approximately equal. Approximately 50% or more of study subjects in both treatment groups had SAR in addition to PAR. The majority (76-84%) of study subjects were non-smokers. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a significant difference between the 2 treatment groups, with the majority of subjects in both groups having 'moderate' PAR symptoms at baseline [283:43].

Analysis of the efficacy variables for the ITT population showed that overall, subjects in the 2 active treatment groups demonstrated an improvement in symptoms which was maintained for the study duration. For the physician's evaluation of the overall condition of PAR, subjects in the mometasone and fluticasone treatment groups demonstrated an improvement by Week 5 of the study which was similar between the 2 treatment groups in terms of raw symptom scores and change in scores (and was additionally supported by the majority of subjects having 'mild' PAR symptoms) and this improvement was maintained through the Week 53 visit [283:163-164]. Since the study was not designed to determine clinical efficacy prior to the Week 5 visit, no conclusion can be made whether mometasone subjects might have demonstrated a statistically significant therapeutic response prior to Week 5 of treatment, as compared with placebo. Subjects' self-evaluation of the overall condition of PAR paralleled that of the physician evaluation; namely that improvement in symptoms was noted by Week 5 of the study (supported by the majority of subjects rating their overall PAR condition as 'mild') and was maintained throughout the study duration [283:170-171]. Both of these findings support maintenance of a therapeutic effect for mometasone and fluticasone throughout the open-treatment period. Physician evaluation of subjects' therapeutic response to treatment (1-5 scale) indicated that the majority of subjects in the 2 treatment groups experienced moderate-complete relief of PAR symptoms starting at Week 5 of the study and which continued throughout the open-treatment period, again providing evidence of maintenance of a therapeutic effect throughout the study duration [283:177-178]. Subjects' evaluation of the therapeutic response paralleled the physician evaluation of subjects' therapeutic response with the majority of study subjects reporting moderate-complete relief in PAR symptoms by Week 5 of treatment [283:182-183]. Again, this response was maintained for the study duration.

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

Table I. **Efficacy Variables of PAR and Treatment with Mometasone 200 µg qd and Fluticasone 200 µg qd** (ITT Population), [283:44-45, 47-48, 50-53, 163-164, 170-171, 177-178, 182-183]

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

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

8.16.4.1.b. Nasal Biopsy Studies [283:67-78, 287:1606-1643]:

Analysis of nasal biopsy histology obtained from 101 active medication subjects pre- and post-treatment (46 mometasone subjects and 55 fluticasone subjects) and 24 normal control subjects indicates that overall there was no marked change in any of the parameters for the active treatment groups and no statistically significant difference between mometasone and fluticasone for any of the parameters examined. Furthermore, there appeared to be no inter-site differences in the appearance of the specimens, nor any differences with regard to gender or race in terms of the specific histologic features. Importantly, steroid (mometasone or fluticasone) treatment failed to demonstrate epithelial atrophy, and indeed appeared to improve epithelial integrity (epithelial 'intactness' which increased from 56.9% to 70.6% in the mometasone group and from 45.5% to 66.0% in the fluticasone group) following treatment for 12 months [283:73, 287:1609]. Mometasone treatment also appeared to normalize the epithelium of allergic rhinitis subjects to comprise a slightly higher % of ciliated stratified columnar epithelial cells and to decrease the degree of focal squamous metaplasia in nasal tissue after treatment [283:73, 287:1607, 1609]. For both mometasone and fluticasone treated subjects, the extent of intra-epithelial eosinophilia and inflammatory cell infiltration (lymphocytes, monocytes, plasma cells, and neutrophils) also decreased post-treatment at 12 months, consistent with known mechanisms of action of steroids in decreasing allergic inflammation (especially eosinophil and lymphocyte trafficking) [287:1609-1610]. A summary of nasal biopsy findings is summarized in Table 22 of the NDA submission [283:76-77] or Vol. 287:1609-1610

8.16.4.3. ADVERSE EVENTS:

The safety analysis was based on 141 subjects in the ITT population: 69 subjects were treated with mometasone 200 µg qd and 72 subjects were treated with fluticasone [283:38, 188]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, an ECG (at screening only), physical, nasal, and clinical laboratory tests relative to baseline [283:25-26, 284:603-604].

Adverse events were similar for the 2 active treatment groups, with viral infection being the most frequently reported treatment-related adverse event. Overall, adverse events were reported in 90% of subjects in the mometasone 200 µg qd treatment group and 92% of subjects treated with fluticasone 200 µg qd treatment group [283:55, 188].

The most frequently reported adverse event was headache, reported by 43% of subjects in the mometasone treatment group and 49% of subjects in the fluticasone treatment group [283:56, 188, 286:1113-1134, 287:1271-1297]. Headache was followed by viral infection as the second most frequently reported adverse event; reported in 32% of mometasone subjects, compared to 38% of fluticasone subjects [283:57, 193, 286:1191-1199, 287:1353-1362]. Reported next in frequency was epistaxis; with 17% of subjects in the mometasone group and 14% of subjects in the fluticasone group recording this adverse event [283:57, 193, 286:1208-1213, 287:1368-1372]. Pharyngitis was reported in 14% of mometasone subjects, and 15% of fluticasone subjects [283:57, 194].

There were no reports of nasal septal perforation in either of the 2 active treatment groups although nasal ulcers were reported in one subject in the mometasone treatment group on Visit 6 (subject I93-180-02, #055) [289:2345] and 2 subjects in the fluticasone treatment group (subject I93-180-01, #004 and #032) on Visit 8 of the study [289:2270, 2291]. Again, no assessments of HPA-axis suppression or glaucoma/cataract formation were performed in this study. No deaths were reported in any of the 2 active treatment groups.

In terms of infection, viral infection was the second most frequently reported ADR in the study for both active treatment groups with a reported incidence of 32% in mometasone treated subjects and 38% in fluticasone treated subjects [283:59, 193]. In this study there was one report of herpes simplex labialis in a fluticasone treated subject (at Visit 5, no reports for mometasone subjects) and two reports of nasal candidiasis in mometasone treated subjects (subject I93-180-02, #051 at Visit 7 and subject I93-180-02, #038 at Visit 4) which were not recorded in the NDA submission as adverse events [283:59, 83, 193, 289:2309, 2331, 287:1345]. Furthermore, one subject in the mometasone treatment group was reported to develop pneumonia during Visit 6 of the study (subject I93-180-03, #008) which was not felt to be related to study medication by the principal investigator [283:193, 286:1220].

A total of 7 subjects discontinued treatment because of adverse events (4 subjects in the mometasone group, and 3 subjects in the fluticasone group) [283:65-66]. The most common reason for discontinuation that was considered

nasal burning. Otherwise, most subject discontinuations due to ADRs (arthritis, pneumonia) were considered unrelated to treatment by the principal investigator.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 2 treatment groups with the exception of several reports of elevated LFTs and one report of a decrease in the WBC. Two subjects total developed elevated LFTs; in 1 case this may have been possibly related to study medication (subject I93-180-01, #018 who received mometasone 200 µg qd and developed an increase in the SGOT from 43 IU/L at screening to 181 IU/L at Visit 7 (Week 37) with a decrease to 54 IU/L by the final visit (normal SGOT range 7-56 IU/L) [283:81, 284:310]. The other mometasone treated subject with normal LFTs on screening (subject I93-018-02, #005, SGOT at screening=31 IU/L and SGPT at screening=24 IU/L) developed an elevated SGOT and SGPT (to 192 IU/L and 372 IU/L, respectively) by Visit 6 of the study, which were attributed to alcohol consumption and which returned to within a normal range on re-testing 3 weeks later [283:81, 284:310]. One subject in the mometasone group (subject I93-180-02, #031) was reported to have a decreased WBC to 2.7 x 10^3/mm^3 (normal range: 3.5-10.8 x 10^3/mm^3) on Visit 7 from a screening value of 4.9 x 10^3/mm^3, which subsequently returned to within the normal range (5.4 x 10^3/mm^3) by Visit 8 [283:82, 284:310]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change with the exception of a slight shift in SGOT values to the high normal range for mometasone treated subjects as compared with fluticasone treated subjects (22% of mometasone subjects vs. 10% of fluticasone treated subjects [284:479]. Adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects <18 or > 65 years of age was too small to draw meaningful conclusions.

8.16.5. CONCLUSIONS:

1. The results of this study support the safety of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 52 weeks (1 year) in subjects with PAR.
2. While not specifically designed to evaluate efficacy, assessment of subject overall condition and response to treatment with mometasone over 52 weeks (by study subjects and their respective physicians), supports the efficacy of mometasone 200 µg qd for the treatment and maintenance treatment of symptoms of PAR.
3. Overall, long-term (12 month) treatment with mometasone did not demonstrate any histologic evidence of worsening nasal atrophy or ulcer formation. Indeed, treatment with mometasone (and fluticasone) appeared to improve nasal epithelial integrity and decrease the number of intra-epithelial eosinophils, lymphocytes, monocytes, plasma cells, and

however, is observational at best, and does not necessarily correlate with clinical benefit.

8.17. Trial C94-052. A Long-term Safety Study of Mometasone Furoate Aqueous Nasal Spray vs. Triamcinolone Acetonide (Nasacort) in Perennial Rhinitis (PAR).

Principal Investigator: Donald W. Aaronson, M.D.

Participating Centers: 20 Centers in the U.S.

8.17.1. OBJECTIVES:

1. To assess the safety effects of long-term treatment with mometasone furoate nasal spray (200 μg qd) vs. triamcinolone acetonide nasal spray (220 μg qd), on PAR subjects.
2. To evaluate long-term efficacy of mometasone aqueous nasal spray in the treatment of symptoms of PAR (efficacy assessment was not the primary objective of this study).

8.17.2. STUDY DESIGN:

This was a randomized, multi-center, open-label, active-controlled, parallel group trial in adult subjects with perennial allergic rhinitis to investigate the long-term safety profile of mometasone 200 μg qd administered for 12 months, focusing on HPA-axis suppression through evaluation of 24 hr urinary cortisol levels and serum cortisol levels 45-60 minutes post-Cortrosyn stimulation with 250 μg cosyntropin.

8.17.3. PROTOCOL:

8.17.3.1.a. POPULATION:

Entry criteria for this study were the following: (1) age ≥ 12 years [262:12, 14, 266:926, 928], (2) presence of IgE-mediated hypersensitivity to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 1 year of study entry via the prick testing or intradermal method [262:14, 20, 266:928], (3) a history of PAR for at least 2 years with sufficient symptoms at screening and baseline (i.e. a total nasal symptom score ≥ 5, nasal congestion and/or rhinorrhea score ≥ 2) [262:14, 20, 22, 24-45, 266:926, 928], (4) evidence at screening of a normal morning (8 a.m. ± 1 hour) cortisol level (≥ 5 μg/100 ml) and a positive response to Cortrosyn stimulation with 250 μg cosyntropin (defined as an increase in serum cortisol level ≥ 7 μg/100ml from baseline 45-60 minutes after Cortrosyn stimulation) [262:14, 266:928, 934, 935], and (5) at study sites -01, -05, -06, and -011, laboratory evidence of a creatinine level within normal limits in study enrollable subjects [262:14, 266:928].

8.17.3.1.b. PROCEDURE:

of Trial C94-052 in the NDA submission [262:13, 266:965]. Mometasone and triamcinolone treatment subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Week 1 (Visit 3), 4 (Visit 4), 12 (Visit 5), 24 (Visit 6), 36 (Visit 7), and 52 (Visit 8) of therapy [262:12, 30, 266:927].

All subjects underwent routine screening during Visit 1 where a history and physical examination (including nasal exam), an assessment of the severity of subject PAR symptoms (according to a 0-3 severity scale, as per subject and physician evaluations), lab tests (including basal serum cortisol levels and serum cortisol levels post-Cortrosyn testing), and a screening ECG was performed [262:20-21, 266:927, 933-935]. At study sites -01, -05, -06, and -011, 24 hour urinary free cortisols and creatinine were additionally measured, along with plasma mometasone concentrations [262:21, 266:927, 934]. On the second study visit (baseline visit) approximately one week later, subject PAR symptom scores were re-evaluated, along with adverse events and concomitant medications, and study enrollable subjects were randomized to one of the following 2 treatments [262:15-18, 21-22, 266:926, 935-937]:

TREATMENT	
(A)	Mometasone nasal spray 200 µg qd q a.m.
(B)	Triamcinolone nasal spray 220 µg qd q a.m.

Subjects in the mometasone and triamcinolone treatment groups began therapy, administered once daily each a.m. [262:22, 266:927, 936-937]. Subjects in the 2 treatment groups were allowed use of rescue medication (not specified in the protocol but to exclude all steroids) for relief of intolerable PAR symptoms but were discouraged from taking other medications for their 'nasal' symptoms [262:19, 266:930-931]. For study Visits 3-8, subjects underwent routine re-assessment of their PAR status and any adverse events, along with a follow-up nasal exam, and on Visits 5-8, had follow-up lab tests, (including follow-up serum cortisol levels and post-Cortrosyn testing cortisol levels on Visits 5, 6 and 8, along with repeat plasma mometasone measurements) [262:22-23, 26-29, 31, 266:938-94-945]. Subjects at study sites -01, -05, -06, and -011 underwent repeat 24 hour urine collection prior to study Visits 5, 6, and 8 [262:23, 31-32, 266:940]. Efficacy evaluation and overall condition of PAR was again based on a 0-3 severity scale [262:24-25, 266:942] and a 1-5 scale of therapeutic response [262:25, 266:943].

A primary efficacy variable was not defined in this study, as assessment of clinical efficacy was not a primary objective of this study. Supplementary efficacy variables consisted of: (1) physician and (2) subject evaluations of overall condition and (3) physician and (4) subject evaluations of therapeutic response in the ITT population, as compared to baseline which were analyzed by 2-way ANOVA [262:37, 266:947]. Pollen counts were not collected in this study. Rescue

this study (data not provided in the submission), thus making it difficult to reach any solid conclusions about clinical efficacy of the different treatments evaluated in this study.

Evaluation of plasma cortisol levels involved calculating the difference in plasma levels from screening [262:32, 266:946]. Analyses of urinary free cortisol levels were based on subjects (from centers -01, -05, -06, -011) whose creatinine value at a given visit was within 35% of the value at screening (subjects who failed this criterion were requested to collect another 24 hour urine for re-analysis) [262:31-21, 34, 266:940-941]. For the pre-cortrosyn value, post-cortrosyn value, the difference between post- and pre-cortrosyn values, and the change from screening in the difference between the post- and pre-cortrosyn values, treatment groups were compared using a 2-way ANOVA, extracting sources of variation due to treatment, center, and treatment by center interaction [262:36,266:946].

8.17.4. RESULTS

8.17.4.1.a. Efficacy

A total of 351 subjects with PAR were randomized into study C94-052, with no study dropouts, leaving 351 subjects in the ITT population [262:39]. One hundred and seventy-five (175) subjects in the ITT population received mometasone and 176 subjects received triamcinolone [262:39]. An efficacy evaluable population was not analyzed in this study [262:39]. The attrition rates for study subjects by Week 52 of study C94-052 were marginally acceptable, with 14.3% (25/175) of mometasone subjects and 13.1% (23/175) of triamcinolone subjects discontinuing treatment by this study endpoint [262:205].

The treatment groups in this study were comparable with regard to demographic and disease characteristics [262:40]. For both active treatment groups, the majority of subjects were Caucasian and female. Approximately 80% of study subjects in both treatment groups had SAR in addition to PAR. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a significant difference between the 2 treatment groups, with the majority of subjects in both groups having 'moderate' PAR symptoms at baseline [262:43].

Analysis of the efficacy variables for the ITT population showed that overall, subjects in the 2 active treatment groups demonstrated an improvement in PAR symptoms which was maintained for the study duration. For the physician's evaluation of the overall condition of PAR, subjects in the mometasone and triamcinolone treatment groups both demonstrated an improvement by Week 1 post-initiation of treatment which was very similar between the 2 treatment groups in terms of raw symptom scores and change in scores (and was additionally supported by the majority of subjects having 'mild' PAR symptoms) and this improvement was maintained through the Week 52 visit [262:205-206]. Subjects'

evaluation; namely that improvement in symptoms was noted by Week 1 of the study (supported by the majority of subjects rating their overall PAR condition as 'mild') and was maintained throughout the study duration [263:248-249]. Both of these findings support maintenance of a therapeutic effect for mometasone and triamcinolone throughout the open-treatment period. Physician evaluation of subjects' therapeutic response to treatment (1-5 scale) indicated that the majority of subjects in the 2 treatment groups experienced moderate-marked relief of PAR symptoms starting at Week 4 (Visit 4) of the study and which continued throughout the open-treatment period, again providing evidence of maintenance of a therapeutic effect throughout the study duration [263:289-290]. Subjects' evaluation of the therapeutic response paralleled the physician evaluation of subjects' therapeutic response with the majority of study subjects reporting moderate-complete relief in PAR symptoms by Week 4 of treatment [263:328-329]. Again, this response was maintained for the study duration.

While this trial was not blinded and hence not designed to provide enough power to conduct inferences on efficacy, results of these supplementary analyses nonetheless provide supportive information that mometasone is effective in the treatment of symptoms of PAR. Overall, subject and physician rated response of PAR symptoms to treatment were very similar between the mometasone and triamcinolone groups. Results of the 4 efficacy variables for the mometasone and triamcinolone treatment groups are summarized in Table I. below.

Table I. Efficacy Variables of PAR and Treatment with Mometasone 200 µg qd (ITT Population), [262:205-206, 263:248-249, 289-290, 329-329]

EFFICACY VARIABLE	Improvement in PAR symptoms throughout study duration: Mometasone 200 µg qd: (Yes/No)	Improvement in PAR symptoms throughout study duration: Triamcinolone 220 µg qd: (Yes/No)
1. Physician's evaluation of subject overall PAR condition compared to baseline	Yes	Yes
2. Subject self evaluation of overall PAR condition compared to baseline	Yes	Yes
3. Physician evaluated response to Rx compared to baseline	Yes	Yes
4. Subject self-evaluated response to Rx compared to baseline	Yes	Yes

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

8.17.4.1.b. Mometasone Bioavailability

Plasma mometasone levels were measured on the Screening Visit and on Visits 5, 6 and 8 (weeks 12, 24, and 52) in study subjects for study sites: -01, -05, -06, and -011 using a HPLC/mass spectrometry method (Phoenix International Life Sciences, Inc.) to determine the concentration of mometasone furoate in human plasma. The lower limit of quantitation of mometasone via this assay method was 50.1 pg/ml while the upper limit of quantitation was 5005 pg/ml [266:1222]. Based on this method, mometasone furoate levels were detected in 4 out of 169 plasma samples analyzed, 3 of which were near the limit of assay quantitation. In all other samples analyzed, mometasone concentrations were below the limit of quantitation [266:1246-1249]. Of note, all 3 subjects in whom mometasone levels were detected were from site -05. Subject findings are summarized in table II. below [262:83]:

Table II. Plasma Mometasone Concentration in PAR Subjects [262:83]:

SUBJECT	SAMPLE TIMEPOINT	Plasma Mometasone Concentration (pg/ml)
C94-052-05, #020	Week 12	58.7
C94-052-05, #023	Week 12	66.1
C94-052-05, #023	Week 24	57.1
C94-052-05, #013	Week 24	*1454

*Presumed pharmacokinetic outlier.

In summary, the levels of mometasone detected in subject plasma samples were less than twice the limit of quantitation in 3/4 subjects, thus providing evidence that systemic bioavailability of mometasone administered at a dose of 200 µg qd to PAR subjects had negligible bioavailability. These findings are consistent with mometasone's overall safety profile in adult SAR and PAR subjects along with previous human PK findings with mometasone administration, as reported in this NDA submission.

8.17.4.3. ADVERSE EVENTS:

The safety analysis was based on 351 subjects in the ITT population: 175 subjects were treated with mometasone 200 µg qd and 176 subjects were treated with triamcinolone 220 µg qd [283:38, 188]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, an ECG (at screening only), physical exam (including nasal exam), and clinical laboratory tests (including plasma cortisol levels pre- and post-cosyntropin stimulation prior to initiation of steroid treatment) on the Screening visit and on Weeks 12, 24, and 52 post-treatment along with a measurement of 24 hour urinary free cortisol levels in a subset of study subjects at these same respective study visits (at study sites -01, -

Adverse events were similar for the 2 active treatment groups, with headache being the most frequently reported treatment-related adverse event. Overall, adverse events were reported in 88% of subjects in the mometasone 200 µg qd treatment group and 88% of subjects in the triamcinolone 220 µg qd treatment group [262:55, 263:367].

The most frequently reported adverse event was headache, reported by 45% of subjects in the mometasone treatment group and 41% of subjects in the triamcinolone treatment group [262:55, 263:368, 269:2404-2505, 270:2837-2942]. Headache was followed by upper respiratory infection as the second most frequently reported adverse event; reported in 30% of mometasone subjects, compared to 36% of triamcinolone subjects [262:56, 263:376, 270:2755-2773, 271:3182-3206]. Reported next in frequency was sinusitis; with 26% of subjects in the mometasone group and 16% of subjects in the triamcinolone group recording this adverse event [262:56, 263:376, 270:2737-2751, 271:3164-3175]. Viral infection was reported in 23% of mometasone subjects and 19% of triamcinolone subjects [262:56, 263:375, 269:2657-2668, 271:3089-3100]. Epistaxis and pharyngitis were reported in 17% of mometasone subjects, and in 13% and 14%, respectively of triamcinolone subjects [262:56, 263:375, 376, 271:2696-2706, 2717-2726, 271:3121-3129, 3141-3151]. Interestingly, for this study musculoskeletal pain was reported in 18% of mometasone subjects and in 15% of triamcinolone subjects [262:55, 253:372, 269:2588-2611, 271:3025-3045].

There were no reports of nasal septal perforation in either of the 2 treatment groups although an erosion of the right nasal septum was reported in one subject in the mometasone treatment group on Visit 8 (Week 52) (subject C94-052-13, #002) [272:4275] and a minimal abrasion of the left nasal septum was reported in 1 additional mometasone subject on Visit 8 of the study (subject C94-052-14, #014) [272:4279]. No assessments of glaucoma/cataract formation were performed in this study. No deaths were reported in any of the 2 active treatment groups.

In terms of infection, viral infection was reported in 23% in mometasone treated subjects and 19% in triamcinolone treated subjects [262:56], hence comparable in frequency to the incidence cited for the other PAR studies in this NDA submission. In this study there were 2 reports of herpes simplex labialis in triamcinolone treated subjects (no reports for mometasone subjects) and no reports of oral or nasal candidiasis in any study subjects that were associated with treatment [263:374]. Furthermore, 1 subject in both the mometasone and the triamcinolone treatment group were reported to develop pneumonia (subject C94-052-02, #016 and -10, #008) however, these occurred during the baseline visit and were not felt to be related to study medication by the principal investigator(s) [270:2727, 271:3152].

A total of 10 subjects discontinued treatment because of adverse events (4 subjects in the mometasone group, 6 subjects in the triamcinolone group)

probably related' to mometasone treatment involved headache, epistaxis, or rhinitis.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal septal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 2 treatment groups with the exception of one report of hyperglycemia (glucose=265 mg/dL on week 24, subject C94-052-01, #018) in a non-insulin dependent diabetic and 1 report of a decrease in the WBC (to 2.88 x $10^3/\mu L$ on week 24 though the subject's screening WBC was the same value, subject C94-052-13, #002) in mometasone treatment subjects [262:81-82, 264:516]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change with the exception of a slight shift in glucose values to the normal-high range for triamcinolone treated subjects as compared with mometasone treated subjects (7% of triamcinolone subjects vs. 3% of mometasone treated subjects [262:80, 265:773] and a slight shift in the WBC to the low-normal range in both treatment groups [265:791]. Adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects <18 or > 65 years of age was too small to draw meaningful conclusions.

8.17.4.3.b. Hypothalamic Pituitary Adrenal (HPA) Axis Suppression Studies [263:472-473, 264:496-497]:

Analysis of HPA function was performed using 2 methods in this study: (1) Cortrosyn testing (cosyntropin stimulation) after baseline plasma cortisol levels were obtained and (2) 24 hour free urinary free cortisol levels pre- and post-treatment with mometasone and triamcinolone. Of note, if a subject's creatinine value at a given visit was not within 35% of the value at screening, then the subject was excluded from the analyses of urinary free cortisol for that visit [262:32].

Cortrosyn stimulation tests revealed small but inconsistent changes in the plasma cortisol post-stimulation with cosyntropin, as compared to screening values for both treatment groups in pooled data for all subjects tested which are summarized in Table III. [263:472]. Furthermore, no statistically significant difference was detected between the 2 steroid treatments. Analysis of the distribution of plasma cortisol levels between the 2 treatment groups showed that similar to screening plasma values post-cosyntropin, the majority (i.e. > 90%) of subjects demonstrated a ≥ 7 µg/100 ml increase in plasma cortisol levels post-cosyntropin administration, indicating that for pooled data, no evidence of HPA-axis suppression was evident at either week 12, 24, or 52 of the study [263:473]. The sponsor states that 1-2 subjects per treatment group had an abnormal response in Cortrosyn stimulation testing post-initiation of treatment but no subject had more than one abnormal response [262:78]. An important flaw and limitation in analysis of pooled data is that pooling tends to obscure abnormal response to Cortrosyn testing in individual subjects which may have laboratory evidence of

positive effect on the HPA-axis in these subjects.

Table III. **Cortrosyn Stimulation Test Result Summary**: Mean Plasma Cortisol Levels, Pre- and Post-Treatment with Mometasone and Triamcinolone and Mean Change (Δ) from Screening (ITT) [262:78, 263:472]

	MOMETASONE			TRIAMCINOLONE			
	n	Mean Plasma Cortisol (µg/dL)	Δ from screening (µg/dL)	n	Mean Plasma Cortisol (µg/dL)	Δ from screening (µg/dL)	[1]P-value
Screening	168	Pre: 16.60 Post: 31.93	NA	168	Pre: 16.70 Post: 32.31	NA	0.64
WEEK 12	167	Pre: 17.39 Post: 31.85	-0.88	167	Pre: 17.12 Post: 32.03	-0.71	0.81
WEEK 24	158	Pre: 17.71 Post: 33.16	0.05	162	Pre: 17.44 Post: 33.14	0.15	0.97
WEEK 52	148	Pre: 17.69 Post: 31.66	-1.48	152	Pre: 16.80 Post: 31.12	-1.15	0.33
ENDPOINT	168	Pre: 17.38 Post: 31.42	-1.30	168	Pre: 16.76 Post: 31.39	-0.98	0.51

NA=Not applicable

[1]P-value for mometasone vs. placebo, α=0.05, 2-way ANOVA.

Evaluation of the 24 hour urinary free cortisol levels at study sites -01, 05, 06, and -011 using pooled data from these sites also failed to reveal an effect or a consistent trend post-treatment in decreasing urinary cortisol levels [264:496], although again pooling of data would be less likely to capture abnormal HPA-axis function in individual subjects. Also of note, a number of subjects failed to have a creatinine value at the respective study visit during which 24 hour urinary free cortisols were collected that was 35% of the value at screening, hence these subjects were excluded from data analysis of the 24 hour urinary free cortisol levels for that visit. As discussed with Ms. Paula Rinaldi, Regulatory Affairs of Schering Plough, Inc. on 08/29/97, the mean screening value for 24 hour urinary free cortisol values was modified to reflect only those subjects that were used in the data analysis for that study visit, i.e. those subjects with a serum creatinine ≥ 35% of the screening value. Results of these modified 24 hour urinary free cortisol levels (taking into account screening 24 hour urinary free cortisol values based on subjects with serum creatinine's ≥ 35% of the screening value) are summarized in Table IV.

Table IV. **24 Hour Urinary Free Cortisol Analysis:** Mean and Mean Change from Screening (ITT Population, study C94-052)
[264:496, FAX Schering Plough, Inc., 08/29/97]

	MOMETASONE		TRIAMCINOLONE		
	n	Mean Urinary Cortisol (µg/day)	n	Mean Urinary Cortisol (µg/day)	[1]P-value
Screening (all subjects)	44	25.63	42	24.17	0.53
Screening WEEK 12 Change	31 31 31	25.13 28.52 3.38	23 23 23	23.61 20.61 -3.00	 0.41 0.43
Screening WEEK 24 Change	28 28 28	23.76 22.90 -0.85	27 27 27	26.16 26.22 0.06	 0.27 0.52
Screening WEEK 52 Change	24 24 24	20.21 20.07 -0.15	24 24 24	22.32 21.49 -0.83	 0.48 0.83
Screening ENDPOINT Change	27 27 27	20.05 20.80 0.75	28 28 28	21.95 22.45 0.49	 0.45 0.94

Study performed at sites -01, -05, -06, and -11. Only subjects with a creatinine ≥ 35% of the screening value were used to determine the screening mean 24 hour urinary free cortisol level used to calculate the change in 24 hour urinary free cortisol.
[1]P-value for mometasone vs. triamcinolone (for treatment difference), α=0.05, 2-way ANOVA..

Review of the subject line listings submitted 07/14/97 per FDA request by the Sponsor indicates that a total of 10 mometasone treatment group subjects failed to have a > 7 µg/dL increase in plasma cortisol post-cosyntropin stimulation after having received at least 12 weeks (or more) of mometasone treatment (13 triamcinolone treated subjects had similar findings) Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, Study Report C94-052, p. 1-55]. Nonetheless, in 9 of the 10 mometasone subjects, all plasma cortisol levels were > 18 µg/dL, indicative of adequate adrenal function. In one subject (subject C94-052-16, #008), plasma cortisol levels pre and post-ACTH stimulation were 15.7 µg/dL and 12.9 µg/dL, respectively, indicative of a blunted adrenal response (of note, one triamcinolone subject (subject C94-052-16, #002) also had a blinded adrenal response). Overall, however, these data indicate that for the majority of subjects, treatment with mometasone 200 µg qd is unlikely to result in either subclinical or clinically significant adrenal suppression.

8.17.5. CONCLUSIONS:

1. The results of this study support the safety of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 52 weeks (1 year) in subjects with PAR.
2. While not specifically designed to evaluate efficacy, assessment of subject overall condition and response to treatment with mometasone over 52 weeks (by study subjects and their respective physicians), supports the efficacy of mometasone 200 µg qd for the treatment and maintenance treatment of symptoms of PAR.
3. Mometasone administration for up to 52 weeks in PAR subjects did not appear to cause HPA-axis suppression in mometasone treated subjects collectively as a group, as assessed via Cortrosyn stimulation testing of adrenal function and via 24 hour urinary cortisol levels on pooled data.
4. Plasma levels of mometasone in PAR subjects from 4 study sites at steady state were undetectable in the majority of subjects analyzed. Of those subjects who were found to have measurable mometasone levels, in 3 of these 4 subjects these were minimally higher than the lower limit of quantitation.

APPEARS THIS WAY
ON ORIGINAL

8.18. Trial C94-092. Safety and Efficacy of Mometasone Furoate Nasal Spray vs. Placebo in the Treatment of Elderly Patients with Perennial Allergic Rhinitis (PAR).

Principal Investigator: None (Multi-center study)

Participating Centers: 24 centers in the U.S.

8.18.1. OBJECTIVES:

1. To evaluate the safety and efficacy of mometasone furoate aqueous nasal spray 200 μg qd in the treatment of symptoms of perennial allergic rhinitis (PAR) in elderly (≥ 65 years of age) subjects.

8.18.2. STUDY DESIGN:

The study was a phase III, randomized, multicenter, double-blind, placebo-controlled, parallel group study with a single-blind, placebo run-in phase (7-14 days) to determine the safety and efficacy of mometasone furoate 200 μg administered intranasally once daily (qd) vs. placebo for a total of 12 weeks for the treatment of perennial allergic rhinitis in subjects ≥ 65 years of age.

8.18.3. PROTOCOL:

8.18.3.1.a. POPULATION:

Entry criteria for this study were the following: (1) age ≥ 65 years [229:13, 15, 231:791], (2) presence of IgE-mediated hypersensitivity to a relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 2 years of study entry via the prick testing or intradermal method (wheal size ≥ 3 mm larger than diluent control (diluent not specified) for prick testing and ≥ 7 mm larger than diluent control for intradermal testing) [229:13, 15, 231:791], and (3) presence of PAR symptoms of sufficient severity (a nasal congestion score at least moderate in severity (≥ 2), a total symptom score ≥ 5 at both screening and baseline, and a nasal congestion score ≥ 2 during 4 of the last 7 days prior to the baseline visit), in order to begin study drug treatment [229:15, 25-26, 31, 231:789, 791, 808].

8.18.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1. of Trial C94-092 in the NDA submission [229:14, 231:819] and is similar to the study design of previous PAR studies reviewed in this NDA submission. Subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Day 8 (Visit 3), 15 (Visit 4), 29 (Visit 5), and Weeks 8 (=Day 56, Visit 6), and 12 (=Day 84, Visit 7) of therapy [229:13, 24, 32, 231:796]. Day 1 was designated as the start of

discussed for the mometasone SAR and PAR studies [229:19-21, 231:793-795], and subjects were not allowed to use rescue medication (including systemic antihistamines) for intolerable PAR symptoms for the duration of the study [229:20, 231:795].

After the screening visit, subjects participated in a 1-2 week single-blind placebo run-in period during which they self-administered a nasal spray from a placebo bottle each morning [229:23, 231:789]. On re-evaluation during the baseline visit (Visit 2), subjects who met all inclusion criteria were randomized to one of the following 2 treatment groups, received diary cards to record symptoms reflectively over the previous 12 hours (upon awakening, before the a.m. dose and before retiring (p.m. recording)) and began therapy with study drug administered every a.m. [229:17, 19, 231:802-803]:

(A) Mometasone aqueous nasal spray 200 µg qd	
a.m. dosing:	Mometasone 200 µg
p.m. dosing	NONE
(B) Placebo (0 µg qd)	
a.m. dosing:	Mometasone placebo
p.m. dosing:	NONE

Subjects underwent clinical efficacy and safety evaluation (including nasal exam) during each study visit [229:22-25, 27-29, 231:798-809, 811-813]. Efficacy evaluation was again based on a 0-3 severity scale [229:26, 231:808], a 0-3 scale of the overall condition of PAR [229:25, 231:808], and a 1-5 scale of therapeutic response [229:26, 231:809].

The primary efficacy variable [229:38, 231:815] was defined as: the mean change from baseline (the mean of the a.m. and p.m. baseline scores and the a.m. and p.m. scores from the 7 prior consecutive days) in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject diaries) where the:

Mean Change in Total nasal symptom score= 15 Day Interval Score[(Nasal a.m. average $_{\text{Day 1-15}}$) + (Nasal p.m. average$_{\text{Day 1-15}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

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

Secondary efficacy variables consisted of the following [229:38, 231:815-816]:

averaged over Days 16-30 (a.m. and p.m. combined), Days 31-45, Days 46-60, Days 61-75, and Days 76-90 [229:38]:

Mean Change in Total nasal symptom score$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$**=Day 16-30 (or Day 31-45, Day 46-60, Day 61-75, Day 76-90) Interval Score**[(Nasal a.m. average $_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$) + (Nasal p.m. average$_{\text{Day 16-30, Day 31-45, Day 46-60, Day 61-75, Day 76-90}}$)]/2- **Baseline Visit Score**[(Nasal a.m. average$_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$) + (Nasal p.m. average $_{\text{Baseline Visit + 7 Consecutive Days Prior to Baseline Visit}}$)]/2

(2) Endpoint total nasal symptom score (a.m. and p.m. combined): Endpoint score defined as the last available post-baseline value for each study subject, pooled across the 24 participating centers [229:38].

(3) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit) [229:38].

(4) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, and the endpoint visit) [229:38].

(5) Physician's evaluation of total nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit) [229:38].

(6) Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit) [229:38].

(7) Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, and the endpoint visit) [229:38].

(8) Subject's self-evaluation of overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, and the endpoint visit [229:38].

(9) Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, and the endpoint visit [229:38].

(10) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, and the endpoint visit [243:44].

(11) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, and the endpoint visit [243:44].

(12) The number of 'symptom-free' days (i.e. total nasal symptom=0) during the entire treatment period (i.e. excluding baseline visit) [229:38].

Pollen counts were not collected in this study.

8.1.8.4 RESULTS

092 and comprised the ITT population (no subject drop-outs) [229:41]. One hundred and seventy (170) subjects in the ITT population received mometasone treatment, while 164 subjects received placebo [229:41]. An additional 20 subjects were excluded from efficacy analyses because of various protocol violations, leaving 314 subjects in the efficacy evaluable population [229:41].

The 2 treatment groups in this study were comparable with regard to demographic and disease characteristics [229:43]. Again, for both treatment groups, the majority of subjects were Caucasian [229:43]. The distribution of male and female subjects in each of the 2 treatment groups was approximately equal. Greater than 50% of the subjects had SAR in addition to PAR. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a significant difference between the 2 treatment groups with the majority of subjects in both groups having 'moderate' PAR symptoms at baseline [229:46].

Analysis of the primary efficacy variable for the ITT population demonstrated greater efficacy of mometasone treatment in decreasing total nasal symptoms for the day 1-15 interval, compared with placebo. The raw total nasal symptom score/unit change for the mometasone treatment group was 4.7 (with a -1.1 unit decrease in total nasal symptoms from baseline or a -16% change), compared with a raw total nasal symptom score of 5.0 (-0.7 unit decrease in total nasal symptoms or -11% change) for the placebo group (p=.02) [229:280]. No significant difference was noted between the a.m. and p.m. total nasal symptom scores or change in scores in the mometasone treatment group for the day 1-15 interval (mometasone group a.m. raw total nasal symptom score/change in raw score=4.8/-1.1 unit change vs. mometasone group p.m. raw total nasal symptom score/change in raw score=4.6/-1.0 unit change), once again supporting once daily dosing of mometasone [231:1105-1106]. Additionally, no significant difference in the primary efficacy variable was noted between the ITT and efficacy evaluable population [229:252, 280] (of note: in both subject populations, 4 study centers with ≤ 5 subjects/center were pooled into one center). A summary of results for the primary and secondary efficacy variables is summarized in Table I. and Table II. below and overall, support the efficacy of mometasone in decreasing the symptoms of PAR. No significant difference in clinical efficacy was noted based on age subgroup analysis into subjects age 65-69 and age ≥ 70 years, sex, or racial group [229:282-283]. In general, however, the number of subjects comprising the sub-groups were too small to make any generalized conclusions regarding possible differences in efficacy. Interestingly, in comparison with total nasal symptom scores evidenced in other PAR studies in this NDA submission, those recorded by elderly subjects in study C94-092 were lower, with a small degree of change in total nasal symptoms (numerical and % change). These results are suggestive of anecdotal evidence that SAR and PAR generally decrease in severity with elderly age due to a waning immune response.

Analysis of subject and physician-rated individual nasal and non-nasal

numerically lower for mometasone treated elderly subjects, in comparison with placebo treated subjects, a statistically significant difference was not noted for any physician rated scores and absent in most subject rated scores. This lack of a statistically significant response in elderly subjects was again, in contrast to findings for subjects age 12-64 in the previous PAR studies. Particularly striking was the lack of statistical significance when mometasone treated subjects were compared with placebo group subjects in subject self-evaluated overall response to treatment at all study visits, in contrast to findings of all previous PAR studies. The implications of these findings in elderly subjects (subjects ≥ 65 years of age) is unknown, but aside from speculation that elderly subjects may not have as severe PAR symptoms as younger subjects, a longer duration of underlying perennial rhinitis in elderly subjects (mean duration 29 and 28 years for mometasone and placebo subjects, respectively [229:43] as compared with a mean duration of PAR of 16-20 years in subjects age 12-64 years) was another distinguishing feature between the two age groups. It is also possible that rhinitis symptoms in some of these older individuals may, in part, have been attributable to other underlying medical conditions (*Reference: Liston SL, Siegel LG, Nasal and sinus disorder in the elderly: which ones are life-threatening?, Geriatrics. 1981; 36(2):91-102*) or medications taken for other underlying medical conditions (e.g. antihypertensives). The number of 'symptom-free' days for the entire study duration, while listed as a secondary efficacy variable, was not included by the Sponsor in the efficacy analysis. A review of subject responses however suggests that the majority of mometasone subjects experienced moderate to marked improvement in PAR symptoms by Visit 7 of treatment (as did the placebo group subjects), with a smaller percentage of subjects (≤ 10%) experiencing complete relief of PAR symptoms [230:415].

In summary, while elderly PAR subjects did not appear numerically (and in terms of percent change) to have the same degree of response in PAR symptom scores with mometasone treatment as did subjects (generally, age 12-64 years) evaluated in the other PAR studies, response to treatment was demonstrable and for some efficacy variables statistically significant compared to placebo. Based on statistically significant efficacy for the primary efficacy variable and an overall trend of lower symptom scores for all secondary efficacy variables in mometasone treated subjects, as compared with placebo; mometasone was overall shown to demonstrate efficacy in decreasing PAR symptoms in elderly subjects.

Table I. Primary Efficacy Variable of PAR and Treatment with Mometasone (ITT Population) [229:280]

1° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)
1.	Subject evaluated mean Δ in Total Nasal Sx Score$_{DAY\ 1\text{-}15}$	*Yes

sx=Symptom

* Note: Statistically significant response for 1° efficacy variable in the efficacy evaluable population (ITT data not provided) carried by 2 of the 21 distinct study centers (i.e. 19/20 centers had a statistically non-significant response) [229:253-273]. 4 study centers (-014, -016, -017, and -019 had ≤ 5 efficacy evaluable subjects hence were combined as 1 single large center [229:273]).

Table II. Secondary Efficacy Variables of PAR and Treatment with Mometasone (ITT Population, except where *otherwise noted), [229:279-280, 357-358, 230:378-379, 399-400, 414-415, 231:1105-1147]

2° EFFICACY VARIABLE		STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
1.	Subject evaluated mean Δ in Total Nasal Sx Score $_{DAY\ 16\text{-}30,\ DAY\ 31\text{-}45,\ DAY\ 46\text{-}60,\ DAY\ 61\text{-}75,\ DAY\ 76\text{-}90}$	No:	All study visits.	
2.	Subject evaluated mean Δ in Endpoint Total Nasal Sx Score	Yes:	Endpoint visit.	
3.	Subject evaluated mean Δ in Total Sx Score $_{DAY\ 1\text{-}15,\ DAY\ 16\text{-}30,\ DAY\ 31\text{-}45,\ DAY\ 46\text{-}60,\ DAY\ 61\text{-}75,\ DAY\ 76\text{-}90,\ Endpoint\ Visit,\ Offset\ Visit}$	Yes: No:	Day 1-15, Endpoint visit. Day 31-45, 46-60, 61-75, 76-90.	
4.	Subject evaluated mean Δ in Total non-nasal Sx Score$_{DAY\ 1\text{-}15,\ DAY\ 16\text{-}30,\ DAY\ 31\text{-}45,\ DAY\ 46\text{-}60,\ DAY\ 61\text{-}75,\ DAY\ 76\text{-}90,\ Endpoint\ Visit,\ Offset\ Visit}$	No:	All study visits.	
5.	Physician Evaluated Total Nasal Sx Score	No:	All study visits.	
6.	Physician Evaluated Total Sx Score	No:	All study visits.	
7.	Physician Evaluated Total non-nasal Sx Score	No:	All study visits.	
8.	*Subject overall condition evaluation	Yes: No:	Study visits: Study visits:	Week 8. Day 8, 15, 29, Week 8, Week 12, Endpoint visit.
9.	*Physician overall condition evaluation	No:	All study visits.	
10.	*Subject overall Rx Response evaluation	Yes: No:	Study visit: Study visit:	Endpoint visit. Day 8, 15, 29, Week 8, Week 12.
11.	*Physician overall Rx Response evaluation	No:	All study visits.	
12.	Proportion of symptom-free days for the entire treatment period (Total nasal sx score=0)	DATA NOT PROVIDED.		

Δ=Change, Sx=Symptom, Rx=Treatment Note: Analyses are for a.m. and p.m. combined symptom scores.
ITT=Intent-to-Treat Population.

Table III. Change in Individual PAR Symptoms (Subject and Physician Evaluated, a.m. and p.m. combined) with Mometasone Treatment (ITT Population). [231:1113, 1116, 1119, 1122, 1125, 1128, 1131, 1134, 1140-1147]

PAR SYMPTOM	STATISTICALLY SIGNIFICANT RESPONSE compared with PLACEBO: (Yes/No)		
Subject Evaluated Individual Nasal Sx Score	Yes:	Rhinorrhea:	Endpoint visit.
		Congestion:	Endpoint visit.
		Sneezing:	Day 1-15.
	No:	Rhinorrhea:	Day 1-15, 16-30, 31-45, 46-60. 61-75, 76-90.
		Congestion:	Day 1-15, 16-30, 31-45, 46-60, 61-75, 76-90 .
		Sneezing:	Day 16-30, 31-45, 46-60, 61-75, 76-90, Endpoint visit.
		Nasal Itch:	All study visits.
Physician Evaluated Individual Nasal Sx Score	Yes:	Congestion:	Endpoint visit.
		Sneezing:	Week 8.
	No:	Rhinorrhea:	All study visits.
		Congestion:	Day 8, 15, 29, Week 8, Week 12.
		Sneezing:	Day 8, 15, 29, Week 12, Endpoint visit.
		Nasal Itch:	All study visits.
Subject Evaluated individual non-nasal Sx Score	Yes:	Eye tear:	Day 1-15, Endpoint visit.
		Eye redness:	Day 1-15, Endpoint visit.
	No:	Eye tear:	Day 1-15, 16-30, 76-90, Endpoint visit.
		Eye Itch:	All study visits.
		Eye redness:	Day 16-30, 31-45, 46-60, 76-90.
		Ear/palate itch:	All study visits.
Physician Evaluated individual non-nasal Sx Score	No:	For all 4 non-nasal sxs:	All study visits.

Sx=Symptom

8.18.4.3. ADVERSE EVENTS:

The safety analysis was based on 334 elderly subjects in the ITT population; 170 subjects were treated with mometasone 200 µg qd and 164 subjects were treated with placebo [229:41]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, and nasal examinations, and clinical laboratory tests relative to baseline [229:22-29, 231:798-807, 811-813].

Adverse events were again similar for both treatment groups, and were similar in frequency and profile to those observed in subjects ≤ 65 years of age in the other clinical studies in this NDA submission. Overall, adverse events were reported in 76% of subjects in both the mometasone and the placebo group [229:68, 70, 230:430]. Again, the most frequently reported adverse event was headache, reported in 24% of mometasone subjects and 20% of placebo subjects [229:68, 69-60, 230:430, 233:3635-3675, 3909-3944]. Headache was followed by pharyngitis as the second most common adverse event, reported in 20% of mometasone subjects and 13% of placebo subjects [229:69, 230:436, 233:3818-3834, 234:4060-4069]. This was followed by cough and epistaxis as the next most frequent adverse events (with 16% of mometasone subjects and 10% of placebo subjects, and 13% of mometasone subjects and 9% of placebo subjects reporting cough and epistaxis, respectively) [229:69, 230:436, 233:3791-3805, 234:4031-4041, 4044-4053]. As in other rhinitis studies in this NDA submission, episodes of epistaxis were generally mild and self-limited in duration. Viral infection was reported in 15% of subjects in the mometasone group and 12% of subjects in the placebo group [229:72, 230:436, 233:3758-3766, 234:4016-4022]. Compared to the other PAR studies in this NDA submission, reports of sinusitis in elderly subjects in study C94-092 were less frequent, being reported in 5% of mometasone treated subjects and 7% of placebo subjects [229:73, 230:437].

There were no reports of nasal septal perforation in either of the 2 treatment groups but 3 mometasone treated subjects were noted to have nasal septal ulcerations on various visits during the study which were absent on screening and baseline (subjects C94-092-08, #001, #008, and #23) [233:3815-3816]. Nasal ulcers were reported in 2 subjects in the mometasone group on Visit 7 of the study (subjects C94-092-08, #034 and -06, #002) [233:4746, 4841] and not reported in any placebo group subjects. No assessment of glaucoma/cataract formation or suppression of the HPA-axis was performed in this PAR study. No deaths were reported in either of the 2 treatment groups.

In terms of infection, viral infection (see above) was reported as one of the more frequent adverse events in the 2 treatment groups in this study. Herpes simplex infection was reported in only 1 subject in the mometasone group on Visit 6 (1% incidence) and in no placebo group subjects [229:72, 230:435, 233:3755]. One subject in the placebo treatment group (subject C94-092-23, #002) was reported to have pneumonia during Visit 4 of the study which was felt by the

No subjects in either of the 2 treatment groups were reported to have nasal or oral candidiasis on any clinic visits [229:72, 230:436].

A total of 11 subjects discontinued treatment because of adverse events (4 subjects in the mometasone group and 7 subjects in the placebo group) [229:83]. Of the subjects who discontinued treatment in the mometasone group, most of these discontinuations were felt to be unrelated to the study medication [229:84].

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in either of the 2 treatment groups. One subject (subject C94-092-17, #004) in the mometasone treatment group was noted to have an elevated SGPT following mometasone treatment (84 IU/L, Visit 7) which increased from a screening value of 17 IU/L and which was attributed to Voltaren use. Discontinuation of Voltaren and re-evaluation of the SGPT 5 days post-discontinuation yielded a decreasing value of 55 IU/L [229:87, 230:433, 504, 233:3725]. Flag shift distributions of laboratory values failed to reveal any significant patterns of change in the 2 subject groups. Adverse events did not appear to differ significantly based on sex or race, although the number of non-Caucasian subjects was too small to draw meaningful conclusions [230:568-688].

8.18.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis in elderly subjects with PAR (age ≥ 65 years of age), as assessed for up to 12 weeks.
2. Mometasone treatment demonstrated a statistically significant effect in decreasing PAR symptoms for the primary efficacy variable and at least some additional study timepoints. Although a numerical difference in response was noted between mometasone and placebo treated subjects for most secondary efficacy variables; for most endpoints, these differences were not statistically significant. In general, the response of elderly subjects to mometasone treatment was somewhat less consistent for the duration of the entire study, as compared with subjects analyzed in the other PAR studies.
3. Mometasone treatment demonstrated adequate duration of effect in treating PAR symptoms over 24 hours, supportive of once a day dosing.
4. Elderly subjects treated with mometasone did not develop an increased rate of infections (bacterial or viral) and overall demonstrated a similar adverse event frequency and profile as subjects age 12-64 years treated with mometasone.

8.19. Trial I93-221. Six Month Safety Study of Mometasone Furoate Nasal Spray in Perennial Allergic Rhinitis (PAR) Patients.

Principal Investigator: Angel Alonso, M.D.

Participating Centers: 23 international centers (Canada, Latin America, Europe, and Australia).

8.19.1. OBJECTIVES:

1. To characterize the safety profile of mometasone furoate nasal spray in doses ranging from 100-400 µg qd (depending on the subject's therapeutic response) for a period of 6 months.
2. To evaluate efficacy of mometasone aqueous nasal spray in the treatment of symptoms of PAR (efficacy assessment was not the primary objective of this study).

8.19.2. STUDY DESIGN:

This was a randomized, multi center, non-comparative, non-placebo controlled trial in adult subjects with perennial allergic rhinitis in which 6 month safety and efficacy data on the use of variable dose mometasone (100, 200, or 400 µg qd) in the treatment of PAR was analyzed.

8.19.3. PROTOCOL:

8.19.3.1.a. POPULATION:

Entry criteria for this study after completion of a washout period (up to 7 days) were essentially the same as those for the majority of PAR studies in this NDA submission, namely: (1) age ≥ 12 years (with the exception of age ≥ 18 in the Netherlands and age ≥ 18 for female subjects in France) [291:13-14, 293:846-847], (2) presence of IgE-mediated hypersensitivity to the relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 2 years of study entry via the prick testing or intradermal method; or in the absence of a positive skin test, history of chronic, perennial allergy documented by nasal eosinophilia [291:13, 293:846, 848], and (3) sufficient severity of PAR symptoms at both screening and baseline to qualify for study randomization (i.e. nasal rhinorrhea and/or congestion scores each ≥ 2 at both screening and baseline and during 4 of the last 7 days (a.m. or p.m.) just prior to the baseline visit and a total nasal symptom score ≥ 5 at both screening and baseline [291:13, 293:846, 848, 861].

8.19.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1. of Trial I93-221 in the NDA submission [291:12, 293:8691. Subjects were

(Visit 4), 12 (Visit 5), and 26 (Visit 6) of therapy [291:11, 293:847, 853].

At screening, in addition to routine history and physical examination, subjects at study sites 18 and 20 underwent measurement of plasma cortisol levels at 8 a.m. ± 1 hour [291:19, 293:839] as a rough screening method to assess underlying adrenal function in potential study subjects prior to treatment with mometasone.

Subjects entered a washout phase (up to 14 days) between the screening and baseline visit, during which they took no medications except for rescue medication (note: no restrictions outlined in the protocol with regard to the type of rescue medication that could be used by a subject with the exception of corticosteroid use), as prescribed by the principal investigator for relief of intolerable PAR symptoms prior to initiation of the open-label treatment [291:16, 18-20, 293:851-852]. On re-evaluation at the baseline visit, subjects who met all inclusion criteria were assigned to one treatment group, received diary cards to record symptoms reflectively over the previous 12 hours and began therapy with mometasone (initiated at 200 µg qd, with the option to increase (to 400 µg qd) or lower (to 100 µg qd) the dose as necessary to treat PAR symptoms) administered once daily in the a.m. [291:14-16, 847, 293:857, 859]:

(A)	**Mometasone aqueous nasal spray 100, 200 or 400 µg qd** (VARIABLE DOSE)-subjects started treatment with mometasone 200 µg qd

Subjects underwent clinical efficacy and safety evaluation (including nasal exam) during each study visit [291:19-22, 24-27, 293:854-860, 863-865]. While eye examinations to assess glaucoma/cataract formation were not performed in this study, a rough assessment of HPA-axis suppression in mometasone treated subjects at 2 study sites was performed via serial a.m. plasma cortisol measurements at the Screening, Week 12 (Visit 5), and Week 26 (Visit 6) visits (-018 and -020) [291:22, 293, 293:838]. Efficacy evaluation was again based on a 0-3 severity scale [291:23, 293:861] and a 1-5 scale of therapeutic response [291:24, 293:862].

Subjects started mometasone treatment at 200 µg qd but were allowed to lower the medication dose to 100 µg qd if nasal symptoms were well controlled or to increase the dose to 400 µg qd in order to improve control of nasal symptoms [291:14-15, 293:853]. Dose titrations were not to be done more frequently than bi-weekly, and an intermediate dose of 300 µg qd was not allowed [291:14-15, 293:857]. Rescue medication use was allowed throughout the study duration, excluding steroid formulations (nasal, inhaled, etc.)[291:17-18, 293:851-852].

A primary efficacy variable was not defined in this study. Supplementary efficacy variables consisted of: (1) physician and (2) subject evaluations of overall condition and (3) physician and (4) subject evaluations of therapeutic response (ITT population) [291:30, 293:866]. Pollen counts were not collected in this study. Rescue medication use amongst the 3 mometasone doses [illegible]

8.19.4. RESULTS

A total of 333 subjects with PAR were randomized into study I93-221, with 2 immediate drop-outs (the subjects did not receive any study drug)[291:32], leaving 331 subjects for the ITT population all of whom received mometasone treatment by virtue of the study design [273:36]. The majority of subjects had PAR; only 2 subjects had a diagnosis of non-allergic rhinitis with eosinophilia (NARES) [291:32]. The attrition rate for study subjects by Week 26 of study I93-221 was approximately 9% (30 dropouts out of 330 subjects) [291:149], an acceptable value.

The treatment groups in this study were comparable with regard to demographic and disease characteristics [291:33]. The majority of mometasone treated subjects were Caucasian, however a sizeable proportion of study subjects (36%) were Hispanic. The distribution of male and female subjects was approximately equal. Approximately 29% study subjects had SAR in addition to PAR.

Analysis of the efficacy variables for the ITT population showed that overall, subjects demonstrated an improvement in symptoms which was maintained for the study duration. For the physician's evaluation of the overall condition of PAR, subjects demonstrated an improvement by Week 4 (Visit 3) of the study (as supported by the majority of subjects having 'mild' PAR symptoms) and this improvement was maintained through the Week 26 visit [291:37-38, 149, 174]. Subjects' self-evaluation of the overall condition of PAR was very similar to that of the physician evaluation; namely that improvement in symptoms was noted by Week 4 of the study (supported by the majority of subjects rating their overall PAR condition as 'mild') and was maintained throughout the study duration [291:39, 183, 206]. In fact, PAR symptom scores for the pooled ITT population were identical between subject and physician rated symptoms. Both of these findings support maintenance of a therapeutic effect for mometasone throughout the open-treatment period. Physician evaluation of subjects' therapeutic response to treatment (1-5 scale) indicated that mometasone treated subjects experienced marked relief in PAR symptoms starting at Week 4 of the study (with concomitant decrease in PAR symptom scores) [291:40-41, 215], which continued throughout the open-treatment period, again providing evidence of maintenance of a therapeutic effect throughout the study duration [291:239]. Subjects' evaluation of therapeutic response, again, was almost identical in terms of symptom scores to the physician evaluation of subjects' therapeutic response with the majority of study subjects reporting marked relief in PAR symptoms by Week 4 of treatment [291:42, 246, 270]. Again, this response was maintained for the study duration.

Regarding the dose distribution for mometasone treated subjects at the time of the last dose in this study, 59/331 (17.8%) of subjects received mometasone 100 µg qd, 211/331 (63.7%) of subjects received mometasone 200 µg qd, and 61/331 (18.4%) of subjects received mometasone 400 µg qd [293:785]. The majority of subjects either remained at the initial 200 µg qd dose

and maintained that dosage level for the remainder of the study (17.5% were titrated upwards to 400 µg qd and 17.5% were titrated downwards to 100 µg qd) [293:786]. The remaining 7.9% of subjects changed their mometasone dose more than once during the study [293:786]. Similar to other 'variable dose' mometasone studies (e.g. C93-014, I93-018) these data suggest that the most effective dose of mometasone for the control of PAR symptoms was 200 µg qd. A gradual increase in dose of mometasone over the course of study I93-221 was not observed.

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

Table I. Efficacy Variables of PAR and Treatment with Mometasone (100, 200, or 400 µg qd) (ITT Population), [291:149, 174, 183, 206, 215, 239, 246, 270]

EFFICACY VARIABLE		Improvement in PAR symptoms throughout study duration: Mometasone 100-400 µg qd: (Yes/No)
1.	Physician's evaluation of subject overall PAR condition compared to baseline	Yes
2.	Subject self evaluation of overall PAR condition compared to baseline	Yes
3.	Physician evaluated response to Rx compared to baseline	Yes
4.	Subject self-evaluated response to Rx compared to baseline	Yes

sx=Symptom, Rx=Treatment, ITT=Intent-to-treat
Statistical analysis for between group differences performed using 2-way ANOVA.
NOTE: The majority of subjects received mometasone 200 µg qd for the duration of the study.

8.19.4.3. ADVERSE EVENTS:

The safety analysis was based on 331 subjects in the ITT population all of whom received mometasone treatment. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical exam (including nasal exam), and clinical laboratory tests relative to baseline (including a.m. plasma cortisol levels at two designated centers in 37 subjects) [291:19-27].

Adverse events were similar to those noted in other SAR and PAR studies of mometasone. Overall, adverse events were reported in 78% of mometasone treated subjects [291:278].

Headache was the most common adverse event, reported in 36% of mometasone subjects [291:278, 294:1046, 1074], followed by viral infection

(reported in 27% of subjects [291:284, 295:2163-2194], pharyngitis (15% of mometasone subjects)[291:285, 295:2281-2299], and epistaxis (13% of mometasone subjects) [291:284, 295:2245-2265]. In this study one case of decreased plasma glucocorticoid (1% incidence, subject I93-221-019, #005 [292:391]) and one case of hypothyroidism (1% incidence, subject I93-221-010, #013 [295:2052]) were reported with mometasone use [291:280]. In the subject (a 12 year old male receiving mometasone 200 µg qd) with a reported decreased a.m. plasma cortisol on week 12 of the study (to 104.0 µg/dL, normal range: 219.7-367.8 µg/dL), mometasone treatment was nonetheless continued and follow-up a.m. plasma cortisol levels approximately 3 and 12 weeks later were within normal limits (319.8 and 272.2 µg/dL, respectively) [292:391..295:2051].

Regarding serious adverse events, one case of spontaneous abortion occurred approximately two weeks after a subject discontinued the study (after 9 weeks of treatment with mometasone) but was felt by the principal investigator to be unrelated to study medication [291:57, 292:391]. One death was reported, however was felt to be unrelated to study drug treatment with 200 µg qd of mometasone (subject I93-221-05, #001, a 67 year old male developed edema and renal dysfunction, and died secondary to arrhythmia and myocardial infarction approximately 7.5 months after the start of the trial) [291:57, 292:390].

There did not appear to be a dose relationship in the overall incidence of ADRs for the different doses of mometasone noted for the study duration (overall incidence of ADRs for mometasone 100 µg qd group=60%, overall incidence of ADRs for mometasone 200 µg qd group=71%, overall incidence of ADRs for mometasone 400 µg qd group=66% [291:62, 292:371]). ADRs which exhibited a mild dose response for the varying doses of mometasone were viral infection (13%, 20%, and 21% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose, respectively [292:382]), pharyngitis (6%, 10%, and 14% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose, respectively [292:384]), epistaxis (8%, 10%, and 10% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose, respectively [292:383]), and myalgia (1%, 2%, and 5% incidence for the 100 µg qd, 200 µg qd, and 400 µg qd dose of, respectively) [292:379]. A similar increased incidence in epistaxis and pharyngitis with increased mometasone dose was likewise noted in the other variable dose mometasone studies (e.g. I93-018). Nonetheless, the relatively small number of study subjects in the variable dose mometasone groups, especially the 100 µg (n=83) and 400 µg (n=86) groups, precludes any definitive conclusion regarding the mometasone dose-relationship of adverse events [292:371].

There were no reports of nasal septal perforation in any mometasone treated subjects, however nasal ulcers were reported in 7 subjects total (4 subjects at Visit 3 (Week 4 post-initiation of treatment) [295:2329, 296:3269, 3272, 297:3318] and 3 subjects at Visit 5 (Week 12 post-initiation of treatment)) [296:3274, 3279, 3285].

In terms of infection, viral infection was the second most frequently

was one report of oral candidiasis (Week 26 of treatment) [291:284, 295:2197] and one report of nasal candidiasis (Week 12 of treatment) [296:3314] in mometasone treated subjects.

A total of 12 subjects discontinued treatment because of adverse events [291:56]. The most common reason for discontinuation that was considered 'possibly or related' to study medication involved headache, epistaxis, or coughing. Otherwise, most subject discontinuations due to ADRs were considered unrelated to treatment by the principal investigator.

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted with the exception of several reports of elevated LFTs. Three subjects developed elevated LFTs (SGOT, SGPT, or total bilirubin) which were not clearly related to study medication [291:59, 292:685-686]. Two subjects receiving mometasone (subject I93-221-02, #014 and #018) developed an increase in serum alkaline phosphatase to the 300-400 IU/L range during Visits 5 and 6 (normal alkaline phosphatase range: 68-160 IU/L) which were not commented on the in the investigator's case report form [291:59] and 1 additional subject (I93-221-01, #001) [295:2106] developed an increase in serum alkaline phosphatase which was not ascribed a laboratory value or described in the abnormal laboratory reports section of the NDA. From the data provided in the NDA submission, it cannot be concluded that these increases in alkaline phosphatase were not related to mometasone treatment. In the latter case, the subject was a 12 year old female whose laboratory abnormality was felt by the principal investigator to be possibly related to treatment.

No significant change in the mean a.m. plasma cortisol level for the endpoint visit as compared to baseline was detected for pooled subjects from the study sites 18 and 20 (n=37) [292:416], however minor changes consisting of: (1) a small increase (17-18% increase from baseline (screening) value) in a.m. plasma cortisol levels at endpoint were detected in subjects age 12-17 years of age (n=2) [292:449] and in female subjects (n=20) [292:545] and (2) a small decrease (~ 13% increase from baseline (screening) value) in a.m. plasma cortisol levels at endpoint were detected in male subjects (n=17) [292:577]. These discrepancies may represent chance findings and because of the small number of subjects, no conclusions can be drawn regarding these observations. Individual line listings of subject a.m. plasma cortisol levels were not submitted by the Sponsor. Flag shift distributions of laboratory values failed to reveal any significant patterns of change, although for a.m. plasma cortisol levels (n=37), most subject flag shifts from the baseline to endpoint visit were in the normal to the high normal range [292:674]. Aside from the discussion above, adverse events did not appear to differ significantly based on age, sex, or race, although the number of non-Caucasian subjects and subjects <18 or > 65 years of age was too small to draw meaningful conclusions.

8.19.5. CONCLUSIONS:

1. The results of this study support the safety of mometasone 100 µg, 200 µg and 400 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 26 weeks (6 months) in subjects with PAR. The use of a.m. cortisol levels to test HPA-axis suppression did not reveal any signals based on the pooled data provided by the Sponsor. Nonetheless, two shortcomings of the methodology used: (1) the inability evaluate subjects' individual responses with treatment in order to screen for subject 'outliers' and (2) use of a crude test of HPA-axis suppression, limit the inferences that can be made from these results.
2. While study I93-221 was not specifically designed to evaluate efficacy or assess the impact of rescue medication use among the 3 different mometasone dosage groups, assessment of subject overall condition and response to treatment with mometasone for up to 26 weeks (by study subjects and their respective physicians), supports the efficacy of mometasone in doses of 100-400 µg qd for the treatment and maintenance treatment of symptoms of PAR.
3. The majority of subjects, given the opportunity to titrate the dose of mometasone up to 400 µg qd, nonetheless chose to remain on a dose of 200 µg qd of mometasone. Some subjects were eventually able to titrate down the dose of medication to 100 µg qd. Based on these findings, the most appropriate starting dose and maintenance dose of mometasone for the treatment of PAR would be 200 µg qd.