8.4. Trial I92-200. Efficacy and Safety of Mometasone Furoate (SCH 32088) Aqueous Nasal Spray in Seasonal Allergic Rhinitis (SAR).

Principal Investigator: 19 international investigators.

Participating Centers: 19 international centers.

8.4.1. OBJECTIVE:

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

8.4.2. STUDY DESIGN

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

8.4.3. PROTOCOL

8.4.3.1.a. POPULATION:

The significant entry criteria were: (1) age ≥ 18 years, (2) Positive skin (prick or intradermal) test results to the appropriate seasonal allergen (grass and/or trees), confirmed by a wheal size ≥ 3 mm larger than saline control [201:824-825], and (3) rating of overall disease as at least moderate in severity (≥ 2 on a 4 point scale) with a combined nasal symptom score of ≥ 6, and nasal congestion plus one other nasal symptom each scored as at least moderate in severity (≥ 2) at both the screening and baseline visits using the 0-3 symptom scale [199:15, 17, 32; 201:834-836].

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

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

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

8.4.3.1.b. PROCEDURE:

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

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

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

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

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

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

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

8.4.4. RESULTS

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

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

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

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

	(A) Mometasone (100 µg)			(B) Mometasone (200 µg)			(C) Beconase (400 µg)			(D) Placebo			PAIRWISE COMPARISONS					
DAYS	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	A-B	A-C	A-D	B-C	B-D	C-D
BASELINE	126	8.2	1.6	125	8.0	1.7	125	7.9	1.6	121	8.1	1.7	0.6	0.21	0.46	0.46	0.82	0.63
DAY 4 RAW	124	5.0	2.4	124	4.5	2.7	124	4.1	2.3	119	5.6	2.8	0.15	<.01	0.06	0.1	<.01	<.01
CHG	124	-3.2	2.7	124	-3.6	2.8	124	-3.8	2.8	119	-2.4	2.8	0.36	0.04	0.02	0.26	<.01	<.01
%CHG	124	-37	29.9	124	-44	33.2	124	-47	31.6	119	-29	35.7						
DAY 8 RAW	123	3.8	2.5	123	3.3	2.2	122	3.2	2.3	113	5.3	3.0	0.08	0.03	<.01	0.7	<.01	<.01
CHG	123	-4.3	2.7	123	-4.7	2.4	122	-4.7	2.6	113	-2.7	2.7	0.15	0.14	<.01	0.97	<.01	<.01
%CHG	123	-52	30.4	123	-58	26.6	122	-59	28.7	113	-35	35.4						

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

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

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

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

While no formal statistical analysis of rescue medication use were performed by the sponsor, overall 41% of subjects in the ITT population used rescue medication at least once. The rates of rescue medication used in the ITT population were 40%, 34%, 35%, and 54%, respectively for the mometasone 100 µg group, mometasone 200 µg group, the beclomethasone group and the placebo group [200:401]. Rates of rescue medication use in the efficacy evaluable population were very similar to those for the ITT population [200:400].

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

8.4.4.3. ADVERSE EVENTS

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

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

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

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

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

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

8.4.5. CONCLUSIONS:

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

8.5. Trial I94-001. Efficacy and Safety of Mometasone furoate aqueous nasal spray vs. placebo and vs. fluticasone propionate (Flonase) in seasonal allergic rhinitis (SAR) patients

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

Participating Centers: 8 Canadian centers.

8.5.1. OBJECTIVE:

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

8.5.2. STUDY DESIGN:

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

8.5.3. PROTOCOL

8.5.3.1.a. POPULATION

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

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

A greater percentage of subjects in the fluticasone and placebo groups

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

8.5.3.1.b. PROCEDURE:

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

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

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

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

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

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

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

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

8.5.4. RESULTS:

A total of 313 subjects with SAR were enrolled into the study, with 2 immediate dropouts, leaving 311 subjects in the ITT population; 104 subjects each received mometasone or fluticasone treatment and 103 subjects received placebo.

Analysis of the primary efficacy variable for the ITT population (mean change in the subject's total nasal symptom score (a.m. and p.m. combined) for Days 1-15) showed that both mometasone and fluticasone were significantly more effective than placebo in decreasing total nasal symptoms of SAR ($p < 0.01$) [215:855]. In mometasone treated subjects, the total nasal symptom score for the day 1-15 interval decreased by 2.8 units (-36% change), compared with a 1.0 unit decrease (11% change) in placebo treated subjects [215:855]. In comparing the response of the primary efficacy variable for the two active treatments, fluticasone was significantly more effective than mometasone ($p=0.03$) [215:855]. The mean decrease in total nasal symptom scores$_{\text{DAYS 1-15}}$ for the mometasone treatment group was 36%, compared with a 45% decrease (3.5 unit decrease in total nasal symptom scores) for the fluticasone treatment group, and an 11% decrease for the placebo group [215:855]. Separate analysis of the a.m. and p.m. nasal symptom scores from subject diaries in the efficacy evaluable population confirmed findings

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

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

Results for the secondary efficacy variables of individual nasal symptoms for the efficacy evaluable population are summarized in Table 14. of the NDA submission [213:53]. In contrast to the other SAR studies in this submission, in trial I94-001, the greatest mean percent change for both active treatment groups was noted for the nasal symptoms of sneezing and nasal itching (48-59% decrease for the symptom of sneezing in the mometasone group and a 29-54% decrease for symptom of nasal itching in the mometasone group) [213:203-205, 206-208, 223, 224, 228, 231], rather than rhinorrhea and nasal congestion [213:53, 197-199, 200-202, 221, 222, 229, 230]. For all four nasal symptoms, both active treatments demonstrated greater efficacy which was statistically significant compared with placebo; with the fluticasone treatment group showing a greater numerical decrease in each individual nasal symptom, as compared with the mometasone treatment group.

For the total non-nasal symptoms, somewhat discordant results were seen in subject vs. physician rated symptoms. A statistically significant decrease was noted in the mean change in the a.m. and p.m. combined total and individual non-nasal symptoms noted for the Days 1-15 of the subject pooled diary data ($p \leq 0.01$) [213:192, 209, 212, 215, 218], whereas statistical significance was not reached in comparing the mometasone and placebo group in the physician evaluated pooled visit data [213:193, 226, 232-235].

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

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

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

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

8.5.4.3. ADVERSE EVENTS:

The safety analysis was based on 311 subjects in the ITT population; 104 subjects were treated with mometasone or fluticasone and 103 subjects were treated with placebo. Adverse events were reported in 46% of subjects in the mometasone treatment group, 38% of subjects in the fluticasone treatment group, and 40% of subjects in the placebo group [213:62]. Most adverse events were mild to moderate in severity. Of subjects discontinuing treatment due to adverse events (4 total), none were in the mometasone treatment group [213:71].

Similar to the findings in other mometasone studies of the SAR population, the most frequent adverse event in all three treatment arms was headache; reported in 13% of subjects in both the mometasone and fluticasone treatment groups and 21% of subjects in the placebo group [213:62, 64]. Coughing was reported by 7% of subjects in the mometasone treatment group, 6% of subjects treated with fluticasone, and 14% of subjects treated with placebo. Pharyngitis was reported in 7% of subjects in the mometasone treatment group, 3% of subjects in the fluticasone treatment group and 4% of subjects in the placebo treatment group [213:64]. Epistaxis was less prevalent in this study as compared with the other SAR studies in this NDA submission; with 2% of subjects in the mometasone and fluticasone treatment groups and 1% of subjects in the placebo group reporting epistaxis [213:66]. There were no reports of nasal septal perforation in any of the three treatment groups, however nasal ulcers were reported in 1 subject (subject I94-001-04, #003) in the mometasone 200 µg treatment group on visit 4 of the study [217:2102] and 2 subjects (subject I94-001-04, #016 and #038) in the fluticasone 200 µg treatment group, on visits 5 and 4, respectively [217:2108, 2110]. No deaths were reported in any of the three treatment groups.

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

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

8.5.5. CONCLUSIONS:

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

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

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

Principal Investigator: Robert Anolik, M.D.

Participating Centers: 18 U.S. centers.

8.6.1. OBJECTIVE:

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

8.6.2. STUDY DESIGN:

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

8.6.3. PROTOCOL:

8.6.3.1.a. POPULATION:

Significant entry criteria consisted of the following: (1) age ≥ 12 years of age [185:14, 188:1022-1023], (2) presence of IgE-mediated hypersensitivity to a local seasonal allergen (grass and/or trees but individual species not specified in protocol), as documented by a positive skin test within 1 year of study entry via the prick testing method (≥ 3 mm in diameter than saline diluent control) [185:14, 23, 188:1023], (3) history of at least moderate SAR symptoms on screening and baseline visits, as determined by a nasal congestion score at least moderate in severity (score ≥ 2), a nasal symptom score ≥ 6, a non-nasal symptom score ≥ 5, and a combined total symptom score ≥ 11 [185:12, 188:1023], and (4) lack of clinically significant abnormalities, including disturbances in conduction and rhythm, or QT_c ≥ 420 msec on the subject's screening ECG [185:14, 188:1024].

8.6.3.1.b. PROCEDURE:

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

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

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

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

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

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

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

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

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

Four primary efficacy pairwise comparisons were performed:

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

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

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

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

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

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

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

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

8.6.4. RESULTS

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

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

An evaluation of the pollen count records for the 18 participating centers in this study, for the most part, was consistent with findings in many of the other SAR studies of this NDA submission. Fifteen of the 18 centers (center C94-145-01, -02, -03, -05, -07, -08, -10, -011, -012, -013, -014, -016, -017, -019, and -020) reported pollen counts which were not significantly elevated relative to baseline for at least part of the study duration [193:3663-3680]. The respective tree, grass, weed, and total pollen counts for each center support this conclusion [193:3682-3727].

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

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

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

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

APPEARS THIS WAY

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

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

CHG=Change, % CHG=Percent Change, Sx=Score
[1]P-values are from 2-way ANOVA and LSmeans Pairwise Comparisons (no adjustment for overall α-value). P-values are those for the change in symptom score (not % change).
Mometasone was administered in all treatment groups as 200 µg qd.
Loratadine was administered in all treatment groups as 10 mg po qd.

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

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

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

8.6.4.2. BIOAVAILABILITY STUDIES:

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

Plasma loratadine (SCH 29851) and loratadine metabolite (SCH 34117) levels were assayed in the same 110 subjects comprising the four treatment groups that underwent analysis of plasma mometasone levels (28 subjects per treatment group) but detectable levels were only found in two of these groups: (1) the combination mometasone plus loratadine group and (2) the loratadine group [191:2167]. Analysis of the results for plasma loratadine (SCH 29851) levels and loratadine metabolite (SCH 34117) levels is summarized in Tables 1. and 2. of Appendix B in the NDA submission [191:2169-2170]. In summary, although no statistically significant treatment difference was noted between the two treatment groups ($p>0.16$), the power to detect a 50% difference in this study was <40% for plasma loratadine levels and was <70% for the plasma loratadine metabolite levels [191:2170]. This low power is related to the high variability of the data, as noted by coefficients of variation which were ≥ 104% for loratadine and ≥ 63% for the loratadine metabolite, respectively [191:2170]. An additional confounding factor consisted of the several outliers which were detected for the 1 hour post-dose concentration difference of loratadine between Day 1 and Day 15 (subject 253) and the 1-hour post-dose concentration difference of the loratadine metabolite between Day 1 and Day 15 (subjects 412 and 439) [191:2168]

8.6.4.3. ADVERSE EVENTS:

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

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

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

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

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

(2) mometasone alone: reports in 2 subjects (both on Visit 4), Visit 4),

(4) placebo: reports in 2 subjects (both on Visit 3).

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

In terms of infection, 1% of subjects in the combination treatment group and mometasone group reported viral infections, while 2% and 0% of subjects reported viral infections in the loratadine and placebo group, respectively [185:79]. In this trial, one subject in the loratadine treatment group (subject C94-145-02, #050) was noted by the examining physician to have nasal candidiasis (on the baseline visit) [196:5939]. No other subjects in either of the other three treatment groups were found to have nasal candidiasis on follow-up clinic visits.

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

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

distributions of laboratory values failed to reveal any significant patterns of change. A flag shift distribution of QT_c intervals for the four treatment groups also failed to reveal significant increase in QT prolongation from baseline. One subject in the combination treatment group was reported as having a QT_c >15-20% the baseline value. One subject (1%) in the combination treatment group, 5 subjects (3%) in the mometasone group, 3 subjects (2%) in the loratadine group, and 1 subject (1%) in the placebo group was reported as having a QT_c >10-15% the baseline value [188:1008].

8.6.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of seasonal allergic rhinitis, as compared with placebo. While not statistically significant, the mean decrease in total nasal symptom scores and total SAR symptom scores was numerically greater for the combination treatment of loratadine plus mometasone, as compared with mometasone alone. For non-nasal symptoms, the combination treatment demonstrated greater efficacy than mometasone treatment alone in reducing the symptom of eye itch.
2. The other two active treatment groups: the combination treatment of mometasone plus loratadine and loratadine alone also showed statistically greater efficacy in the treatment of symptoms of SAR, as compared with placebo.
3. Analysis of plasma mometasone, loratadine and loratadine metabolite levels in 110 SAR subjects from 4 study centers designated to perform the pharmacokinetic studies, revealed undetectable mometasone levels in all subjects studied, undetectable loratadine (SCH 29851) and loratadine metabolite (SCH 34117) levels in the mometasone and the placebo treatment groups, and no statistically significant difference in the loratadine or loratadine metabolite levels in the combination mometasone plus loratadine treatment group vs. the loratadine treatment group.

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

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

Participating Center: Nassau County Medical Center
East Meadow, NY

8.7.1. OBJECTIVE:

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

8.7.2. STUDY DESIGN:

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

8.7.3. PROTOCOL:

8.7.3.1.a. POPULATION:

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

8.7.3.1.b. PROCEDURE:

After fulfilling entry criteria and the screening and baseline visits and completing the required physical exam and laboratory testing, study enrollable

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

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

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

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

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

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

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

8.7.4. RESULTS:

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

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

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

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

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

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

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

8.7.4.3.ADVERSE EVENTS:

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

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

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

8.7.5. CONCLUSIONS:

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

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

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

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

8.8.1. OBJECTIVE:

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

8.8.2. STUDY DESIGN:

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

8.8.3. PROTOCOL:

8.8.3.1.a. POPULATION:

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

8.8.3.1.b. PROCEDURE

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

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

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

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

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

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

ECP [301:27, 271].

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

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

8.8.4. RESULTS:

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

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

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

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

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

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

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

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

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

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

8.8.4.3.ADVERSE EVENTS:

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

8.8.5. CONCLUSIONS:

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

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

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

Participating Centers: 9 U.S. Centers

8.9.1. OBJECTIVE:

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

8.9.2. STUDY DESIGN:

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

8.9.3. PROTOCOL:

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

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

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

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

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

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

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

at least 2 years prior to screening.

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

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

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

(A) General Considerations:

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

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

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

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

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

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

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

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

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

8.9.3.1.b. PROCEDURE:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Evaluation visits to the physician were defined as follows:

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

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

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

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

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

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

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

Table 1

Schedule of Study Procedures and Evaluations (Protocol No. C93-015)

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

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

8.9.3.2. CLINICAL ENDPOINTS:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.9.4. RESULTS:

8.9.4.1. SUBJECT DEMOGRAPHICS:

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

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

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

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

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

	MFNS (n=116)	BDP (n=116)	Placebo (n=115)	Overall Treatment P-Value[a]
Age (years)				
Mean	35.6	33.2	33.7	0.26
Median	34.5	33.5	34	
Range (Min-Max)	12-69	12-60	13-62	
Sex				
Female	63	61	52	0.29
Male	53	55	63	
Race				
White	113	109	105	0.14
Black	2	3	6	
Hispanic	0	2	3	
Other	1	2	1	
Weight (lbs)				
Mean	169.4	165.5	174.5	0.19
Median	165	160	170	
Range (Min-Max)	95-360	98-272	109-296	
Duration of Condition (Years)				
Mean	19.0	19.2	19.4	0.99
Median	19.0	16.5	18.0	
Range (Min-Max)	2-62	2-51	2-60	

MFNS=Mometasone
BDP=Beclomethasone

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

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

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

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

(D) Subject Discontinuation

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

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

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

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

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

(E) Subject Validity

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

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

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

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

8.9.4.2. EFFICACY ENDPOINT OUTCOMES:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table V.
Efficacy of Mometasone vs. Beclomethasone vs. Placebo in the Prophylactic Treatment of SAR: Primary and Secondary Efficacy Variables--Proportion of Days with Total Nasal Symptom Score ≤ 2
Intent-to-Treat (ITT) POPULATION* [179:219, 223]

	(A) Mometasone			(B) Beclomethasone			(C) Placebo			Pooled	ANOVA P-Values			PAIRWISE COMPARI A-B	A-C	
EVALUATION	N	Mean	SD	N	Mean	SD	N	Mean	SD	SD	TRT	INV	T X I	A-B	A-C	B-(
Primary Efficacy Variable: POLLEN (RAGWEED) SEASON																
--am & pm nasal	115	0.84	0.24	112	0.79	0.29	109	0.63	0.36	0.29	<.01	<.01	0.02	0.11	<.01	
Secondary Efficacy Variable: FIRST WEEK OF POLLEN SEASON (*Efficacy population)																
--am & pm nasal	114	0.92	0.21	112	0.89	0.26	104	0.79	0.31	0.25	<.01	<.01	0.01	0.23	<.01	
Secondary Efficacy Variable: ENTIRE STUDY																
--am & pm nasal	116	0.89	0.19	116	0.85	0.22	115	0.75	0.26	0.22	<.01	<.01	0.19	0.15	<.01	
Supplementary Efficacy Variable: PROPHYLAXIS PERIOD (Prior to Pollen Season)																
--am & pm nasal	116	0.95	0.16	116	0.93	0.17	115	0.88	0.23	0.19	0.02	<.01	0.9	0.35	0.01	

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

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

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

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

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

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

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

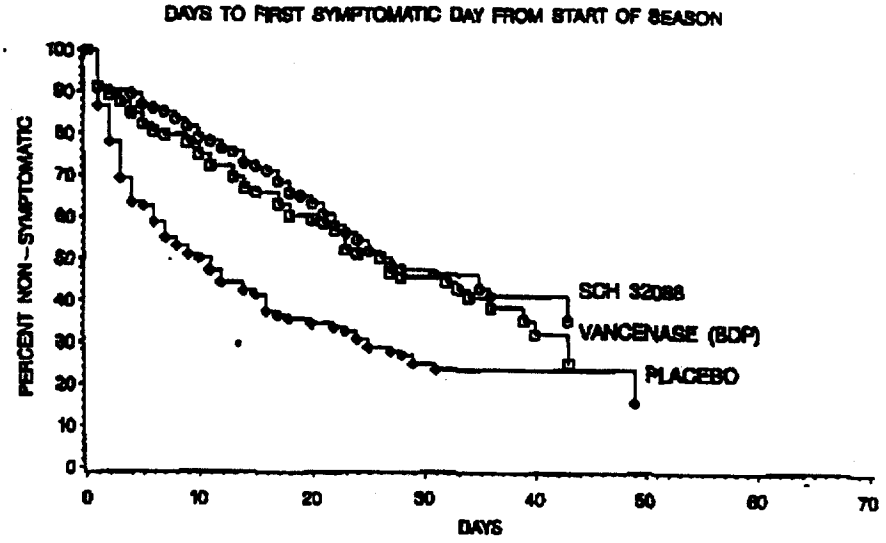

Figure 2. [182:1057]