8.20. Trial I94-078. Efficacy and Safety of Mometasone Furoate Nasal Spray vs. Budesonide Aqueous Nasal Spray, and vs. Placebo in the Treatment of Perennial Allergic Rhinitis (PAR).

Principal Investigator: None (Multi-center study)

Participating Centers: 25 centers in North, Central, and South America, and in Western Europe, Africa, and Australia.

8.20.1. OBJECTIVE:

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

8.20.2. STUDY DESIGN:

The study was a phase III, randomized, multi-center, double-blind, double-dummy, active- and placebo-controlled, parallel group study to determine the safety and efficacy of mometasone furoate 200 µg administered intranasally once daily (qd), vs. the active control, budesonide (Rhinocort Aqua) 400 µg administered once daily (qd), and vs. placebo for a total of 12 weeks for the treatment of perennial allergic rhinitis (plus 1 additional week of observation at the end of the double-blind treatment period (the 'offset' or Week 13 visit) [A51.1:15, A51.1:16, 38, A51.4:1062].

8.20.3. PROTOCOL:

8.20.3.1.a. POPULATION:

Entry criteria for this study were very similar to those for all other PAR studies, namely: (1) age ≥ 12 years (with the exception of age ≥ 18 years at sites -03 and -05 in Canada, site -08 in Denmark, site -021 in Norway, and site -022 in South Africa) [290:3, 20-21, 23, A51.1:16, 18, A51.4:1061, 1063], (2) presence of IgE-mediated hypersensitivity to a relevant perennial allergen (e.g. dust mite, cockroach, mold, or animal dander), as documented by a positive skin test within 2 years of study entry via the prick testing or intradermal method; or in the absence of a positive skin test, a diagnosed or suspected history of non-allergic rhinitis with eosinophilia syndrome (NARES) which had been corroborated by nasal cytology demonstrating eosinophilia [290:21, 23, 32, A51.1:16, 18, A51.4:1061, 1064, 1075-1076], and (3) presence of PAR symptoms of sufficient severity (nasal rhinorrhea and/or congestion scores at least moderate in severity (≥ 2), a total symptom score ≥ 5 at both screening and baseline, and rhinorrhea and/or congestion scores ≥ 2 during 4 of the last 7 days prior to the baseline visit), in order to begin study drug treatment [290:3-4, 21, 23, 42, A51.1:18, 28, 38, A51.4:1061-1062, 1064, 1078].

8.21.3.1.b. PROCEDURE:

A summary of the study procedure is provided by the Sponsor in Table 1. of Trial I94-078 and in an amendment (Volumes A51.1-A51.4, submitted by the Sponsor, Schering Plough, Inc. to the Pulmonary Division, HFD-570 on 04/16/97) to the NDA submission [290:55, A51.1:17, A51.4:1102], and is similar to the study design of PAR studies I92-293 and I94-079. Subjects were assessed at screening (Visit 1), baseline (Visit 2), and at Day 8 (Visit 3), 15 (Visit 4), 29 (Visit 5), and Weeks 8 (=Day 57, Visit 6), and 12 (=Day 85, Visit 7) of therapy [290:4, 29, 31-33, A51.1:16, 38, A51.4:1062, 1072, 1076-1077]. Subjects were also evaluated at Week 13 at the end of the 'off-set' period (Visit 8) when subjects were no longer receiving double-blind medication in order to assess duration of effect of each treatment in decreasing PAR symptoms [290:29, A51.1:16, 38, A51.4:1062]. Day 1 was designated as the start of treatment date [A51.1:16, 38]. Medication restrictions consisted of those previously discussed for the mometasone SAR and PAR studies [290:25-28, A51.1:24-26, A51.4:1067-1070], although subjects were allowed to use a rescue medication (loratadine, up to 10 mg po qd maximum dose) for intolerable PAR symptoms starting with the screening visit (the 7-14 day 'run-in' phase) and continuing for the duration of the study, including the offset period [290:31, 33, 45, A51.1:22, 28, A51.4:1063, 1069, 1073, 1077, 1081, 1091].

Subjects who met all inclusion criteria were randomized to one of the following 3 treatment groups, received diary cards to record symptoms reflectively over the previous 12 hours (upon awakening, before the a.m. dose and before retiring (p.m. recording)) and began therapy with study drug every a.m. and p.m. (4 bottles utilized for this double dummy design--each active drug had a matching placebo) [290:21-22, 34-37, A51.1:20-21, A51.4:1062-1063, 1071-1072, 1079-1081]:

(A) Mometasone aqueous nasal spray 200 µg qd		
a.m. dosing:	Bottle 1: Mometasone 200 µg	Bottle 2: Budesonide Placebo
p.m. dosing	NONE	
(B) Budesonide nasal spray (Rhinocort Aqua) 400 µg qd		
a.m. dosing:	Bottle 1: Mometasone Placebo	Bottle 2: Budesonide 400 µg
p.m. dosing:	NONE	
(C) Placebo (0 µg qd)		
a.m. dosing:	Bottle 1: Mometasone placebo	Bottle 2: Budesonide Placebo
p.m. dosing:	NONE	

Subjects underwent clinical efficacy and safety evaluation (including nasal exam on Visits 2 (baseline) and 7 (Week 12) during each study visit [290:22, 37

41, 46-48, A51.1:29-36, 47-48, A51.4:1077-1094]. Efficacy evaluation was again based on a 0-3 severity scale [290:42, A51.1:31-32, A51.4:1087], a 0-3 scale of the overall condition of PAR [290:42-43, A51.1:32, A51.4:1088], and a 1-5 scale of therapeutic response [290:43, A51.1:33, A51.4:1088-1089].

The primary efficacy variable [290:22, 50, A51.1:41, 45, A51.4:1097-1098] was defined as: the mean change from baseline (the mean of the a.m. and p.m. baseline scores and the a.m. and p.m. scores from the 7 prior consecutive days) in the total nasal symptom score over the initial 15 day study period (using a.m. + p.m. scores averaged from subject diaries) where the:

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

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

Secondary efficacy variables consisted of the following [290:51, A51.1:46, A51.4:1098]:

(1) The mean change from baseline in the total (diary) nasal symptom scores averaged over Days 16-30 (a.m. and p.m. combined), Days 31-45, Days 46-60, Days 61-75, and Days 76-90, [A51.1:46]:

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

(2) Endpoint total nasal symptom score (a.m. and p.m. combined): Endpoint score defined as the last available post-baseline value for each study subject, pooled across the 24 participating centers [A51.1:46].

(3) Mean change in the total nasal symptom score for the 'offset' (Week 13) visit [A51.1:46].

(4) Subject's self-evaluation of total symptom scores (nasal + non-nasal for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, endpoint visit, and the offset visit) [A51.1:46].

(5) Subject's self-evaluation of total non-nasal symptom scores (for days 1-15, days 16-30, days 31-45, days 46-60, days 61-75, days 76-90, endpoint visit, and the offset visit) [A51.1:46].

(6) Physician's evaluation of total nasal symptoms (for the Baseline visit, Day

[A51.1:46].

(7) Physician's evaluation of total symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit) [A51.1:46].

(8) Physician's evaluation of total non-nasal symptoms (for the Baseline visit, Day 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit) [A51.1:46].

(9) Subject's self-evaluation of overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [A51.1:46].

(10) Physician's evaluation of subject's overall disease condition using the PAR 0-3 point severity scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [A51.1:46].

(11) Subject's self-evaluation of overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [A51.1:46].

(12) Physician's evaluation of the subject's overall therapeutic response using the 1-5 point therapeutic response scale for study days 8, 15, 29, Week 8, Week 12, endpoint visit, and the offset visit [A51.1:46].

(13) The proportion of 'symptom-free' days (i.e. total nasal symptom=0) during the entire treatment period (i.e. excluding baseline visit) [A51.1:46].

Pollen counts were not collected in this study. Rescue medication use between the 3 treatment groups was not analyzed statistically but a frequency of rescue medication for all 3 treatment groups was tabulated, thus providing a general overview of differences in rescue medication use. Centers with 15 or fewer efficacy evaluable subjects were combined as a single large center for the purpose of efficacy analysis [A51.1:42]. Furthermore, since treatment-by-center interactions were not statistically significant (p=0.11), pooling of data across centers to obtain an overall assessment of treatment differences was considered acceptable [A51.1:44].

8.20.4. RESULTS

A total of 523 subjects with PAR were randomized into study I94-078, with no immediate drop-outs, leaving 523 subjects evaluable in the ITT population [A51.1:49]. One hundred and seventy one (171) subjects in the ITT population received mometasone treatment, 179 subjects received budesonide, and 173 subjects received placebo [A51.1:49]. An additional 60 subjects were excluded from efficacy analyses because of various protocol violations, leaving 463 subjects in the efficacy evaluable population [A51.1:43, 49].

The treatment groups in this study were comparable with regard to demographic and disease characteristics [A51.1:50]. Again, for all 3 treatment groups, the majority of subjects were Caucasian, although approximately 32-35%

Approximately 1.5-2 times the number of female than male subjects per treatment group were enrolled in this study [A51.1:51]. Approximately 25% of the subjects had SAR in addition to PAR and the majority did not have the NARES syndrome (15 subjects total were diagnosed with NARES; 4 subjects in the mometasone treatment group, 7 subjects in the budesonide group, and 4 in the placebo group) [A51.1:53, 206-208]. Additionally, evaluation of subjects by severity (0-3 scale) of PAR at baseline failed to reveal a statistically significant difference among the 3 treatment groups with the majority of subjects in all 3 groups having 'moderate' PAR symptoms at baseline [A51.1:53]. Numerically, a slightly greater percentage of 'severe' PAR subjects comprised the budesonide and placebo treatment groups [A51.1:53].

Analysis of the primary efficacy variable for the ITT population demonstrated greater efficacy of both active treatment groups in decreasing total nasal symptoms for the day 1-15 interval, compared with placebo. The raw total nasal symptom score/unit change for the mometasone treatment group was 4.1 (with a -2.4 unit decrease in total nasal symptoms from baseline or a -34% change), compared with a raw total nasal symptom score of 4.9 (-1.6 unit decrease in total nasal symptoms or -23% change) for the placebo group ($p<.01$) [A51.2:310], and a raw total nasal symptom score of 3.8 (-2.7 unit decrease in total nasal symptoms or -39% change) for the budesonide treatment group ($p<.01$ for budesonide vs. placebo) [A51.2:310]. No statistically significant difference was noted between the mometasone and budesonide treatment groups, although a greater numerical response in total nasal symptoms was noted in budesonide treated subjects. Furthermore, no significant difference was noted between the a.m. and p.m. total nasal symptom scores or change in scores in the mometasone treatment group for the day 1-15 interval (mometasone group a.m. raw total nasal symptom score/change in raw score=4.2/-2.5 unit change vs. mometasone group p.m. raw total nasal symptom score/change in raw score=4.1/-2.3 unit change), again supporting once daily dosing of mometasone [A51.2:337, 339]. Additionally, no significant difference in the primary efficacy variable was noted between the ITT and efficacy evaluable population [A51.2:310, 344].

A summary of results for the primary and secondary efficacy variables is summarized in Table I. and Table II. below and overall, support the efficacy of mometasone in decreasing the symptoms of PAR. While no statistically significant difference was demonstrable between mometasone and budesonide treatment, in general, budesonide treated subjects demonstrated greater numerical decreases in their respective symptom scores than did mometasone treated subjects.

No significant difference in clinical efficacy was noted based on age or gender, with the exception that ITT female subjects in the 18-64 year age range for the 2 active treatment groups showed a greater mean reduction in the total nasal symptom scores from baseline than did ITT male subjects or ITT female subjects 12-17 years or >64 years of age [A51.2:350]. Nonetheless, the number of subjects comprising the sub-groups were too small (i.e. age 12-17 or >64 years) to make

group analyses were not performed in this study.

Analysis of subject and physician-rated individual nasal and non-nasal symptoms are summarized in Table III. below. Results of this study are similar to previous PAR studies; namely, that mometasone treatment was more effective in decreasing the nasal symptoms of PAR than non-nasal symptoms. Interestingly, in this PAR study (similar to study I94-079) mometasone treatment was noted to have a statistically significant effect on nasal congestion--a symptom generally shown to be minimally affected by mometasone treatment in the other studies reviewed in this NDA submission. Mometasone treatment likewise demonstrated a very small numerical response in decreasing the individual non-nasal symptoms of PAR (Table III.), however these changes were not always found to be statistically significant as compared with placebo. Analysis of the 'offset' visit indicates that for nasal symptoms, the mometasone subjects, while not always statistically significant, did demonstrate a greater decrease in PAR symptoms than did placebo treated subjects one week after discontinuation of treatment. These findings suggest that mometasone (also budesonide) continues to provide some relief of PAR symptoms 1 week after discontinuation of medication and suggests that mometasone has a somewhat prolonged duration of action once subjects reach steady state dosing. Also, while numerically small, mometasone treatment increased the mean proportion of 'symptom-free' days for the entire study duration to 13.1 days, compared to 5.2 'symptom-free' days for placebo treated subjects ($p<.01$, no significant difference noted between the mometasone and budesonide treatment groups) [A51.2:341].

Analysis of rescue medication use (ITT population) in the 3 treatment groups revealed lower rates of rescue medication use in the two active drug groups (30% of mometasone subjects, 31% of budesonide subjects, and 34% of placebo subjects used rescue medication > 1 time during the study) [A51.2:305]. A greater percentage of placebo group subjects tended to use rescue medication > 6 times throughout the study duration than did subjects in either of the 2 active drug groups [A51.2:305].

Table I. Primary Efficacy Variable of PAR and Treatment with Mometasone (ITT Population) [A51.2:310]

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

sx=Symptom

* Note: Statistically significant response for 1° efficacy variable in the efficacy evaluable population (ITT data not provided) carried by 2 of the 25 distinct study centers (i.e. 23/25 centers had a statistically non-significant response, although 2 of these 23 centers were close to being statistically significant) [A51.2:311-335]. Centers 001, 002, 008, 015, and 023 were combined into a single large center for analysis because each center had ≤ 10 subjects [A51.1:65].

Table II. Secondary Efficacy Variables of PAR and Treatment with Mometasone (ITT Population), [A51.2:310, 341, 354, 383, 387, 390, 392, 415-416, 452-453, 489-490, 516-517]

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

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

Table III. Change in Individual PAR Symptoms (Subject and Physician Evaluated, a.m. and p.m. combined) with Mometasone Treatment (ITT Population), [A51.2:395-398, 400-403, 405-408, 410-413]

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

Sx=Symptom

8.20.4.3. ADVERSE EVENTS:

The safety analysis was based on 523 subjects in the ITT population; 171 subjects were treated with mometasone 200 μg qd, 179 subjects were treated with with budesonide 200 μg qd, and 173 subjects were treated with placebo [A51.1:78]. Safety analysis consisted of an assessment of adverse events and changes in vital signs, ECGs, physical, and nasal examinations, and clinical laboratory tests relative to baseline [A51.1:33-36, A51.4:1076-1086].

Adverse events were again similar for all three treatment groups, with headache, closely followed by viral infection being the most frequently reported treatment-related adverse events. Overall, adverse events were reported in 61% of subjects in the mometasone group, 66% of subjects in the budesonide treatment group, and 53% of subjects in the placebo group [A51.1:78-79, A51.2:544]. Headache was reported in 18% of mometasone subjects and 19% of budesonide subjects, compared to 21% of placebo subjects [A51.1:80, A51.2:545]. Viral infection was reported in 15% of subjects in the mometasone group, 20% of subjects in the budesonide group, and 18% of subjects in the placebo group [A51.1:81, A51.2:550]. Reported next in frequency were epistaxis and pharyngitis; with 13% of subjects in the mometasone group, 16% of subjects in the budesonide group, and 7% of placebo subjects reporting epistaxis [A51.1:81, A51.2:551], and 9% of subjects in the mometasone group, 13% of subjects in the budesonide group, and 11% of placebo subjects reporting pharyngitis, respectively [A51.1:81, A51.2:551]. In terms of the demographic distributions of adverse events, headache and pharyngitis were noted to be reported more frequently in females than males. Headache, epistaxis, and pharyngitis were less frequent in subjects < 18 years of age (n=74) than in subjects 18-64 years of age. Viral infection, epistaxis and pharyngitis were more frequent in Caucasians than in Hispanics [51.2:573-633]. While noted, none of these differences were likely clinically significant.

There were no reports of nasal septal perforation in any of the 3 treatment groups but again, several subjects in both active drug treatments were noted to have nasal ulcerations post-treatment (individual subject line listings of nasal examinations were not submitted with the study report for I94-078). No assessment of glaucoma/cataract formation or suppression of the HPA-axis was performed in this PAR study. No deaths were reported in any of the 3 treatment groups but one case of spontaneous abortion in a 32 year old female > 30 days after completion of the study was reported in a mometasone treatment subject (subject I94-078-21, #019) [290:10, A51.1:95, A51.3:636]. This event was felt not to be related to study medication by the principal investigator, as the subject was using an intrauterine device (IUD) as a contraceptive throughout the study and at the time of conception which may have contributed to and/or resulted in spontaneous abortion.

In terms of infection, viral infection (see above) was reported as the most frequent ADR in all 3 treatment groups in this study. Herpes simplex infection

or placebo group) [A51.2:550]. No subjects in either of the three treatment groups were reported to have nasal or oral candidiasis on any clinic visits [A51.2:550].

A total of 11 subjects discontinued treatment because of adverse events (1 subject in the mometasone group, 5 subjects in the budesonide group, and 5 subjects in the placebo group) [A51.1:93]. The one mometasone subject (subject I94-078-02, #010) discontinued the study because of a severe facial rash which was felt to be 'probably' related to study drug [A51.1:94, 295].

No clinically relevant changes in vital signs, physical exam (with the exception of the above nasal ulcer findings), ECGs, or laboratory tests from pretreatment were noted in any of the 3 treatment groups with the exception of one report of an increased SGPT (from 12 U/L at screening to 92 U/L by Week 12 (Visit 7), subject I94-078-07 , #001) [A51.1:97, A51.3:640] and one report of a decrease in the WBC (from 4.04 x 10^3/mm^3 at screening to 2.5 x 10^3/mm^3 by Week 12, subject I94-078-09, #008) [A51.1:97, A51.3:640] in mometasone treated subjects. Flag shift distributions of laboratory values failed to reveal any significant patterns of change in any of the 3 treatment groups or for any of the demographic sub-groups.

8.20.5. CONCLUSIONS:

1. The results of this study support the safety and efficacy of mometasone 200 µg qd for the treatment of symptoms of perennial allergic rhinitis, as assessed for up to 12 weeks (plus 1 week off medication) in subjects with PAR.
2. In terms of individual PAR symptoms, mometasone treatment demonstrated a statistically significant effect in decreasing the PAR symptoms of rhinorrhea, nasal congestion, sneezing, and nasal itch for most study visits, as compared with placebo. Mometasone did not show a statistically significant response in decreasing the non-nasal symptoms of PAR although a small degree of improvement was demonstrated in mometasone treated subjects, as compared with placebo for all 4 non-nasal symptoms.
3. Mometasone treatment demonstrated adequate duration of effect in treating PAR symptoms over 24 hours, supportive of once a day dosing. Mometasone treatment also appeared to continue to provide efficacy in the treatment of PAR symptoms for at least one week after discontinuation of treatment.

9.0. INTEGRATED SUMMARY OF EFFICACY

The clinical program for mometasone furoate (Sch 32088) nasal spray evaluated efficacy for 3 major clinical indications: (1) seasonal allergic rhinitis (SAR), (2) prophylaxis of seasonal allergic rhinitis, and (3) perennial allergic rhinitis (PAR), in adult subjects ≥ 12 years of age. A total of 20 clinical studies were reviewed for efficacy in NDA 20-762.

9.1. Summary of Efficacy Studies for each indication reviewed in NDA 20-762:

(1) The database of efficacy for seasonal allergic rhinitis (SAR) was generated from 8 studies (U.S. and international) in NDA 20-762, which consisted of the following:

(A) Four (4) phase III randomized, multi-center, double-blinded, active- and placebo-controlled trials of mometasone 200 µg qd in adult SAR subjects at least 2 weeks in duration (studies C93-013 (pivotal SAR study), I92-200, I94-001, and C94-145).

(B) One (1) phase II, randomized, multi-center, placebo-controlled, parallel group, dose ranging study of mometasone nasal spray (50, 100, 200, and 800 µg qd) vs. placebo for 2 weeks for the treatment of adult SAR (study C92-011).

(C) One (1) phase III randomized, double-blinded, placebo-controlled, parallel group, two-arm mometasone onset of action study of mometasone 200 µg qd vs. placebo for the treatment of adult SAR (study C93-184).

(D) Two (2) phase III, randomized, double-blinded, placebo-controlled, parallel group nasal provocation studies with allergens investigating the effect of mometasone pre-treatment on early and late phase allergic inflammation in adult subjects with SAR (studies C93-193 and I94-139).

(2) For prophylaxis of seasonal allergic rhinitis in adult subjects ≥ 12 years of age, two (2) studies (one U.S. (study C93-215, the pivotal prophylaxis study) and the other, an international (study I93-133)) were submitted in NDA 20-762 and reviewed. Both studies were randomized, multi-center, active- and placebo-controlled.

(3) The efficacy database for perennial allergic rhinitis (PAR) in adult subjects ≥ 12 years of age consisted of a total 10 studies, 9 of which were submitted to NDA 20-762 at the time of filing (October 1, 1996). Four (4) of these 10 studies were randomized, placebo-controlled trials (studies C92-280 (pivotal PAR study), I92-293, I94-079, and I94-078). Another 4 studies (C93-014, I93-018, I93-180, and C94-052) were active- but not placebo

controlled and one (1) study (I93-221) was a 6 month open label, noncomparative (no placebo group) study. One additional study (study C94-092) was a placebo controlled study that assessed the response of PAR symptoms in elderly subjects (defined as age ≥ 65 years).

The general trial design and subject accounting for the intent-to-treat (ITT) population (the population generally used in this review to assess efficacy, in addition to safety) for the 20 studies reviewed in the efficacy database for mometasone furoate nasal spray is summarized below in Tables I.-III.

Table I. Seasonal Allergic Rhinitis (SAR) Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)
Phase III, active- and placebo controlled.	C93-013 (Pivotal SAR),	4 weeks	C93-013: Mometasone (200 µg qd): 112 Beclomethasone (168 µg bid): 116 Placebo (0 µg qd): 116
	I92-200	• • •	I92-200: Mometasone (100 µg qd): 126 Mometasone (200 µg qd): 125 Beclomethasone (200 µg bid): 125 Placebo (0 µg qd): 121
Phase III, active- and placebo controlled.	I94-001,	2 weeks	I94-001: Mometasone (200 µg qd): 104 Fluticasone (200 µg qd): 104 Placebo (0 µg qd): 103
	C94-145	• • •	C94-145: Mometasone (200 µg qd): 176 Mometasone (200 µg qd) + Loratadine (10 mg po qd): 169 Loratadine (10 mg po qd): 181 Placebo (0 µg qd): 176
Phase II, dose ranging, placebo controlled.	C92-011	4 weeks	C92-011: Mometasone (50 µg qd): 96 Mometasone (100 µg qd): 95 Mometasone (200 µg qd): 98 Mometasone (800 µg qd): 95 Placebo (0 µg qd): 95
Phase III, onset of action, placebo controlled.	C93-184	2 weeks	C93-184: Mometasone (200 µg qd): 101 Placebo (0 µg qd): 99
Phase III, placebo controlled, 2-period crossover, nasal provocation studies.	C93-193	2 weeks	C93-193: Mometasone (200 µg qd): 20 Placebo (0 µg qd): 21
	I94-139	• • •	I94-139: Mometasone (200 µg qd): 24 Placebo (0 µg qd): 24

Table II. Prophylaxis of SAR Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)
Phase III, active- and placebo controlled.	C93-215 (Pivotal Prophylaxis of SAR),	8 weeks total; (4 week prophylaxis period, followed by a 4 week ragweed period assessment)	C93-215: Mometasone (200 µg qd): 116 Beclomethasone (168 µg bid): 116 Placebo (0 µg qd): 115
	I93-133	- - -	I93-133: Mometasone (200 µg qd): 168 Budesonide (400 µg qd): 172 Placebo (0 µg qd): 173

Table III. Perennial Allergic Rhinitis (PAR) Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)
Phase III, active- and placebo controlled.	C92-280 (Pivotal PAR),	12 weeks	C92-280: Mometasone (200 µg qd): 164 Beclomethasone (168 µg bid): 163 Placebo (0 µg qd): 163
	I92-293	12 weeks	I92-293: Mometasone (200 µg qd): 143 Beclomethasone (200 µg bid): 146 Placebo (0 µg qd): 138
	I94-079	12 weeks (+ 1 week off treatment: offset period)	I94-079: Mometasone (200 µg qd): 181 Fluticasone (200 µg qd): 183 Placebo (0 µg qd): 184
	[1]I94-078	12 weeks (+ 1 week off treatment: offset period)	I94-078: Mometasone (200 µg qd): 171 Fluticasone (200 µg qd): 179 Placebo (0 µg qd): 173
Phase III, active-controlled (no placebo).	[2]C93-014 (1 yr. F/U of C92-280)	Up to 52 weeks (1 year)	C93-014: Mometasone (200 µg qd): 100 Mometasone (100-400 qd): 95 Beclomethasone (168 µg bid): 95
	[2]I93-018 (1 yr. F/U of I92-293)	Up to 52 weeks (1 year)	C94-145: Mometasone (200 µg qd): 77 Mometasone (100-400 qd): 80 Beclomethasone (200 µg bid): 71
	[2]I93-180 (Nasal bx study)	Up to 52 weeks (1 year)	I93-180: Mometasone (200 µg qd): 69 Fluticasone (200 µg qd): 72
	[2]C94-052 (HPA study)	Up to 52 weeks (1 year)	C94-052: Mometasone (200 µg qd): 175 Triamcinolone (220 µg qd): 176
Phase III, placebo controlled geriatric study (age ≥ 65 yrs.)	C94-092	12 weeks	C94-092: Mometasone (50 µg qd): 170 Placebo (0 µg qd): 164
Noncomparative (no placebo).	[2]I93-221	26 weeks (6 months)	C93-184: Mometasone (100, 200 or 400 µg qd): 331

[1]Study I94-078 was amended to the original NDA for mometasone.

[2]Safety assessment (and not efficacy) was the primary objective of these studies. Hence these placebo uncontrolled studies were not designed to statistically evaluate efficacy of mometasone.

In summary, greater than 3000 (a total of 3381) mometasone treated subjects (all doses) comprised the ITT population for efficacy evaluation for the 3 clinical indications assessed in NDA 20-762. For the SAR indication, 812 mometasone treated subjects were evaluated in active- and placebo-controlled trials, and of these 812 subjects, 517 received mometasone 200 µg qd. A total of 284 mometasone treated subjects were evaluated in active- and placebo-controlled trials for the prophylaxis of SAR indication, all of whom were treated with mometasone 200 µg qd. A total of 829 mometasone 200 µg qd treated subjects were evaluated in placebo controlled trials for the PAR indication, and of these 829 mometasone subjects, 659 were evaluated in active- and placebo-controlled trials. Nine hundred and twenty seven (927) mometasone subjects were evaluated in uncontrolled trials for the PAR indication.

9.2. Study Design Issues and Efficacy Results

9.2.1. Seasonal Allergic Rhinitis (SAR)

9.2.1.a. Study Design

The study design of all SAR studies (including the pivotal study C93-013) were overall similar with minor modifications from study to study. Study subjects were to have a history of SAR to aeroallergens (trees, grass, pollen) for at least 2 years (confirmed by skin prick or intradermal skin testing) and were to be symptomatic at the screening and baseline visits. The SAR symptoms assessed in all studies consisted of nasal (rhinorrhea, congestion, sneezing, and nasal itch), non-nasal (eye redness, eye itch, eye tearing, and ear and/or palatal itch), and total (nasal plus non-nasal) SAR symptoms which were rated on a 0-3 (no, mild, moderate, and severe) symptom severity scale. Subjects rated their SAR symptoms reflectively over the previous 12 hours in the a.m. and p.m. (twice daily). Instantaneous symptom scores were not recorded. Additionally, subjects' overall condition of rhinitis and therapeutic response to treatment were rated using a 0-3 and 1-5 point scale, respectively. Rescue medication use was only allowed in 3 of the 4 active- and placebo-controlled trials (C93-013, I92-200, and I94-001). Subjects received study medication for at least 2 weeks total in all SAR studies submitted in NDA 20-762.

The primary efficacy endpoint for 3 of the 4 active- and placebo-controlled trials (C93-013, C94-145, and I94-001) was defined as the subject rated mean change in the total nasal symptom score over the initial 15 day study period for combined a.m. and p.m. scores. Study I92-200 defined the primary efficacy variable as the subject rated mean change in the total nasal symptom score over the first week for combined a.m. and p.m. scores. For the dose-ranging study (C92-011) the primary efficacy variable was prospectively defined as the physician rated mean change in the total nasal symptom score over the initial 15 day study period for combined a.m. and p.m. scores, however the subject rated mean change in total nasal symptom scores for days 1-15 was also examined. For the onset of action

study (C93-184), the primary efficacy variable was defined as the clock time (in hours) from the start of treatment that the subject first experienced 'moderate' relief of total nasal symptoms, 'moderate' being defined as a therapeutic response score ≥ 3 (as per the 1-5 rating system discussed above). For this study as well, the subject rated mean change in total nasal symptom scores for days 1-15 was also examined. And while the main objective of the two nasal provocation studies (C93-193 and I94-039) was to evaluate nasal lavage levels of specific chemical mediators of allergic rhinitis before and after treatment with mometasone and not to determine clinical efficacy per se, these 2 studies did nonetheless evaluate total and individual nasal symptom scores.

9.2.1.b. SAR Efficacy Results

Analysis of efficacy for the 8 SAR trials indicates that mometasone administered once daily was more effective in decreasing SAR symptoms than placebo and was not statistically significantly different from the active comparator(s) in terms of efficacy in those studies which incorporated an active control arm.

9.2.1.b.1. Active- and Placebo- Controlled Studies

Results of the 4 active- and placebo-controlled trials which includes the pivotal SAR study (C93-013) are summarized below in Table IV. and support the conclusion that mometasone was statistically significantly more effective in decreasing subject rated mean total nasal symptom scores for the initial 15 day study period (the primary efficacy endpoint), as compared with placebo.

ARTWORK THIS WAY
ON ORIGINAL

Table IV. **Efficacy of Mometasone vs. Placebo in the Treatment of SAR:** Primary Efficacy Variable for the ITT Population for Active- and Placebo-Controlled Trials in NDA 20-762

STUDY	MOMETASONE 200 µg qd: (unless otherwise specified): [1]Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	PLACEBO: Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	[2]P-Value
C93-013	-2.3/(-25%)	-1.5/(-16%)	<.01
I92-200	Mometasone 100 µg qd: -4.3/(-52%)	-2.7/(-35%)	<.01
	Mometasone 200 µg qd: -4.7/(-58%)	-2.7/(-35%)	<.01
I94-001	-2.8/(-36%)	-1.0/(-11%)	<.01
C94-145	Mometasone 200 µg qd: -2.7/(-32%)	-1.3/(-13%)	<.01
	Mometasone 200 µg qd + Loratadine 10 mg po qd: -3.0/(-35%)	-1.3/(-13%)	Direct comparison not performed.

Δ= Change, [1]Study I92-200: the primary efficacy variable was defined for Week 1 of treatment, not days 1-15.
[2]P-value is for comparison of mometasone vs. placebo using 2-way ANOVA.
NOTE: Total nasal symptom score for a.m. and p.m. combined.

In general, mometasone treated subjects demonstrated a 2.3-4.7 unit decrease in total nasal symptom scores (25-58% decrease) for the primary efficacy variable compared with a 1.0-2.7 unit decrease (13-35% decrease) with placebo treatment. For study C94-145, addition of the antihistamine loratadine to mometasone treatment demonstrated a small, additive effect in decreasing total nasal symptom scores for the day 1-15 study period but in this study, the majority of efficacy was carried by mometasone treatment.

Analysis of the a.m. total nasal symptom scores (end of dosing interval) and separate a.m. and p.m. symptom scores for these 4 active- and placebo-controlled studies demonstrated that mometasone treatment had statistically greater efficacy in the a.m. than placebo (supporting a 24 hour duration of action), with no significant difference in a.m. vs. p.m. symptom scores. In general, of the 4 nasal symptoms, rhinorrhea (nasal discharge) was the only nasal symptom which consistently demonstrated a statistically significant decrease post-mometasone treatment. While nasal congestion also showed a statistically significant decrease with mometasone, as compared to placebo treatment (especially in the pivotal SAR study C93-013), this was not consistently shown in all SAR studies.

Review of the total and individual non-nasal symptoms for these 4 studies revealed that mometasone treatment did not show a consistent effect in decreasing non-nasal symptoms although a slight numerical advantage (though not statistically significant) for mometasone treatment was evident in decreasing non-nasal symptoms compared with placebo at some study timepoints.

Review of rescue medication use in the 3 studies that allowed it indicated that mometasone treated subjects (also active comparator subjects) used less rescue medication and used it less frequently than placebo treated subjects, although the studies did not perform a statistical comparison of these treatment group differences.

9.2.1.b.2. Nasal Provocation Studies

Inclusion of the 2 nasal provocation studies (C93-193 and I94-139) as supportive studies of efficacy confirmed the findings of the other SAR studies; namely that mometasone treatment resulted in a statistically significant difference in the mean change in total nasal symptom scores post-treatment during nasal challenge with allergen, as compared with placebo.

Analysis of subject SAR response to treatment by demographics (age, gender, and race) overall failed to reveal any consistent pattern of differential response. Worth noting only because it was a pivotal study, was the greater response in SAR symptoms of female subjects over male subjects in study C93-013. This treatment by gender interaction most likely represents sampling variation as there are no known or reported gender differences in nasal mucosa or the allergic response that would account for a different response in female subjects (Also, refer to Statistical Review and Evaluation, Dr. James Gebert, NDA 20-762, p. 4). This pattern of response was not noted in any of the other 7 SAR studies individually although a post-hoc pooled analysis of total nasal symptom scores for female vs. male subjects in 4 SAR studies (C93-013, C93-184, I94-001, and C94-145) revealed that female subjects had a -3.0 unit decrease in total nasal symptoms from baseline (-36% decrease) for the initial 15 day study period, compared to a -2.5 unit decrease in total nasal symptoms from baseline (-29% decrease) in male study subjects for the initial 15 day study period [302:43-44].

9.2.1.b.3. Mometasone Dose Ranging Results in SAR

One phase II, dose ranging study of mometasone (C92-011) was conducted to determine the optimum dose of mometasone in the treatment of SAR in adult subjects, although one other study (I92-200) for the SAR indication in NDA 20-762 compared two doses of mometasone (100 and 200 µg qd) against an active comparator (beclomethasone), and against placebo.

The phase II dose ranging study of mometasone treatment compared doses of 50, 100, 200, and 800 µg qd of mometasone against placebo, administered for up to 4 weeks. All doses of mometasone demonstrated a statistically significant decrease in physician (the primary efficacy variable) and subject rated total nasal

symptom scores by Day 7 of treatment. Whereas doses of 50 and 100 μg qd of mometasone showed less consistent effectiveness on Days 3 and 7 of treatment, the 200 μg qd dose provided consistent and statistically significant efficacy compared with placebo for the 4 weeks of the study. In summary, the 200 μg qd dose of mometasone demonstrated the most favorable dose response, with a decrease in physician and subject rated total nasal symptom scores similar, if not superior at Day 3, 7, 14, 21, and 28 of treatment to the 800 μg qd dose of mometasone. In other words, the 800 μg qd dose of mometasone offered no additional efficacy in reducing SAR symptoms than did the 200 μg qd dose. Review of the response of non-nasal SAR symptoms at the different doses of mometasone likewise revealed a less consistent numerical response of the 50 and 100 μg qd doses in decreasing non-nasal symptoms than the 200 μg qd dose, with no added benefit seen with the 800 μg qd dose. A.m. vs. p.m. SAR symptom scores were not assessed in this study, hence no comment can be made regarding end of dosing interval efficacy in study C92-011.

Results for the different demographic subgroups (age, gender, and race) were similar in inference for the different doses of mometasone, with no significantly different patterns of response noted across these subgroups.

Evaluation of the 100 μg qd dose of mometasone vs. the 200 μg qd dose of mometasone in the treatment of total nasal symptoms of SAR (Study I92-200) revealed more consistent efficacy of the 200 μg qd dose of mometasone in numerically decreasing total nasal symptoms during the first week of treatment, although statistical significance in efficacy was reached by both doses of mometasone, as compared with placebo. Both doses showed that after Day 3 of treatment, a.m. total nasal symptom scores were statistically significantly lower than placebo, thus supporting maintenance of activity during once daily dosing of mometasone.

9.2.1.b.4. Mometasone Onset of Action Results for SAR

One study (C93-184) in NDA 20-762 specifically examined the onset of action of mometasone 200 μg qd vs. placebo, where treatments were administered to SAR subjects over 14 days. Analysis of the primary efficacy variable of time to onset of 'noticeable' relief of SAR symptoms in hours post-initiation of treatment with mometasone or placebo in subjects who were 'censored' or excluded from data analysis at 72 hours if they did not notice any improvement in nasal symptoms showed that the mean and median (50%) onset time to relief of symptoms was 39.2 and 35.9 hours, respectively, for the mometasone 'responder' subjects, and 53.4 and >72 hours, respectively, for placebo subjects (p-value =0.0001 for mometasone vs. placebo via the log-rank test). Based on a different endpoint evaluated in this study but using the same 'censored' subjects--the 'percentage' of subjects experiencing at least moderate relief of SAR symptoms; results obtained from this study indicated that for most mometasone treated subjects, onset of action occurred somewhat later than 1.5 days (or 39.2 hours). At day 3 of treatment, slightly greater than 50% of mometasone treated subjects experienced

moderate SAR symptom relief, compared with approximately 30% of placebo subjects. The onset of 'moderate' nasal symptom relief data for mometasone vs. placebo treated subjects are summarized in Table I. below. Comparison of the a.m. and p.m. symptom scores and the proportion of subjects experiencing at least 'moderate' symptom relief in the mometasone treatment group revealed a statistically significant response of mometasone subjects in the a.m. scores compared with placebo treatment, once again, indicating a 24 hour duration of action of mometasone and supporting once daily dosing of mometasone. Greater efficacy of mometasone in decreasing non-nasal symptoms of SAR, as compared with placebo, was not demonstrated in this study. Again, no significant demographic differences in response based on age, gender, or race were demonstrable in this study.

Table I: Percentage and Proportion of Subjects Experiencing at Least Moderate Relief (Efficacy Population), Study C93-184 [175:, 47, 122]

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

* Fisher's exact test.

Review of total nasal symptoms for the efficacy population (ITT not available in NDA 20-762) for Days 1-8 (data for days 5-8 not depicted in Table II. below) of treatment in study C93-184 indicates that although a greater numerical decrease in the total nasal symptom score in mometasone treated subjects was demonstrable by 12 hours post-initiation of treatment, as compared with placebo [175: 126], a statistically significant mean change in the total nasal symptom score for mometasone treated subjects, as compared with placebo was only seen in the

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

Evaluation of the onset of action of mometasone 200 µg qd vs. placebo, in the treatment of the total nasal symptoms of SAR was also examined in the pivotal SAR study C93-013, using ITT population data generated from primary SAS Datafiles by Dr. James Gebert, Biostatistics, FDA. These results are summarized in Table III. below and indicate that a statistically significant mean change in total nasal symptoms (a -2.1 mean change in total nasal symptoms in mometasone treated subjects vs. a -1.1 mean change in total nasal symptoms in placebo subjects, p=0.01) was demonstrable in mometasone treated subjects by the Day 3 p.m. score (approximately 60 hours or 2.5 days), as compared to placebo subjects. Thus these onset of action results for mometasone are consistent with the onset of action data of study C93-184.

In summary, based on studies C93-184 and C93-013, statistically significant and consistent efficacy of mometasone 200 µg qd in decreasing total nasal symptoms of SAR (i.e. onset of action), as compared with placebo, appears to be between 2.0-2.5 days after initiation of treatment, although some subjects may experience SAR symptom relief earlier than this time point.

Table II: Total Nasal Symptom Scores and Mean Change in Total Nasal Symptom Scores for Mometasone vs. Placebo Treatment; Days 1-4, Post-Initiation of Treatment (Efficacy Population), Study C93-184 [175:125-126]

		Mometasone (200 µg)	Placebo	*P-Value
Baseline				
–a.m.		8.5	8.5	0.82
–p.m.		8.2	8.6	0.21
Day 1				
–a.m.	RAW	-	-	-
	CHANGE	-	-	-
[1]–p.m.	RAW	6.9	7.9	0.01
	CHANGE	-1.4	-0.7	0.09
Day 2				
[2]–a.m.	RAW	7.1	8.0	0.01
	CHANGE	-1.3	-0.6	0.01
–p.m.	RAW	6.4	7.1	0.06
	CHANGE	-1.8	-1.5	0.35
Day 3				
–a.m.	RAW	6.3	7.4	<.01
	CHANGE	-2.2	-1.1	<.01
–p.m.	RAW	5.6	6.8	0.01
	CHANGE	-2.6	-1.8	0.05
Day 4				
–a.m.	RAW	5.8	7.1	<.01
	CHANGE	-2.7	-1.4	<.01
–p.m.	RAW	5.2	6.8	0.01
	CHANGE	-3.0	-1.8	0.05

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

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

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

Table III: Total Nasal Symptom Scores and Mean Change in Total Nasal Symptom Scores for Mometasone vs. Placebo Treatment; Days 1-5, Post-Initiation of Treatment (ITT Population), SAR Study C93-013 [SAS Datafiles, C93-013, Dr. James Gebert]

		Mometasone (200 µg)	Placebo	*P-Value
Baseline				
–a.m.		7.7	7.7	0.98
–p.m.		7.5	7.4	0.74
Day 1				
–a.m.	RAW	-	-	-
	CHANGE	-	-	-
[1]–p.m.	RAW	6.7	6.9	0.54
	CHANGE	-0.8	-0.6	0.47
Day 2				
[2]–a.m.	RAW	6.9	7.0	0.79
	CHANGE	-0.8	-0.7	0.77
–p.m.	RAW	6.0	6.3	0.46
	CHANGE	-1.5	-1.1	0.29
Day 3				
–a.m.	RAW	6.3	6.6	0.48
	CHANGE	-1.4	-1.1	0.46
–p.m.	RAW	5.5	6.4	0.01
	CHANGE	-2.1	-1.1	<.01
Day 4				
–a.m.	RAW	5.8	6.6	0.03
	CHANGE	-1.9	-1.1	0.03
–p.m.	RAW	5.3	6.5	<.01
	CHANGE	-2.1	-1.0	<.01

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

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

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

9.2.2. Prophylaxis of Seasonal Allergic Rhinitis (SAR)

9.2.2.a. Study Design

Two studies (C93-215 and I93-133) were conducted to assess whether prophylaxis with mometasone treatment 4 weeks prior to the anticipated onset of the allergy season would statistically significantly decrease SAR symptoms compared with placebo prophylaxis. An important flaw in the design of both studies was the omission of a mometasone treatment group at the start of the allergy season which would allow a direct comparison of the mometasone prophylaxis group with mometasone treatment initiated at the onset of the allergy season.

Important inclusion criteria for both studies included an asymptomatic clinical status for study subjects, defined as a total nasal symptom score ≤ 2 on a 0-3 symptom severity scale. Again, subject rated SAR symptoms (nasal and non-nasal) reflectively over the previous 12 hours, twice daily (in the a.m. and p.m.). Rescue medication use was not allowed in study C93-215 (the pivotal study) but was allowed in I93-133 (loratadine, up to 10 mg po qd). Subjects were treated for up to 8 weeks total with study medication in both studies (4 weeks of prophylaxis treatment and 4 weeks of continued treatment during the 'pollen' season). The primary efficacy variable for both studies was defined as the mean proportion of minimal symptom days (total nasal symptom score ≤ 2 for combined a.m. and p.m. scores) from the start of the pollen season, through the last day of treatment. An assessment of the total nasal symptom score for the day 1-15 interval during the pollen season was also performed and comprised one of the many supplementary efficacy variables in both studies.

9.2.2.b. Prophylaxis of SAR Efficacy Results

A summary of the efficacy results for the primary efficacy variable and the mean change in the total nasal symptom score for days 1-15 of the pollen season (analogous to the primary efficacy variable in the SAR studies) for studies C93-215 and I93-133 are summarized in Table V. and Table VI. below.

Table V. **Primary Efficacy Variable Analysis for Mometasone vs. Placebo in Prophylaxis of SAR:** Proportion of 'Minimal' Symptom Days During the Pollen Season (defined as a Total Nasal Symptom Score ≤ 2), ITT Population.

STUDY	MOMETASONE 200 µg qd:	PLACEBO:	[1]P-Value
C93-215	0.84	0.63	<.01
I93-133	0.84	0.65	<.01

[1]P-value is for comparison of mometasone vs. placebo using 2-way ANOVA and LSMeans pairwise comparisons.
NOTE: Total nasal symptom score for a.m. and p.m. combined.

Table VI. **Efficacy of Mometasone vs. Placebo in the Prophylaxis of SAR:** Mean Change in the Total Nasal Symptom Score for Days 1-15 of the Pollen Season, [1]ITT Population

STUDY	MOMETASONE 200 µg qd:	PLACEBO:	[2]P-Value
	Mean Δ in total nasal symptom score day 1-15 of pollen season (% Δ)	Mean Δ in total nasal symptom score day 1-15 (% Δ)	
C93-215	0.4/(86.6% increase in symptoms from the prophylaxis period)	1.6 /(367% increase in symptoms from the prophylaxis period)	<.01
[1]I93-133	0.3/(149% increase in symptoms from the prophylaxis period)	1.2/(230% increase in symptoms from the prophylaxis period)	<.01

Δ= Change, [1]ITT population except where otherwise noted (study I93-133), efficacy evaluable subjects analyzed.
[2]P-value is for comparison of mometasone vs. placebo using 2-way ANOVA and LSMeans pairwise comparisons.
NOTE: Total nasal symptom score for a.m. and p.m. combined.

In both studies, mometasone treated subjects demonstrated a statistically significantly greater proportion of minimal symptom days with treatment and a lower increase in the total nasal symptom score with onset of the pollen season, compared with placebo treated subjects. Again, lack of a mometasone treatment arm at the onset of the pollen season does not allow for any conclusions as to whether pretreatment with mometasone would afford greater overall efficacy than treatment with mometasone at the onset of the pollen season. Based on the onset of action of mometasone (< 1 week), pre-treatment for 1 week should afford adequate SAR prophylaxis. Indeed, in both studies a number of mometasone subjects did not receive the full 4 weeks of mometasone treatment, but rather received 2-3 weeks of prophylaxis. These subjects did not overall exhibit a different efficacy response with onset of the pollen season than did subjects pre-treated for a longer period of time. No significant difference in clinical response

was noted for any of the demographic groups (based on age, gender, and race) evaluated in either study. Rescue medication use in the one study where it was allowed (C92-280), again showed that mometasone treated subjects used less rescue medication and used it less frequently than placebo treated subjects.

Like the SAR studies, analysis of the separate a.m. and p.m. symptom (nasal and non-nasal) scores for the prophylaxis studies revealed no significant difference between a.m. and p.m. scores and efficacy at the end of dosing interval (the a.m. score) for mometasone treated subjects, compared with placebo. Again, this supports once a day dosing of mometasone for the treatment of SAR symptoms.

Review of the response of non-nasal symptoms to mometasone prophylaxis indicates a somewhat greater numerical response in decreasing non-nasal symptoms than noted in the SAR studies discussed previously where subjects received mometasone only during the pollen season. For the pivotal prophylaxis study C93-215, this response in non-nasal symptoms was statistically significant compared with placebo, however the active comparator arm (beclomethasone) also demonstrated a statistically significant effect in decreasing non-nasal symptoms. An explanation for this differential effect of prophylaxis is not readily apparent based on the pathophysiology of allergic rhinitis or the mechanism of and onset of action of mometasone and again, this response may be the result of subject sampling variation. Thus, based on data in the NDA submission regarding mometasone's onset of action and results of these 2 prophylaxis studies, prophylaxis with mometasone 2-4 weeks prior to onset of the allergy season was found to be effective in decreasing SAR symptoms with onset of the allergy season, compared with placebo treatment.

9.2.3. Perennial Allergic Rhinitis (PAR)

9.2.3.a. Study Design

The 10 PAR studies evaluated in this NDA submission were similar in design to the SAR studies with the exception of a longer duration of treatment and longer duration of assessment of nasal and non-nasal SAR symptoms (12 to 52 weeks). In order to qualify for study enrollment, subjects were to be allergic to a perennial allergen (dust mite, cockroach, mold, or animal dander), and were to have clinical evidence of active symptoms at both the screening and baseline visits. Symptom scores for nasal and non-nasal symptoms were rated on a 0-3 severity scale, overall condition of rhinitis was rated on a 0-3 scale, and therapeutic response to treatment was rated on a 1-5 scale, same as the symptom rating scores utilized in the SAR and prophylaxis of SAR studies. With the exception of study C94-092 (PAR study in elderly subjects), rescue medication use was allowed for all PAR studies in NDA 20-762.

For the 4 active- and placebo controlled PAR studies (C92-280, I92-293, I94-079, and I94-078) and the placebo-controlled geriatric PAR study (C94-092), the primary efficacy variable was the same as that in the SAR studies: the mean

change in the total nasal symptom score for the initial 15 day study period for the ITT population (for a.m. and p.m. combined scores). For the 4 open label studies (C93-014, I93-018, I93-180, I93-221), a primary efficacy variable was not defined, as assessment of clinical efficacy was not a primary objective of these studies. Supplementary efficacy variables for the open label studies consisted of 4 distinct endpoints: (1) physician and (2) subject evaluations of overall rhinitis condition, and (3) physician and (4) subject evaluations of therapeutic response for the ITT population which were based on the scoring system previously defined.

Duration of treatment for the 4 active- and placebo-controlled PAR studies was 12 weeks; with 2 of the 4 studies, study I94-079 and I94-078, having an additional 13th or 'offset' week to assess the duration of effect of mometasone in decreasing PAR symptoms post-discontinuation of treatment at week 12 of the study. The geriatric study was likewise 12 weeks in duration. The open label studies, whose primary goal it was to assess safety of mometasone treatment, were up to 52 weeks in duration. One additional safety study (I93-221) was 6 months in duration.

9.2.3.b. PAR Efficacy Results

9.2.3.b.1. Active- and Placebo- Controlled PAR Studies

Results of the 10 PAR studies reviewed in NDA 20-762 indicate that mometasone treatment was effective in decreasing and maintaining a decrease in PAR symptoms. For most of the PAR studies, additional decrease in PAR symptoms was gained from the 3rd-12th, or to the 52nd week, respectively, of mometasone treatment, in addition to efficacy achieved by the second week of mometasone treatment. Primary efficacy variable results for the 4 active- and placebo-controlled PAR studies are summarized in Table VII. below and indicate that mometasone treatment in general, decreased total nasal symptoms for the initial 15 day period of treatment by 1.5-2.4 units (a 20-37% decrease in total nasal symptoms), compared with a 1.0-1.6 unit decrease (13-23%) in total nasal symptoms in placebo treated subjects. Again, no significant difference was noted in these 4 studies in total nasal symptom scores for the a.m. vs. the p.m. Additionally, a.m. total nasal symptom scores of the mometasone treated subjects demonstrated a statistically significant decrease in mean change in scores for the 15 day period, compared with placebo, supporting once daily dosing of mometasone. For the individual nasal symptoms, mometasone treatment consistently decreased the rhinorrhea score and overall demonstrated the greatest decrement in this parameter. Nasal congestion scores were significantly decreased in 2 of these 4 studies, but again, the overall response in nasal congestion was not consistent across all 4 studies reviewed.

Table VII. Efficacy of Mometasone vs. Placebo in the Treatment of PAR: Primary Efficacy Variable for the ITT Population for Active- and Placebo-Controlled Trials in NDA 20-762

STUDY	MOMETASONE 200 µg qd:	PLACEBO:	[1]P-Value
	Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	
C92-280	-1.5/(-20%)	-1.0/(-13%)	0.02
I92-293	-1.7/(-26%)	-1.0/(-13%)	<.01
I94-079	-2.3/(-37%)	-1.3/(-17%)	<.01
I94-078	-2.4/(-34%)	-1.6/(-23%)	<.01

Δ= Change, [1]P-value is for comparison of mometasone vs. placebo using 2-way ANOVA.
NOTE: Total nasal symptom score for a.m. and p.m. combined.

Analysis of the non-nasal symptom scores for the 4 active- and placebo-controlled trials revealed that mometasone treatment decreased the numerical score of many of the non-nasal symptoms, as compared with placebo, however these differences were not generally statistically significant. In summary, mometasone's effect on non-nasal symptoms was inconsistent, with no particular pattern of response (or trend in response) noted for the individual non-nasal symptoms. Subject rescue medication use was lower (no statistical comparison performed in these studies between treatment groups for rescue medication use) in the mometasone treatment group (also lower in the active comparator groups), as compared with the placebo treatment group. No significant demographic differences in treatment response were seen in these 4 studies, based on age, gender, or race.

9.2.3.b.2. Placebo-controlled Study in Elderly Subjects (Age ≥ 65 years)

One study of PAR in elderly subjects (n=334, ITT population) was specifically performed to assess any differences in efficacy or safety of mometasone treatment in this population, as compared to subjects age 18-64. The study design was essentially identical to the 4 active- and placebo controlled trials with the exception that no active comparator group was included.

Overall, elderly subjects demonstrated a statistically significant decrease in the primary efficacy variable of total nasal symptoms over the initial 15 day period with mometasone treatment, however numerically this decrease was lower than that seen in the elderly subgroups in the other PAR studies and lower than that seen for subjects age 12-64 in the 4 active- and placebo-controlled PAR studies. Primary efficacy variable results for elderly subjects are summarized in Table VIII.

Table VIII. Efficacy of Mometasone vs. Placebo in the Treatment of PAR: Primary Efficacy Variable for the ITT Population for the Placebo-Controlled Trial in Elderly Subjects (Age ≥ 65 years) in NDA 20-762.

STUDY	MOMETASONE 200 µg qd:	PLACEBO:	[1]P-Value
	Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	Mean Δ in total nasal symptom score day 1-15 (1° Efficacy Variable)/ (% Δ in 1° Efficacy Variable)	
C94-092	-1.1/(-16%)	-0.7/(-11%)	p=.02

Δ= Change, [1]P-value is for comparison of mometasone vs. placebo using 2-way ANOVA.
NOTE: Total nasal symptom score for a.m. and p.m. combined.

The meaning of this small numerical difference in total nasal symptom scores (which was also noted for the non-nasal symptom scores) is not clear, and these results represent those of only one study. Similar to the gender by treatment interaction noted for the pivotal SAR study C93-013, these results may simply represent sampling variation and if enough placebo-controlled studies in elderly subjects were performed, different numerical differences in symptom scores might be obtained.

9.2.3.b.3. Open label (no placebo group) PAR studies

A total of 5 open label studies for PAR were evaluated in NDA 20-762. Because the main objective of these studies was safety monitoring and not efficacy, no comparison with placebo was provided. Thus, any conclusions gained from these studies are only supportive of those shown the active- and placebo-controlled PAR studies discussed in section 9.4.1.b.1. above. Results of the 4 supplementary efficacy variables of: physician and subject evaluation of overall PAR condition compared to baseline, and physician and subject rated response to treatment compared to baseline, indicate that for all 5 studies improvement in PAR symptoms were evident throughout the study duration for mometasone treated subjects. Clinical findings in these 5 open label studies thus support the efficacy of mometasone in decreasing PAR symptoms.

9.2.3.b.4. PAR Dose Ranging Data for Mometasone

Three of the 5 open label PAR mometasone studies included a 'variable dose' mometasone group in which subjects began treatment with mometasone 200 µg qd and were given the option to increase this dose to 400 µg qd for worsening PAR symptoms, or decrease this dose to 100 µg qd for well-controlled PAR symptoms. Because of the study design of these 3 trials, the variable dose group was treated as a single treatment group with no sub-analysis of efficacy performed for the different doses of mometasone. Thus, the information obtained from the variable dose mometasone group is limited from the perspective of a statistical

comparison of efficacy between the 100, 200, and 400 µg qd dose of mometasone.

Nonetheless, for all 3 studies, the majority of study subjects remained on mometasone 200 µg qd throughout the study with approximately 60% of study subjects for all 3 studies remaining on 200 µg qd of mometasone at the time of completion of the trials, 10-18% of study subjects remaining on 100 µg qd of mometasone at the time of completion of the trials, and 18-30% of study subjects remaining on 400 µg qd of mometasone at the time of completion of the trials. A gradual increase in the dose of mometasone over the course of the study was not observed in either of the 3 studies.

9.3. CONCLUSION:

Results of the SAR, prophylaxis of SAR, and PAR studies in adult subjects summarized in this integrated summary of efficacy support the efficacy of mometasone for these clinical indications. Mometasone treatment demonstrated an adequate 24 hour duration of activity, supporting once a day dosing via nasal spray. A statistically significant and consistent onset of action of mometasone was shown to be between 2.0 and 2.5 days of treatment with maximal benefit of total nasal symptom relief achieved by 2 weeks of treatment with mometasone, based on the data reviewed in the clinical studies of NDA 20-762. The most appropriate dose of mometasone for the treatment of rhinitis is adult subjects is 200 µg qd, although lower doses of mometasone (50 and 100 µg qd) also demonstrated a statistically significant decrease in rhinitis symptoms, as compared with placebo. At the 50 µg qd and 100 µg qd doses of mometasone, decrease in rhinitis symptoms were not as consistent during the first few days of treatment as with the 200 µg qd dose of mometasone. Conversely, a higher dose of mometasone, given as 800 µg qd did not provide a statistically or consistently numerically greater efficacy response in reducing rhinitis symptoms, than the 200 µg qd dose of mometasone. No significant demographic differences, based on age, gender, or race were seen in the SAR (except for the minor treatment by gender effect in the pivotal SAR study C93-013), prophylaxis of SAR, or PAR studies with mometasone, although the number of subjects in the different demographic sub-groups for the individual studies were too small to draw meaningful conclusions.

10.0 INTEGRATED SUMMARY OF SAFETY:

The clinical program for mometasone furoate (SCH 32088) nasal spray evaluated safety in greater than 3000 subjects age 12 years or older exposed to mometasone treatment for at least one visit post-baseline. Although a total of 20 studies were reviewed for safety in NDA 20-762, pooling of safety data was performed only on those studies (19 total) submitted to NDA 20-762 at the time of filing. Thus, the data that forms the basis of this safety summary are taken from the Integrated Summary of Safety (ISS) originally supplied in the Mometasone NDA, as well as from the 120 day safety update, which likewise is a single document submitted to the Mometasone NDA. These documents include summaries of safety data from 10 U.S. and 10 non-U.S. studies. All studies which form this safety database were performed with the 'to-be-marketed' formulation of mometasone nasal spray , thus there are no formulation differences in the mometasone used from study to study. Likewise, placebo tested in these trials had the same chemical formulation as mometasone furoate nasal spray minus the active ingredient, mometasone (i.e. the same excipients, humectants, etc.).

Although similar to the database presented in the medical officer's 'Integrated Summary of Efficacy', the subject safety database which comprised ITT subjects is summarized in Tables. I-IV. below and incorporates phase I studies (human HPA-axis suppression studies) submitted with NDA 20-762.

Table I. Phase I Mometasone Studies (HPA Axis Assessment)

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)
Phase I, active- and placebo controlled HPA study.	I90-664	Single dose	C93-215: Mometasone (1000, 2000, 4000 µg qd nasal spray, and 2000, 4000, 8000 µg po qd): 16 Dexamethasone (200, 400, 800 µg qd): 8 Placebo (0 µg qd): 24
	C92-022	29 days	C92-022: Mometasone (400 and 1200 µg qd nasal spray): 24 Prednisone (10 mg po qd): 12 Placebo (0 µg qd): 12
	C93-196	36 days	C93-196: Mometasone (200 and 400 µg qd nasal spray): 32 Prednisone (10 mg po qd): 16 Placebo (0 µg qd): 16
Phase I.	C91-101/-102/-103/-328 (combined into 1 study report).	Single dose	C91-101: Mometasone 200 µg qd nasal spray, 6 Mometasone 1000 µg po/I.V. qd 30
Phase I	C95-050	Single dose	C95-050: Mometasone 400 µg qd nasal spray, 6 Mometasone 1000 µg po qd 18

Table II. Phase II and Phase III Studies: Seasonal Allergic Rhinitis (SAR) Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)
Phase III, active- and placebo controlled.	C93-013 (Pivotal SAR),	4 weeks	C93-013: Mometasone (200 µg qd): 112 Beclomethasone (168 µg bid): 116 Placebo (0 µg qd): 116
	I92-200	" " "	I92-200: Mometasone (100 µg qd): 126 Mometasone (200 µg qd): 125 Beclomethasone (200 µg bid): 125 Placebo (0 µg qd): 121
Phase III, active- and placebo controlled.	I94-001,	2 weeks	I94-001: Mometasone (200 µg qd): 104 Fluticasone (200 µg qd): 104 Placebo (0 µg qd): 103
	C94-145	" " "	C94-145: Mometasone (200 µg qd): 176 Mometasone (200 µg qd) + Loratadine (10 mg po qd): 169 Loratadine (10 mg po qd): 181 Placebo (0 µg qd): 176
Phase II, dose ranging, placebo controlled.	C92-011	4 weeks	C92-011: Mometasone (50 µg qd): 96 Mometasone (100 µg qd): 95 Mometasone (200 µg qd): 98 Mometasone (800 µg qd): 95 Placebo (0 µg qd): 95
Phase III, onset of action, placebo controlled.	C93-184	2 weeks	C93-184: Mometasone (200 µg qd): 101 Placebo (0 µg qd): 99
Phase III, placebo controlled, 2-period crossover, nasal provocation studies.	C93-193	2 weeks	C93-193: Mometasone (200 µg qd): 20 Placebo (0 µg qd): 21
	I94-139		I94-139: Mometasone (200 µg qd): 24 Placebo (0 µg qd): 24

Table III. Phase III Prophylaxis of SAR Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)
Phase III, active- and placebo controlled.	C93-215 (Pivotal Prophylaxis of SAR),	8 weeks total; (4 week prophylaxis period, followed by a 4 week ragweed period assessment)	C93-215: Mometasone (200 µg qd): 116 Beclomethasone (168 µg bid): 116 Placebo (0 µg qd): 115
	I93-133	" " "	I93-133: Mometasone (200 µg qd): 168 Budesonide (400 µg qd): 172 Placebo (0 µg qd): 173

Table IV. Phase III Perennial Allergic Rhinitis (PAR) Studies

STUDY TYPE	Study Number(s)	Duration of Treatment	Subject Population (ITT) (# subjects/treatment group)
Phase III, active- and placebo controlled.	C92-280 (Pivotal PAR),	12 weeks	C92-280: Mometasone (200 µg qd): 164 Beclomethasone (168 µg bid): 163 Placebo (0 µg qd): 163
	I92-293	12 weeks	I92-293: Mometasone (200 µg qd): 143 Beclomethasone (200 µg bid): 146 Placebo (0 µg qd): 138
	I94-079	12 weeks (+ 1 week off treatment: offset period)	I94-079: Mometasone (200 µg qd): 181 Fluticasone (200 µg qd): 183 Placebo (0 µg qd): 184
	[1]I94-078	12 weeks (+ 1 week off treatment: offset period)	I94-078: Mometasone (200 µg qd): 171 Budesonide (200 µg qd): 179 Placebo (0 µg qd): 173
Phase III, active-controlled (no placebo).	[2]C93-014 (1 yr. F/U of C92-280)	Up to 52 weeks (1 year)	C93-014: Mometasone (200 µg qd): 100 Mometasone (100-400 qd): 95 Beclomethasone (168 µg bid): 95
	[2]I93-018 (1 yr. F/U of I92-293)	Up to 52 weeks (1 year)	C94-145: Mometasone (200 µg qd): 77 Mometasone (100-400 qd): 80 Beclomethasone (200 µg bid): 71
	[2]I93-180 (Nasal bx study)	Up to 52 weeks (1 year)	I93-180: Mometasone (200 µg qd): 69 Fluticasone (200 µg qd): 72
	[2]C94-052 (HPA study)	Up to 52 weeks (1 year)	C94-052: Mometasone (200 µg qd): 175 Triamcinolone (220 µg qd): 176
Phase III, placebo controlled geriatric study (age ≥ 65 yrs.)	C94-092	12 weeks	C94-092: Mometasone (200 µg qd): 170 Placebo (0 µg qd): 164
Noncomparative (no placebo).	[2]I93-221	26 weeks (6 months)	C93-184: Mometasone (100, 200 or 400 µg qd): 331

[1]Study I94-078 was amended to the original NDA for mometasone.
[2]Safety assessment (and not efficacy) was the primary objective of these studies. Hence these placebo uncontrolled studies were not designed to statistically evaluate efficacy of mometasone.

Excluding PAR study I94-078 which was submitted to NDA 20-762 after the filing date, a total of 3210 subjects comprised the ITT population for mometasone. Of these 3210 subjects from phase II and III studies, a total of 3120 distinct subjects received treatment with mometasone and had at least 1 follow-up evaluation for safety. Thus, in most instances, the evaluation of safety is based on the 3210 subjects, as subjects in the 2 PAR studies C92-280 and I92-293 could re-enroll for long-term treatment, up to 1 year, in the 'rollover' studies C93-014 and I93-018. Because treatment assignment in the 2 'roll-over' studies was re-randomized, subjects were counted separately for most safety measures. The 2 exceptions were for calculation of the extent of exposure and for adverse events grouped by duration of treatment. Subjects who received treatment in the

'rollover' studies were counted only once and exposure/duration was considered cumulative.

10.1. Demographics of the Exposed Population

The demographic profiles of 'all mometasone dose' subjects, the mometasone 200 µg qd subjects, and placebo subjects were overall similar. Most subjects were 18-64 years of age ('all doses of mometasone' group=83%, mometasone 200 µg qd group=82%, and placebo group=78%) and the remainder were generally balanced between 12-17 years and ≥ 65 years of age. One female subject (in the 'all doses of mometasone' group) was < 12 years of age.

The proportion of male and female subjects were likewise balanced in all 3 groups ('all doses of mometasone' group=45% male subjects vs. 55% female subjects, mometasone 200 µg qd group=47% male subjects vs. 53% female subjects, and placebo group=46% male subjects vs. 54% female subjects) and across the 3 main age categories (12-17 years, 18-64, and ≥ 65 years) within each group. The majority of study subjects were Caucasian (all doses of mometasone group=85%, mometasone 200 µg qd group=88%, and placebo group=85%). Of non-Caucasian subjects, the majority were of Hispanic origin. A summary of the demographic data for mometasone treated subjects, all active comparator groups and placebo for the ITT population is presented in Table H8 of the Integrated Summary of Safety in the NDA submission [302:40]. Salient demographic data for the mometasone and placebo group are summarized below in Table V.

Table V. **Summary of Demographic Data for Mometasone and Placebo Subjects** (Pooled Safety Population, Controlled and Uncontrolled Studies[1]) [302:4, 131-141].

Variable	All Mometasone Doses	Mometasone 200 µg qd	Placebo
Total subject # (n)	3210	2103	1671
Age:			
< 12 years	1	0	0
12-17 years	335	191	181
18-64 years	2671	1714	1305
≥ 65 years	203	198	185
Gender:			
Female	1453	993	764
Male	1757	1110	907
Gender within Age:			
< 12 years			
female	1	0	0
male	0	0	0
12-17 years			
female	120	63	59
male	215	128	122
18-64 years			
female	1221	822	607
male	1450	892	698
≥ 65 years			
female	111	108	98
male	92	90	87
Race:			
Caucasian	2732	1841	1428
Non-Caucasian	478	262	243

[1]Excludes study C94-078.

10.2 Duration of Subject Exposure/Subject Disposition

The extent of exposure to mometasone and placebo treatment for all subjects in the phase II and phase III (controlled and uncontrolled studies) pooled safety population is summarized in Table VI. Greater than 3000 'distinct' study subjects received the various doses of mometasone once daily for at least 2 weeks, approximately 1300 mometasone subjects were treated for at least 12 weeks, and 350 mometasone subjects were treated for at least 1 year. At least 2/3 of these subjects received mometasone 200 µg qd, the recommended dosage.

Subjects exposed to mometasone 400 µg qd in the PAR studies C93-014, I93-018 and I93-221 comprised 144 subjects treated for at least 2 weeks and 105 subjects treated for at least 12 weeks. Of the 506 subjects who participated in these 'variable-dose' studies, 54% (275 subjects) did not change the dose of mometasone from 200 µg qd, 21% (107 subjects) increased the mometasone dose to 400 µg qd at some point in the studies, and 15% (76 subjects) decreased the mometasone dose to 100 µg qd and maintained it, and 10% (48 subjects) changed the mometasone dose more than once.

Table VI. **Subject Exposure to Mometasone Treatment** (Pooled Safety Population, [1]Controlled and Uncontrolled Studies) [302:42, 143]

Length of Exposure	All Doses of Mometasone	Mometasone 50 µg qd	Mometasone 100 µg qd	Mometasone 200 µg qd	Mometasone 400 µg qd	Mometasone 800 µg qd	Placebo
≥ 1 Dose	3120	96	220	2018	153	95	1665
≥ 1 Week	3094	91	216	2004	153	93	1638
≥ 2 Weeks	3018	88	205	1955	144	89	1553
≥ 4 Weeks	2370	82	177	1511	140	84	1121
≥ 8 Weeks	1695	0	0	1187	117	0	776
≥ 12 Weeks	1315	0	0	838	105	0	460
≥ 26 Weeks	712	0	0	363	42	0	0
≥ 39 Weeks	487	0	0	349	23	0	0
≥ 52 ≤ 69 Weeks	350	0	0	273	2	0	0
Unknown	26	0	1	20	*	0	6

* There were 5 subjects in the pooled variable dose group whose extent of exposure could not be calculated; hence they could not be assigned to any particular dose.

[1]NOTE: This table does not depict the 169 subjects in the mometasone + loratadine group for study C94-145 and the 21 cross-over mometasone vs. placebo subjects in study C93-193, which are accounted for in the 'all doses of mometasone' column .

10.3. Adverse Events (AE's)

The overall incidence of all adverse events were generally similar among the treatment groups, including placebo. The most frequent adverse events across all studies reviewed in NDA 20-762 were headache, viral infection, pharyngitis, epistaxis, and coughing.

A summary of all reported adverse events ('treatment emergent', i.e. occurring during treatment) for all doses of mometasone in controlled and uncontrolled trials (n=3210 mometasone subjects) are summarized in Table VII. A summary of all reported adverse events ('treatment emergent', i.e. occurring during treatment) for subjects treated with the 200 µg qd dose of mometasone in all controlled trials (n=2103) and in placebo group subjects in controlled studies of NDA 20-762 are summarized in Table VIII. Again, based on these 2 tables, most adverse events in mometasone treated subjects were not generally significantly different in frequency from placebo subjects. The most frequently reported adverse event in mometasone 200 µg qd treated subjects was headache (26%), followed by viral infection (14%), and pharyngitis (12%). Adverse events relating to the upper or lower respiratory tract were slightly more frequent in mometasone treated subjects than in placebo, in particular epistaxis. The incidence of epistaxis was consistently several percentage points higher with mometasone and the active comparator treatments than with placebo treatment. Other adverse events slightly

more prevalent in mometasone treated subjects, as compared with placebo controlled subjects were the following: headache, musculoskeletal pain, dysmenorrhea (in female subjects), viral infection, coughing, pharyngitis, sinusitis, and upper respiratory tract infection.

Table VII. Adverse Event (AE) Frequency:
AE's ≥ 1% in Mometasone Treated Subjects (All doses combined) by Organ System and Preferred Term, Pooled Safety Population, n=3210 Mometasone Subjects for Controlled and Uncontrolled Trials [302:151-185, 303:310-326].

BODY SYSTEM	Preferred Term	Mometasone n (%)
All Systems	Any AE	2049 (64%)
Autonomic Nervous System Disorders	Dry Mouth	20 (1%)
Body as a Whole	Chest Pain	46 (1%)
	Edema	17 (1%)
	Fatigue	53 (2%)
	Fever	84 (3%)
	Headache	***882 (27%)***
	Influenza-like Symptoms	114 (4%)
	Injury, Accidental	19 (1%)
	Malaise	18 (1%)
CNS and PNS Disorders	Dizziness	51 (2%)
	Dysphonia	31 (1%)
Gastro-intestinal System Disorders	Abdominal Pain	49 (2%)
	Diarrhea	54 (2%)
	Dyspepsia	70 (2%)
	Gastritis	32 (1%)
	Gastroenteritis	20 (1%)
	Nausea	81 (3%)
	Tooth Disorder	70 (2%)
	Vomiting	37 (1%)
Hearing and Vestibular Disorders	Ear Disorder NOS	17 (1%)
	Earache	105 (3%)
Musculoskeletal System Disorders	Arthralgia	63 (2%)
	Musculoskeletal Pain	***169 (5%)***
	Myalgia	98 (3%)
Psychiatric Disorders	Depression	17 (1%)
	Insomnia	40 (1%)
	Somnolence	21 (1%)
Reproductive Disorders, Female	*Dysmenorrhea*	***72 (5%)***
	Vaginitis	8 (1%)
Resistance Mechanism Disorders	Infection	19 (1%)
	Bacterial Infection	27 (1%)
	Viral Infection	***431 (13%)***

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' italic type.

Table VII. CONTINUED:
Adverse Event (AE) Frequency ≥ 1% in Mometasone Treated Subjects: (All mometasone doses combined) by Organ System and the Preferred Term for Controlled and Uncontrolled Trials, (Pooled Safety Population, n=3210 Mometasone Subjects) [302:151-185, 303:310-326].

BODY SYSTEM	Preferred Term	Mometasone n (%)
Respiratory System Disorders	Asthma	62 (2%)
	Asthma Aggravated	24 (1%)
	Bronchitis	69 (2%)
	Coughing	***234 (7%)***
	Dyspnea	39 (1%)
	Epistaxis	***315 (10%)***
	Nasal Burning	64 (3%)
	Nasal Congestion	35 (1%)
	Nasal Irritation	84 (3%)
	Pharyngitis	***371 (12%)***
	Respiratory Disorder	36 (1%)
	Rhinitis	129 (4%)
	Sinusitis	***154 (5%)***
	Sneezing	68 (2%)
	Tonsillitis	19 (1%)
	Upper Respiratory Tract Infection	***159 (5%)***
	Wheezing	43 (1%)
Skin and Appendages Disorders	Pruritus	51 (2%)
	Urticaria	32 (1%)
Special Senses Other, Disorders	Taste Perversion	30 (1%)
Urinary System Disorders	Urinary Tract Infection	20 (1%)
Vascular (Extracardiac) Disorders	Migraine	44 (1%)
Vision Disorders	Conjunctivitis	102 (3%)
	Eye Pain	31 (1%)
	Eyes, Dry	24 (1%)
White cell and RES Disorders	Lymphadenopathy	19 (1%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' italic type.

Table VIII. Treatment Emergent Adverse Event (AE) Frequency: AE's ≥ 1% in Mometasone 200 µg qd Treated Subjects for All Controlled Clinical Trials. Pooled Placebo Subjects from all [1]Controlled Trials Included for Comparison [302:187-235, 303:261-307].

BODY SYSTEM	Preferred Term	Mometasone 200 µg qd (n=2103)	Placebo (n=1671)
		n (%)	n (%)
All Systems	Any AE	1344 (64%)	979 (59%)
Autonomic Nervous System Disorders	Mouth Dry	11 (1%)	9 (1%)
Body as a Whole	Chest Pain	38 (2%)	10 (1%)
	Edema	11 (1%)	9 (1%)
	Fatigue	32 (2%)	32 (2%)
	Fever	50 (2%)	26 (2%)
	Headache	***551 (26%)***	***366 (22%)***
	Influenza-like Symptoms	91 (4%)	51 (3%)
	Injury Accidental	12 (1%)	7 (<1%)
	Malaise	15 (1%)	5 (<1%)
CNS and PNS Disorders	Dizziness	31 (1%)	28 (2%)
	Dysphonia	18 (1%)	10 (1%)
Gastro-intestinal System Disorders	Abdominal Pain	31 (1%)	19 (1%)
	Diarrhea	36 (2%)	19 (1%)
	Dyspepsia	41 (2%)	24 (1%)
	Gastritis	13 (1%)	3 (<1%)
	Gastroenteritis	12 (1%)	1 (<1%)
	Nausea	56 (3%)	29 (2%)
	Tooth Disorder	48 (2%)	13 (1%)
Hearing and Vestibular Disorders	Ear Disorder *NOS	15 (1%)	8 (<1%)
	Earache	71 (3%)	40 (2%)
Musculoskeletal System Disorders	Arthralgia	40 (2%)	21 (1%)
	Musculoskeletal Pain	***112 (5%)***	***50 (3%)***
	Myalgia	77 (4%)	31 (2%)
Psychiatric Disorders	Depression	12 (1%)	1 (<1%)
	Insomnia	30 (1%)	25 (1%)
	Somnolence	14 (1%)	14 (1%)
Reproductive Disorders, Female	***Dysmenorrhea***	***50 (5%)***	***26 (3%)***
Resistance Mechanism Disorders	Infection	15 (1%)	7 (<1%)
	Bacterial Infection	16 (1%)	2 (<1%)
	Viral Infection	***292 (14%)***	***181 (11%)***

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' italic type.
[1]Excludes PAR study C94-078, which was submitted after the filing date for NDA 20-762.
*NOS: Not otherwise specified.

Table VIII. CONTINUED:
Treatment Emergent Adverse Event (AE) Frequency:
AE's ≥ 1% in Mometasone 200 µg qd Treated Subjects for All Controlled Clinical Trials. Pooled Placebo Subjects from all [1]Controlled Trials Included for Comparison [302:187-235, 303:261-307].

BODY SYSTEM	Preferred Term	Mometasone 200 µg qd (n=2103)	Placebo (n=1671)
		n (%)	n (%)
Respiratory System Disorders	Asthma	39 (2%)	18 (1%)
	Asthma Aggravated	17 (1%)	11 (1%)
	Bronchitis	41 (2%)	20 (1%)
	Coughing	***155 (7%)***	***97 (6%)***
	Dyspnea	20 (1%)	17 (1%)
	Epistaxis	***223 (11%)***	***104 (6%)***
	Laryngitis	15 (1%)	2 (<1%)
	Nasal Burning	60 (3%)	63 (4%)
	Nasal Congestion	25 (1%)	14 (1%)
	Nasal Irritation	52 (2%)	53 (3%)
	Pharyngitis	***246 (12%)***	***162 (10%)***
	Respiratory Disorder	28 (1%)	11 (1%)
	Rhinitis	82 (4%)	56 (3%)
	Sinusitis	***114 (5%)***	***58 (3%)***
	Sneezing	38 (2%)	64 (4%)
	Upper Respiratory Tract Infection	***136 (6%)***	***40 (2%)***
	Wheezing	26 (1%)	12 (1%)
Skin and Appendages Disorders	Pruritus	31 (1%)	22 (1%)
	Rash	30 (1%)	19 (1%)
	Urticaria	24 (1%)	11 (1%)
Special Senses Other, Disorders	Taste Perversion	22 (1%)	4 (<1%)
Urinary System Disorders	Urinary Tract Infection	12 (1%)	3 (<1%)
Vascular (Extracardiac) Disorders	Migraine	31 (1%)	7 (<1%)
Vision Disorders	Conjunctivitis	74 (4%)	32 (2%)
	Eye Pain	22 (1%)	16 (1%)
	Eyes, Dry	17 (1%)	6 (<1%)
White cell and RES Disorders	Lymphadenopathy	13 (1%)	5 (<1%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' type.
[1]Excludes PAR study C94-078, which was submitted after the filing date for NDA 20-762.

10.3.1. Adverse Events Due to Viral and Fungal Infections

Since several reports of viral and fungal infections (herpes simplex, varicella, oral and/or nasal candidiasis) were noted in mometasone treated subjects on review of the individual studies in the NDA submission, a pooled analysis of the incidence of these resistance mechanism disorders for mometasone and placebo group subjects by dose of mometasone was performed using the sponsor's database for controlled clinical trials in the mometasone NDA. Results are summarized in Table IX. below and indicate that the majority of resistance mechanism disorders were prevalent in the 200 µg qd mometasone group and comprised herpes simplex infection. No obvious dose response in resistance mechanism disorder AE frequency was noted except that almost no subjects receiving < 200 µg qd mometasone group reported any of these adverse events. Overall, no significant difference between the different doses of mometasone and placebo were found regarding these selective viral and fungal infections.

Table IX. Incidence of Selective Viral and Fungal Infections: Mometasone Treated Subjects (Stratified by Dose) compared with Placebo Treated Subjects for all [1]Controlled Clinical Trials in NDA 20-762, Pooled Safety Population [302:217-219, 303:290-292]

Resistance Mechanism Disorder AE	Mometasone 50 µg qd (n=96)	Mometasone 100 µg qd (n=221)	Mometasone 200 µg qd (n=2103)	Mometasone 100-400 µg qd (n=506)	Mometasone 800 µg qd (n=95)	Placebo (n=1671)
Herpes Simplex	0 (0%)	0 (0%)	7 (<1%)	1 (<1%)	0 (0%)	8 (<1%)
Herpes Zoster	0 (0%)	0 (0%)	4(<1%)	1 (<1%)	0 (0%)	1 (<1%)
Infection, Fungal	0 (0%)	1 (<1%)	8 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Measles	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Oral Candidiasis	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
GI Candidiasis	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Varicella	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

[1]Excludes PAR study I94-078, which was submitted after the filing date for NDA 20-762.

Review of the individual uncontrolled studies for NDA 20-762 however revealed an additional 3 reports of oral candidiasis in mometasone subjects enrolled in PAR studies and 3 reports of nasal candidiasis (no reports for either in placebo subjects). Importantly, these subjects all received mometasone for > 1 month of treatment.

10.3.2. Nasal Perforation and Nasal Ulcer Frequency

Regarding nasal perforation and nasal ulcer frequency in mometasone treated subjects vs. placebo treated subjects, there were no reports of nasal perforation at any of the mometasone doses tested in this NDA submission or in placebo group subjects. Nasal ulcers, however, were noted in slightly higher frequency in mometasone treated subjects (and other steroid active comparator groups) as compared with placebo treated subjects on physical examinations during follow-up study visits (these were not submitted as part of the adverse event reports, and thus are not included in the AE database submitted by the sponsor). While nasal ulcers were not rated by the examining physician in terms of the extent of involvement of the nasal mucosa, of the 42 reports of nasal ulcer in mometasone treated subjects, only one (1) subject receiving mometasone 800 µg qd was noted to have a nasal ulcer of 'moderate' severity. Of mometasone treated subjects with nasal ulcers, 4 subjects were noted to have nasal septal ulcers which may be more prone to perforate (of note, 3 out of 4 of these subjects were ≥ 65 years). A tabulation of nasal ulcer frequency in mometasone and placebo subjects for all SAR, prophylaxis of PAR and PAR studies (excluding study I94-078) is summarized in Table X. The denominators for the percentages were 3210 mometasone subjects and 1692 placebo subjects.

Table X. Incidence of Nasal Ulcers
Mometasone Treated Subjects vs. Placebo for all [1]Controlled and Uncontrolled Trials in NDA 20-762, ITT Population (n=3210 for mometasone subjects, n=1692 for placebo subjects), [Compiled from the Medical Officer Review of Adverse Events for Individual Studies in NDA 20-762]

	Mometasone (All Doses)			Placebo		
	Controlled Trials (n=2283)	Uncontrolled Trials (n=927)	ALL TRIALS n (%)	Controlled Trials (n=1692)	Uncontrolled Trials	ALL TRIALS n (%)
SAR	7	NA	7	2	NA	2
Prophylaxis of SAR	0	NA	0	2	NA	2
PAR	11	24	35	5	NA	5
All Studies	18	24	42 (1.3%)	9	NA	9 (0.5%)

[1]Excludes PAR study I94-078, which was submitted after the filing date for NDA 20-762. NA=Not applicable.
NOTE: Although all doses of mometasone were included in this analysis, review of the individual cases indicate that the majority of subjects received mometasone 200 µg qd.

While sub-analysis of mometasone associated nasal ulcers was not possible by dose (i.e. 50, 100, 200 µg qd, etc.) because physical examination data for variable

dose' mometasone subjects (uncontrolled PAR studies C93-014, I93-018, and I93-221) was not recorded by the dose of mometasone (with the exception of treatment emergent adverse events), review by the medical officer of data for all mometasone studies excluding the 'variable dose' studies indicate that all nasal ulcers were reported in subjects taking the 200 µg qd dose of mometasone. Based on these reports, the incidence of nasal ulcers associated with mometasone use was low but higher than the incidence reported in placebo subjects. Furthermore, nasal ulcers were more prevalent in subjects receiving a longer course of mometasone treatment, as noted in the virtual absence of nasal ulcers in SAR subjects (treated less than 4 weeks). A review of the individual nasal ulcer cases for the PAR studies indicates that the majority of nasal ulcers occurred at or later than 4 weeks (Visit 3) post-initiation of mometasone treatment. Subjects who presented with nasal ulcers during the screening or baseline visit (pre-treatment) were discounted from these analyses.

Additionally, of the 35 PAR subjects who were found to have nasal ulcers, 5 of these were elderly subjects who received mometasone 200 µg qd in study C94-092 (incidence=2.9% (5/170)), compared with no findings of nasal ulcers in placebo treated elderly subjects (incidence=0%). Although based on a small number of elderly subjects which make it impossible to draw meaningful conclusions, the incidence of nasal ulcers in elderly subjects in this study was approximately twice that in the 'all ages combined' group of subjects summarized in Table X. above.

10.3.3. Adverse Event Stratification By Duration of Treatment

A longer duration of treatment with mometasone generally resulted in an increased incidence of adverse events, in particular adverse events related to the upper and lower respiratory tract and increased nasal ulcer formation discussed above in Section 10.3.2. Nonetheless, no distinct pattern was evident that indicated an additional or different risk with mometasone treatment as compared with the active comparators (different steroid preparations: beclomethasone, fluticasone, budesonide, triamcinolone and the antihistamine: loratadine). For example, no increased risk for developing liver function test abnormalities, metabolic or endocrine disorders was identified on or after 12 months of treatment with mometasone, compared with 3 months or less of treatment. The sponsor sub-analyzed adverse events by duration of treatment by arbitrarily sub-dividing adverse events by <3 months vs. ≥ 12 months of treatment to better differentiate additional adverse event risk(s) that may be conferred with long-term mometasone use at 200 µg qd. A summary of these results are presented in Table XI. below.

Based on a stratification of adverse events by duration of treatment, (< 3 months or ≥ 12 months), an increase in the adverse events of headache, musculoskeletal pain, dysmenorrhea, viral infection, pharyngitis, sinusitis, and upper respiratory tract infection were noted in subjects treated with mometasone 200 µg qd for 12 months or longer, as compared to those treated for < 3 months. No conclusions can be based on these data because the '12 month and longer'

mometasone treatment group had too few subjects and especially because one would need to correct for the expected increase in adverse events with longer duration of treatment, resulting in no significant proportional increase in adverse event frequency. Hence, the pattern of increased adverse events with prolonged intranasal mometasone use are only minimally suggestive of the known long-term effects of steroid use on immune function, muscle function and possibly adrenal function. While not included in Table XI., a comparison of the other active comparator nasal steroids evaluated in NDA 20-762 to the mometasone treatment, revealed that the active comparator nasal steroids also demonstrated a similar pattern of increased adverse events (again, particularly related to the upper and lower respiratory tract) in subjects treated ≥ 12 months, as compared to < 3 months of treatment [302:53-54].

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table XI. Treatment Emergent Adverse Event (AE) Frequency, AE's ≥ 1%: Mometasone 200 µg qd Treated Subjects vs. Placebo Stratified for a Duration < 3 months and ≥ 12 months for All Controlled Clinical Trials. Pooled Placebo Subjects from all [1]Controlled Trials Included for Comparison.
[302:52-56, 303:391-470, 566-625]

BODY SYSTEM Preferred Term	TREATMENT < 3 Months		TREATMENT ≥ 12 Months
	Mometasone 200 µg qd (n=1639)	Placebo (n=1607)	Mometasone 200 µg qd (n=280)
	n (%)	n (%)	n (%)
All Systems ***Any AE***	***956 (58%)***	***935 (58%)***	***251 (90%)***
Body as a Whole Chest Pain Fatigue Fever ***Headache*** ***Influenza-like Symptoms***	 26 (2%) 19 (1%) 29 (2%) ***374 (23%)*** ***42 (3%)***	 8 (<1%) 32 (2%) 23 (1%) ***350 (22%)*** ***45 (3%)***	 7 (3%) 6 (2%) 15 (5%) ***120 (43%)*** ***28 (10%)***
CNS and PNS Disorders Dizziness	 25 (2%)	 25 (2%)	 4 (1%)
Gastro-intestinal System Disorders Abdominal Pain Diarrhea Dyspepsia Nausea ***Tooth Disorder***	 18 (1%) 18 (1%) 22 (1%) 37 (2%) ***21 (1%)***	 19 (1%) 19 (1%) 23 (1%) 28 (2%) ***12 (1%)***	 9 (3%) 15 (5%) 15 (5%) 12 (4%) ***23 (8%)***
Hearing and Vestibular Disorders Earache	 47 (3%)	 37 (2%)	 19 (7%)
Musculoskeletal System Disorders Arthralgia ***Musculoskeletal Pain*** ***Myalgia***	 23 (1%) ***60 (4%)*** ***36 (2%)***	 20 (1%) ***46 (3%)*** ***28 (2%)***	 13 (5%) ***42 (15%)*** ***28 (10%)***
Reproductive Disorders, Female ***Dysmenorrhea***	 ***21 (3%)***	 ***26 (4%)***	 ***25 (16%)***
Resistance Mechanism Disorders ***Viral Infection***	 ***168 (10%)***	 ***167 (10%)***	 ***76 (27%)***

NOTE: All AE's that increased ≥ 5% in frequency from the 3 month to the 12 month interval are denoted in 'bold-face' italic type.
[1]Excludes PAR study C94-078, which was submitted after the filing date for NDA 20-762.

Table XI. CONTINUED:
Treatment Emergent Adverse Event (AE) Frequency ≥ 1%:
Mometasone 200 µg qd Treated Subjects vs. Placebo Stratified for a Duration < 3 months and ≥ 12 months for All Controlled Clinical Trials. Pooled Placebo Subjects from all [1]Controlled Trials Included for Comparison.
[302:52-56, 303:391-470, 566-625]

BODY SYSTEM Preferred Term	TREATMENT < 3 Months		TREATMENT ≥ 12 Months
	Mometasone 200 µg qd (n=1639)	Placebo (n=1607)	Mometasone 200 µg qd (n=280)
	n (%)	n (%)	n (%)
Respiratory System Disorders			
Asthma	***16 (1%)***	***13 (1%)***	***16 (6%)***
Bronchitis	***19 (1%)***	***18 (1%)***	***28 (6%)***
Coughing	***115 (7%)***	***93 (6%)***	***27 (10%)***
Epistaxis	***154 (9%)***	***100 (6%)***	***43 (15%)***
Nasal Burning	45 (3%)	57 (4%)	7 (3%)
Nasal Irritation	34 (2%)	50 (3%)	11 (4%)
Pharyngitis	***168 (10%)***	***153 (10%)***	***52 (19%)***
Rhinitis	***53 (3%)***	***50 (3%)***	***23 (8%)***
Sinusitis	***37 (2%)***	***55 (3%)***	***60 (21%)***
Sneezing	34 (2%)	60 (4%)	3 (1%)
Upper Respiratory Tract Infection	***54 (3%)***	***37 (2%)***	***70 (25%)***
Skin and Appendages Disorders			
Pruritus	22 (1%)	20 (1%)	5 (2%)
Vision Disorders			
Conjunctivitis	***49 (3%)***	***30 (2%)***	***17 (6%)***

NOTE: All AE's that increased ≥ 5% in frequency from the 3 month to the 12 month interval are denoted in 'boldface' italic type.
[1]Excludes PAR study C94-078, which was submitted after the filing date for NDA 20-762.

10.3.4. Adverse Event Stratification by Mometasone Dose

For most adverse events, there was no evidence of a dose response among subjects who were treated with mometasone. Importantly, PAR subjects receiving mometasone 200 µg qd and 'variable' dose (100-400 µg qd) mometasone received these treatments for a longer duration of time than the SAR mometasone 50 and 100 µg qd subjects, hence duration of treatment is a potential confounder, in addition to dose of mometasone when assessing adverse event frequency in these 2 subgroups of subjects. Nonetheless, a small dose response was evident for epistaxis, ranging in incidence from 3% in mometasone 50 µg qd subjects to 11% in mometasone 800 µg qd subjects, and perhaps an even smaller dose response was evident for viral and upper respiratory infection. Of the nasal ulcers reported as adverse events (3 cases total), 2 cases were reported for the mometasone 200 µg qd group and 1 case was reported in the 'variable' dose mometasone group [302:223]. Within the 'variable' dose mometasone group, a very small increase in the incidence of earache, pharyngitis, and nasal irritation was evident with increasing doses of mometasone, however the number of subjects in each group was too small to make meaningful conclusions, especially since this trend was not as appreciable for 'non-variable' dose mometasone subjects.

In general, adverse events were less frequent at the mometasone 50 µg qd and 100 µg qd dosage. Although headache and pharyngitis were again more frequent adverse events for all mometasone dose groups, no consistent dose response was seen with higher mometasone doses. A summary of the absolute number of reports of adverse events and the frequency of adverse events for the different doses of mometasone administered during the controlled clinical trials for all SAR, prophylaxis of SAR, and PAR indications are presented in Table XII.

Table XII. Stratification of Adverse Events by Mometasone Dose as Compared with Placebo, Pooled Safety Population
[302:68-69, 303:237-259]

BODY SYSTEM Preferred Term	Mometasone, n (%)								Placebo, n (%) (n=1671)
	50 µg qd (n=96)	100 µg qd (n=221)	200 µg qd (n=2103)	800 µg qd (n=95)	[1]Variable dose (100-400) µg qd			200 µg qd + loratadine 10 mg qd (n=169)	
					100 µg qd (n=112)	200 µg qd (n=501)	400 µg qd (n=155)		
All Systems Any AE	62 (65%)	115 (52%)	1344 (64%)	65 (68%)	66 (59%)	344 (69%)	103 (66%)	63 (37%)	979 (59%)
Body as a Whole									
Chest Pain	1 (1%)	0 (0%)	38 (2%)	1 (1%)	1 (1%)	3 (1%)	2 (1%)	0 (0%)	10 (1%)
Fatigue	3 (3%)	2 (1%)	32 (2%)	1 (1%)	1 (1%)	10 (2%)	2 (1%)	3 (2%)	32 (2%)
Fever	2 (2%)	1 (<1%)	50 (2%)	3 (3%)	7 (6%)	17 (3%)	4 (3%)	0 (0%)	26 (2%)
Headache	31 (32%)	52 (24%)	551 (26%)	39 (41%)	20 (18%)	145 (29%)	41 (26%)	32 (19%)	366 (22%)
Influenza-like Symptoms	3 (3%)	2 (1%)	91 (4%)	0 (0%)	1 (1%)	12 (2%)	6 (4%)	0 (0%)	51 (3%)
CNS and PNS Disorders									
Dizziness	3 (3%)	6 (3%)	31 (1%)	1 (1%)	2 (2%)	6 (1%)	1 (1%)	1 (1%)	28 (2%)
Gastro-intestinal System Disorders									
Abdominal Pain	0 (0%)	2 (1%)	31 (1%)	0 (0%)	3 (3%)	8 (2%)	4 (3%)	1 (1%)	19 (1%)
Diarrhea	0 (0%)	3 (1%)	36 (2%)	3 (3%)	2 (2%)	5 (1%)	4 (3%)	1 (1%)	19 (1%)
Dyspepsia	1 (1%)	7 (3%)	41 (2%)	0 (0%)	3 (3%)	13 (3%)	2 (1%)	3 (2%)	24 (1%)
Nausea	3 (3%)	3 (1%)	56 (3%)	3 (3%)	1 (1%)	12 (2%)	3 (2%)	0 (0%)	29 (2%)
Tooth Disorder	0 (0%)	1 (<1%)	48 (2%)	0 (0%)	5 (4%)	8 (2%)	7 (5%)	1 (1%)	13 (1%)
Hearing and Vestibular Disorders									
Earache	6 (6%)	4 (2%)	71 (3%)	2 (2%)	***0 (0%)***	***15 (3%)***	***8 (5%)***	1 (1%)	40 (2%)
Musculoskeletal System Disorders									
Arthralgia	3 (3%)	3 (1%)	40 (2%)	1 (1%)	3 (3%)	12 (2%)	3 (2%)	0 (0%)	21 (1%)
Musculoskeletal Pain	4 (4%)	6 (3%)	112 (5%)	3 (3%)	6 (5%)	28 (6%)	12 (8%)	1 (1%)	***50 (3%)***
Myalgia	1 (1%)	2 (1%)	77 (4%)	2 (2%)	1 (1%)	9 (2%)	5 (3%)	2 (1%)	31 (2%)

NOTE: All AE's that show an increase in frequency with increased mometasone dose are denoted in 'bold-face' italic type.
Excludes PAR study C94-078, which was submitted after the filing date for NDA 20-762.
[1]Variable dose mometasone subject number is > 506 in the pooled safety population because AE at each mometasone dose change were counted as new AE's.

II. CONTINUED: Stratification of Adverse Events by Mometasone Dose as Compared with Placebo, Pooled Safety Population [302:68-69, 217, 303:237-259]

STEM / Term	Mometasone, n (%)								Placebo, n (%) (n=1671)
	50 µg qd (n=96)	100 µg qd (n=221)	200 µg qd (n=2103)	800 µg qd (n=95)	Variable dose (100-400) µg qd			200 µg qd + loratadine 10 mg qd (n=169)	
					100 µg (N=112)	200 µg (n=501)	400 µg (n=155)		
tive Disorders, Female									
rrhea	1 (4%)	1 (2%)	50 (5%)	1 (3%)	1 (2%)	14 (5%)	3 (4%)	3 (4%)	***26 (3%)***
e Mechanism Disorders									
	0 (0%)	0 (0%)	15 (1%)	0 (0%)	0 (0%)	3 (1%)	1 (1%)	0 (0%)	7 (<1%)
Infection	0 (0%)	0 (0%)	16 (1%)	0 (0%)	0 (0%)	7 (1%)	3 (2%)	1 (1%)	2 (<1%)
ction	***4 (4%)***	***4 (2%)***	***292 (14%)***	***1 (1%)***	***14 (13%)***	***93 (19%)***	***28 (18%)***	***2 (1%)***	***181 (11%)***
y System Disorders									
	2 (2%)	1 (<1%)	39 (2%)	0 (0%)	1 (1%)	19 (4%)	3 (2%)	0 (0%)	18 (1%)
	1 (1%)	0 (0%)	41 (2%)	1 (1%)	1 (1%)	22 (4%)	5 (3%)	0 (0%)	20 (1%)
	8 (8%)	9 (4%)	155 (7%)	6 (6%)	8 (7%)	35 (7%)	13 (8%)	4 (2%)	97 (6%)
	3 (3%)	***9 (4%)***	***223 (11%)***	***10 (11%)***	11 (10%)	44 (9%)	14 (9%)	***6 (4%)***	***104 (6%)***
ning	0 (0%)	10 (5%)	60 (3%)	3 (3%)	4 (4%)	12 (2%)	4 (3%)	3 (2%)	63 (4%)
tation	6 (6%)	6 (3%)	52 (2%)	1 (1%)	***1 (1%)***	***9 (2%)***	***9 (6%)***	0 (0%)	53 (3%)
tis	17 (18%)	14 (6%)	246 (12%)	11 (12%)	***7 (6%)***	***52 (10%)***	***19 (12%)***	7 (4%)	162 (10%)
	2 (2%)	9 (4%)	82 (4%)	6 (6%)	3 (3%)	25 (5%)	4 (3%)	0 (0%)	56 (3%)
	2 (2%)	4 (2%)	114 (5%)	1 (1%)	5 (4%)	23 (5%)	7 (5%)	1 (1%)	58 (3%)
	4 (4%)	7 (3%)	38 (2%)	5 (5%)	1 (1%)	11 (2%)	1 (1%)	1 (1%)	64 (4%)
spiratory Tract Infection	***0 (0%)***	***1 (<1%)***	***136 (6%)***	***1 (1%)***	1 (1%)	6 (1%)	1 (1%)	***1 (1%)***	***40 (2%)***
ders									
	1 (<1%)	3 (1%)	31 (1%)	2 (2%)	1 (1%)	12 (2%)	4 (3%)	0 (0%)	22 (1%)
orders									
itis	3 (3%)	3 (1%)	74 (4%)	3 (3%)	2 (2%)	16 (3%)	3 (2%)	0 (0%)	32 (2%)

E's that show an increase in frequency with increased mometasone dose are denoted in 'bold-face' italic type.
AR study C94-078, which was submitted after the filing date for NDA 20-762.
se mometasone subject number is > 506 in the pooled safety population because AE at each mometasone dose change were counted as new AE's.

10.3.5. Adverse Event Stratification by Demographics (Age, Gender, Race)

Stratification of adverse events by age, gender, or race failed to reveal a significant differential response to mometasone treatment as compared to placebo, although the overall incidence of adverse events with both mometasone 200 µg qd and placebo treatment tended to be greater in:

(1) older (i.e. age ≥ 65 years: 147 AE reports (74% incidence)) than younger subjects (18-64 years: 1109 AE reports (65% incidence) and age 12-17 years: 88 AE reports, 46% incidence). No AE's were reported in the one mometasone subject <12 years of age [304:759],

(2) female than male subjects (female subjects: 695 AE reports (70% incidence), male subjects: 649 AE reports (58% incidence),

(3) Caucasian than non-Caucasian subjects (Caucasian subjects: 1214 AE reports (66% incidence), non-Caucasian subjects: 130 AE reports (50% incidence)).

The incidence of AE reports by these demographic groups for all doses of mometasone were similar to those reported for mometasone 200 µg qd [304:759-939, 305:941-1252, 306:1254-1630, 307:1633-1728].

Individual adverse events that appeared to increase with age (a 3-18 percentage point increase in incidence in subjects age 65 years or older as compared with subjects age 12-17) included earache, coughing, epistaxis, pharyngitis, upper respiratory tract infection, arthralgia, myalgia, musculoskeletal pain, and nasal ulcers; the latter, as noted on review of subject nasal examination reports and review of PAR study C94-092 (geriatric study) [302:60-65]. These adverse events were noted to increase with age in both mometasone and placebo treated subjects [302:60-61].

Stratification of individual adverse events by gender revealed that female subjects in both mometasone and placebo treatment groups tended to report most adverse events more frequently (approximately 1-5 percentage points more) than male subjects. The greatest reporting difference between male and female subjects was for headache, with 31% of females and 22% of males treated with mometasone 200 µg qd and 26% of females and 18% of males treated with placebo reporting this adverse event [302:62]. Review of all AE's failed to indicate that either male or female subjects are preferentially at risk for any specific adverse event coincident with administration of mometasone nasal spray. In other words, no gender-specific trend for adverse events was detected with the safety database provided in NDA 20-762.

Review of adverse events by subject racial background revealed that most adverse events were several percentage points (1-3) higher in Caucasian than non-Caucasian subjects, regardless of treatment. The greatest differences were seen for headache, epistaxis, pharyngitis, and sinusitis; with incidences ranging from 2-15 percentage points greater in Caucasian than non-Caucasian subjects [302:64-65]. Because the number of non-Caucasian subjects was small, the overall difference (generally 4-7 percentage points) was small between Caucasians and non-Caucasians and there is no clear biologic rationale to account for such racial

differences, it is unlikely that the differential effect noted in these studies is one which is real.

10.3.6. Subject Discontinuations due to Adverse Events

Incidence of subject discontinuation due to adverse events were low for all mometasone groups (as well as the active comparator nasal steroids and loratadine), and placebo; ranging from 1%-5%. The most common adverse events leading to subject discontinuation in mometasone groups were respiratory disorders, namely epistaxis (13 subject discontinuations (0.4%)), sinusitis (7 subject discontinuations (0.2%), and pharyngitis (5 subjects (0.2%)). Discontinuation rates for these 3 adverse events were likewise similar in placebo group subjects [302:78-85]. As discussed for the individual SAR, prophylaxis of SAR, and PAR studies, the most common reasons for treatment discontinuation were not due to adverse events per se but lack of subject follow-up or non-compliance. Of those discontinuations that were due to adverse events, most of these were unrelated to treatment. A summary table of subject disposition (all reasons for study discontinuation) for all clinical studies in NDA 20-762 was not provided in the NDA submission. Individual subject discontinuations due to adverse events are summarized in Vol 303:78-85 of the NDA submission and are tabulated by organ system in Table XIII. below.

Table XIII. Subject Discontinuation due to Adverse Events by Mometasone Dose as Compared with Placebo, Poole Safety Population [302:76-77]

BODY SYSTEM Organ Class	Mometasone, n (%)							
	50 µg qd (n=95)	100 µg qd (n=221)	200 µg qd (n=2103)	800 µg qd (n=95)	[1]Variable dose (100-400) µg qd			200 µg qd + loratadine 10 mg qd (n=169)
					100 µg qd (n=77)	200 µg qd (n=316)	400 µg qd (n=113)	
All Systems-Any AE	3 (3%)	7 (3%)	60 (3%)	3 (3%)	3 (4%)	13 (4%)	6 (5%)	2 (1%)
Autonomic Nervous System	0	0	2 (<1%)	0	0	0	0	0
Body as a Whole-General	0	1 (<1%)	12 (1%)	1 (1%)	0	3 (1%)	1 (1%)	0
Cardiovascular System	0	0	0	0	0	1 (<1%)	0	0
CNS/PNS Disorders	0	1 (<1%)	6 (<1%)	0	0	2 (1%)	0	0
GI System Disorders	0	2 (1%)	2 (<1%)	0	0	1 (<1%)	0	0
Hearing/Vestibular Disorders	0	1 (<1%)	2 (<1%)	0	0	0	0	0
Heart Rate and Rhythm	0	0	1 (<1%)	0	0	1 (<1%)	0	0
Liver and Biliary System	0	0	0	1 (1%)	0	0	0	0
Metabolic and Nutritional	0	0	1 (<1%)	0	0	0	0	0
Musculoskeletal System Disorders	0	0	5 (<1%)	0	0	0	1 (1%)	0
Myo-, Endo-, Pericardial and Valve	0	0	1 (<1%)	0	0	0	0	0
Neoplasm	0	0	1 (<1%)	0	0	0	0	0
Psychiatric	0	0	2 (<1%)	0	0	0	0	0
Reproductive Disorders, Female	0	0	0	0	1*	2*	0	0
Resistance Mechanism (Infection)	1 (1%)	1 (<1%)	4 (<1%)	0	0	1 (<1%)	1 (1%)	1 (1%)
Respiratory System	2 (2%)	1 (<1%)	33 (2%)	1 (1%)	2 (3%)	4 (1%)	3 (3%)	1 (1%)
Skin	0	0	4 (<1%)	0	0	1 (<1%)	1 (1%)	0
Urinary System	0	0	0	0	0	1 (<1%)	0	0
Vision	0	1 (<1%)	1 (<1%)	0	0	0	0	0

Excludes PAR study C94-078, which was submitted after the filing date for NDA 20-762. *No proportion was calculated because the # of female subjects was not identified in 'va

10.3.7. Serious Adverse Events and Death

Among all subjects treated in all treatment groups, 75 subjects (1.1%) were defined by the sponsor as having a 'serious' adverse event, as per the regulatory definition of 'serious'; however on review of the patient capsule summaries [307:1876-1950] many of these subjects never required hospitalization for their problem (e.g. all the subjects with liver function test abnormalities), and had complete reversal of the abnormality on discontinuation of mometasone treatment. 1.2% of all mometasone and 0.8% of placebo treated subjects developed 'serious' adverse events, respectively [302:85]. Of these serious adverse events, many were elective surgeries, and only 6 subjects for all treatment groups combined had serious events that were considered by the principal investigator(s) to be at least 'possibly' related to treatment. For the 4 mometasone treated subjects who developed 'serious' adverse events, these consisted of the following:

(1) One subject (subject C92-011-01, #014) experienced dizziness, wooziness, blurred vision, and disorientation 3.5 hours after the first dose of mometasone 100 µg qd. The subject was evaluated in the emergency room and recovered. Mometasone causality was based on the temporal relationship between mometasone use and onset of symptoms.

(2) One subject (subject I93-221-03, #016) experienced sternal pressure, palpitations, and dyspnea after 10 days of treatment with mometasone 200 µg qd ('variable' dose mometasone group). Two days later the subject stopped using mometasone for 1 day and her symptoms abated. When she resumed mometasone use the following day, the symptoms reappeared, so the subject discontinued mometasone treatment.

(3) One subject (subject C92-011-05, #028) had normal liver function tests at screening consisting of an SGPT=42 IU/L and an SGOT=27 IU/L but developed elevated levels of these 2 parameters (SGPT=79 IU/L, SGOT=159 IU/L) at his final visit after completing a full 4-week course of mometasone 100 µg qd. His LFTs returned to normal range during a repeat evaluation 1-2 weeks later.

(4) The final subject (subject C92-011-05, #015) who had normal liver function tests of an SGPT=17 IU/L and SGOT=14 IU/L at screening, developed elevated levels of these 2 parameters (SGPT=123 IU/L, SGOT=169 IU/L) after 15 days of treatment with mometasone 800 µg qd. The subject discontinued mometasone treatment 3 days later when repeat evaluation showed continued elevation of LFTs (SGPT=175 IU/L, SGOT=80 IU/L). His LFTs returned to normal 5 weeks after the end of treatment.

Other potentially relevant adverse events classified as 'serious' by the sponsor

reported with mometasone use which relate to the known effects of steroids are summarized as follows:

Changes in liver function tests (which consisted of abnormalities of SGOT and SGPT) were reported by the sponsor as 'serious' adverse events in a total of 12 study subjects, 6 of whom were treated with mometasone [302:88-91]. Three of these 6 subjects (a 26 year old male subject treated with mometasone 100 µg qd (subject C92-011-01, # 014) [302:88], a 28 year old male treated with mometasone 200 µg qd (subject C93-215-01, #043) [302:88] and, a 31 year old male treated with mometasone 800 µg qd (subject C92-011-05, #015) [302:89] may have developed LFT abnormalities related to mometasone treatment. None of these subjects were symptomatic and none required hospitalization for their problem (serial laboratory testing in these subjects was performed at the study site(s)). Two subjects (I93-018-02, #008 and I94-079-11, #016) developed viral hepatitis while receiving mometasone treatment which was confirmed by viral serology tests [307:1923, 1948].

One 12 year old male subject treated with mometasone 200 µg qd for 12 weeks (a 'variable' dose mometasone subject) had an abnormally low 8 a.m. plasma cortisol level of 104.0 µg/dL on week 12 of the study that was reported as a serious event, however re-evaluation 3 weeks and 12 weeks later, despite continuation of mometasone treatment, revealed a normal plasma cortisol level (319.8 µg/dL) [292:391, 295:2051, 302:89].

One report of pregnancy and spontaneous abortion occurred in a 33 year old female (subject I93-221-17, # 019) who discontinued mometasone treatment (200 µg qd) 2 weeks earlier, having received a total of 9 weeks of mometasone treatment. The relationship of the spontaneous abortion to mometasone treatment is not clear in that the approximate age of the fetus age at the time of abortion was not known [291:57, 292:391, 302:89].

Three subject deaths (for all treatments) were reported in NDA 20-762; one death due to cerebrovascular accident reported in a 74 year old female who received mometasone 200 µg qd (subject C94-092-02, #02), one death due to renal failure and fatal myocardial infarction reported in a 67 year old male who was discontinued from the 'variable' dose mometasone group 4.5 months earlier (last dose of mometasone received was 200 µg qd, subject I93-221-05, #01), and one death due to an automobile accident reported in a 20 year old male in the placebo group (subject I94-079-21, #07) [302:87].

10.4. Laboratory Test Results

Laboratory tests performed throughout the study duration and which consisted of a complete blood count, blood chemistries, urinalysis, and serum pregnancy test (for all women) did not reveal any unexpected abnormalities in mometasone treated subjects, as compared with placebo. The most notable change in mometasone treated subjects (and also in the active comparator nasal steroids) was a decrease in the peripheral blood eosinophil count (-8.3% median change for mometasone 200 µg qd subjects), with a smaller decrease noted in the total white

blood cell (WBC) count (-4.9% median change for mometasone 200 µg qd subjects) [302:93]. No significant median change or flag shift changes for blood chemistries or urinalysis was noted in mometasone treated subjects, as compared with placebo for the pooled safety population [302:93-94, 96-97, 308:1953-2122]. Stratification by age, gender, and race also failed to reveal any consistent pattern of change in any laboratory tests [302:99-107, 308:2125-2284, 309:2286-2614, 310:2616-2879].

Of the small number of mometasone treated subjects who developed clinically significant laboratory test abnormalities [311:2881-2894], the majority of these involved liver function test or WBC abnormalities and occurred in subjects receiving mometasone 200 µg qd (27/2103 subjects, 1.3% incidence) and 'variable' dose mometasone subjects who received mometasone 200 µg qd (19/506 subjects or 3.8% incidence) [302:107]. These subjects were clinically asymptomatic and did not require hospitalization or further clinical intervention for resolution of their laboratory abnormality with the exception of discontinuation of mometasone treatment. Clinically significant laboratory abnormalities for mometasone treated subjects are summarized in Table XIV. below.

Table XIV. Clinically Meaningful Laboratory Abnormalities in Mometasone Treated Subjects, as compared with Placebo ≥ 1% in Frequency (Pooled Safety Population, Controlled and Uncontrolled Studies), [302:108]

VARIABLE	NUMBER (%) of SUBJECTS	
	All Mometasone Doses (n=3210)	Placebo (n=1671)
↓ WBC	18 (1%)	7 (<1%)
↑ SGPT	13 (<1%)	9 (1%)
↑ SGOT	12 (<1%)	3 (<1%)
↑ Alkaline Phosphatase	6 (<1%)	3 (<1%)
↑ Bilirubin	4 (<1%)	4 (<1%)
↑ Glucose	2 (<1%)	2 (<1%)
↑ Phosphorus	2 (<1%)	2 (<1%)
↓ Hemoglobin	1 (<1%)	2 (<1%)
↑ Albumin	1 (<1%)	0
↑ BUN	1 (<1%)	1 (<1%)
↑ Creatinine	0	1 (<1%)

10.4.1. Special Studies:

10.4.1.a. Hypothalamic-Pituitary-Adrenal (HPA)-Axis Suppression Studies:

Four studies were performed in NDA 20-762 to specifically to assess mometasone's effect on human HPA-axis suppression. These studies and their findings are summarized as follows:

(1) Study C93-196: Multiple-dose Comparative Systemic Bioactivity Study of Mometasone Nasal Spray in Adult Volunteers with Allergic Rhinitis [1.2:19-21].

Study design: This was a randomized, placebo- and positive-controlled (prednisone 10 mg po qd), parallel group, multiple-dose study of mometasone nasal spray administered at 200 µg qd and 400 µg qd vs. placebo and vs. prednisone 10 mg po q a.m. for 36 consecutive days in a total of 64 male volunteers with at least a 2 year history of SAR and documented skin test positivity to a seasonal allergen. Volunteers underwent a.m. plasma cortisol testing and a 6 hour Cortrosyn stimulation test (250 µg of cosyntropin administered intravenously over 6 hours with plasma sampling at 2, 4, and 6 hours during the infusion at both the baseline visit and the final (day 36) visit to assess HPA-axis suppression. An abnormal response in plasma cortisol was defined a priori as an incremental increase in plasma cortisol 6 hours post-ACTH infusion of < 7 µg/dL or a 6 hour post-ACTH infusion plasma cortisol value < 18 µg/dL.

24 hour urinary free cortisol levels were also acquired at the baseline and day 36 visit. Plasma and urine cortisol levels were analyzed via a validated HPLC method. Results from these analyses were statistically analyzed using a 1-way ANOVA to extract treatment effects. Pairwise comparisons for each treatment combination were based on 'Dunnett's multiple comparison procedure.

Results:

Review of HPA-axis suppression data from study C93-196 indicates that overall, no statistically significant decrease in mean plasma cortisol levels or 24 hour urinary free cortisol levels was seen with mometasone nasal spray, given at a dose of either 200 or 400 µg qd. A statistically significant suppression of both mean plasma and 24 hour urinary free cortisols was detected with the positive control, prednisone given at a dose of 10 mg po qd for 36 days. Notable however, was the small decrement on Day 36 in both the plasma and 24 hour urinary free cortisol levels post-ACTH infusion at all time points in mometasone treated volunteers, which was slightly more profound with the 400 µg qd dose. A similar pattern of response was also noted in the placebo volunteers, hence the meaning of this finding is unclear in terms of the mometasone treated volunteers. The plasma cortisol and 24 hour urinary free cortisol data are summarized in Tables XV. and XVI. below.

Importantly however, several outliers in adrenal response were detected in both the mometasone 200 and 400 µg qd groups; namely 2 volunteers (volunteers #28 and 32) in the mometasone 200 µg qd group (2/16 mometasone 200 µg qd volunteers total) and 1 volunteer (volunteer #31) in the mometasone 400 µg qd group (1/16 mometasone 400 µg qd volunteers total) [Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, Study Report for C93-196, p. 14-15]. A total of 11 volunteers (volunteers #5, 13, 21, 27, 36, 47, 48, 49, 56, 57, and 58) in the prednisone 10 mg po qd group had abnormal responses to cosyntropin (ACTH) stimulation. One volunteer (#51) in the placebo group also had an abnormal response to cosyntropin stimulation. Based of these results, one may conclude that most volunteers treated with mometasone at 200 µg qd (or 400 µg qd) would not be expected to have HPA-axis suppression after short-term use (i.e. < 1 month) however, individual adrenal responses may vary, and in rare individual volunteers, mild adrenal suppression could occur at a total daily intranasal dose of 200 µg qd.

Table XV. Mean Plasma Cortisol Levels Pre- and Post-Cosyntropin (ACTH) Simulation Testing. Study C93-196. (Before and After 36 Days of Treatment with Mometasone, Prednisone, or Placebo)
[1.2:20, Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, p. 27]

TREATMENT GROUP	N	TREATMENT PHASE	Hours of ACTH Infusion				[1]Change in Cosyntropin Stimulated Plasma Cortisol Concentration (µg/dL)
			0	2	4	6	
Mometasone 200 µg qd	16 16	Baseline (Day 1) Final visit (Day 36)	11.0 9.2	19.9 18.8	24.4 20.5	30.0 23.3	19.0 14.1
Mometasone 400 µg qd	16 16	Baseline (Day 1) Final visit (Day 36)	11.5 9.4	21.2 18.5	26.3 20.4	32.5 22.3	21.0 12.9
Placebo	16 16	Baseline (Day 1) Final visit (Day 36)	11.9 8.5	21.6 19.0	25.9 21.1	32.3 22.2	20.4 13.7
Prednisone 10 mg po qd	16 16	Baseline (Day 1) Final visit (Day 36)	11.6 6.0[b]	20.5 11.8[a]	24.8 11.7[a]	29.9 14.8[a]	18.3 8.8[a]

[1]Change denotes change from baseline to Day 36.
[a]: $p<0.01$ compared with placebo (Dunnett's test). [b]: $p \leq 0.05$ compared with placebo (Dunnett's test).

Table XVI. Mean 24 Hour Urinary Free Cortisol Levels Pre- and Post-Cosyntropin (ACTH) Simulation Testing. Study C93-196. (Before and After 36 Days of Treatment with Mometasone, Prednisone, or Placebo) [Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, p. 27]

TREATMENT GROUP	N	TREATMENT PHASE	Urinary Free Cortisol (µg/24 hrs) (Pre-ACTH Infusion)	N	Urinary Free Cortisol (µg/24 hrs) (Post-ACTH Infusion)	N	¹Change in 24-hours urinary free cortisol (µg/24 hours)
Mometasone 200 µg qd	6 16	Baseline (Day 1) Final visit (Day 36)	16.2 12.1	6 16	477 383	6 16	461 371
Mometasone 400 µg qd	11 15	Baseline (Day 1) Final visit (Day 36)	30.3 13.5	11 15	306 395	11 15	276 382
Placebo	11 15	Baseline (Day 1) Final visit (Day 36)	43.1 14.2	11 15	629 484	11 15	586 470
Prednisone 10 mg po qd	13 15	Baseline (Day 1) Final visit (Day 36)	24 0.7*	13 15	479 329	13 15	455 328

¹Change denotes change from baseline to Day 36.
*: p<0.01 compared with placebo (Dunnett's test).

(2) Study C92-022: Multiple-dose Safety and Tolerance Study of Mometasone in Healthy Male Volunteers [1.2:16]

Study design: This was a randomized, placebo- and positive-controlled (prednisone 10 mg po qd), parallel group, multiple-dose study of mometasone nasal spray administered at 400 µg qd and 1600 µg qd vs. placebo and vs. prednisone 10 mg po q a.m. for 29 consecutive days in a total of 48 male volunteers.

Volunteers underwent 8 a.m. plasma cortisol testing on Day 1 and serial plasma cortisol testing to determine the plasma cortisol area under the curve (AUC_{0-24}) at 3 a.m., 4 a.m., 5 a.m., 6 a.m. 7 a.m., 8 a.m., 9 a.m., 10 a.m., 11 a.m., 12 noon, 1 p.m., 3 p.m., 5 p.m., 7 p.m., 9 p.m., and 11 p.m. on Days 0, 7, 14, 21, and 28 of the study. An 8 hour Cortrosyn stimulation test (250 µg of cosyntropin administered intravenously over 8 hours with plasma sampling at 2, 4, and 6 hours during the infusion was performed at both the baseline visit and the final (day 29) visit to assess HPA-axis suppression. An abnormal response in plasma cortisol was again defined as an increase in plasma cortisol 6 hours post-ACTH infusion of < 7 µg/dL or a 6 hour post-ACTH infusion plasma cortisol value < 18 µg/dL. Urine was collected as 24-hour block samples for the determination of 24-hour urinary free cortisol and 17-hydroxycorticosteroid levels during both the 24 hour period prior to ACTH stimulation and the 24 hour period following initiation of

the cosyntropin infusion. Plasma and urine samples were analyzed for cortisol using a commercial radioimmunoassay (RIA) method. The area under the plasma cortisol concentration time curve for the 24-hour period following each treatment (AUC_{0-24}) was calculated for each volunteer using the trapezoidal rule. Plasma cortisol levels below 2.0 µg/dL (the lower limit of quantitation) were recorded as zero.

The primary variables of interest in this study were $AUC_{(3-23)}$ (3 a.m. to 11 p.m.), C_{max}, and $C_{(8\ a.m.)}$. For each individual time point, values below assay sensitivity were excluded by the sponsor from statistical analysis. Plasma concentration data were analyzed statistically using ANOVA, extracting the effect due to treatment group.

Results:

In this study, 2 problems were encountered with the methods employed in executing the study which have bearing on interpretation of study results. First, no restrictions were initially placed on volunteers' sleep habits (prior to study Day 7), resulting in plasma cortisol profiles prior to Day 14 of the study that did not have a characteristic diurnal pattern. Hence, the sponsor considered HPA data only to be appropriate for Days 14, 21, and 28. Secondly, use of the RIA to detect plasma cortisol levels exhibited cross-reactivity between cortisol and prednisone in the RIA which precluded interpretation of the prednisone treatment group in this study and limits the conclusions that can be derived from the cosyntropin stimulation test since interpretability of these data are predicated upon a statistically significant difference between the prednisone group and the placebo group.

A summary of the primary variables of interest is presented in Table XVII. below and overall, did not indicate any significant reduction in the plasma cortisol AUC_{3-23}, C_{max}, or $C_{(8\ a.m.)}$ for Days 14, 21, and 28 of the study in mometasone treated volunteers [1.2:18].

Table XVII. Effects of Intranasal Mometasone (400 µg and 1600 µg qd) vs. Placebo on Plasma Cortisol AUC_{3-23}, C_{max}, and $C_{(8\ a.m.)}$ on Study Day 28. Study C92-022. [1.2:18]

	Plasma Cortisol $AUC_{(3-23)}$ (µg/dL)	[1](%CV)	Plasma Cortisol C_{max} (µg/dL)	(%CV)	8 a.m. Plasma Cortisol Level $C_{(8\ a.m.)}$ (µg/dL)	(%CV)
Placebo	200.0	13	18.4	12	13.7	16
[2]Mometasone 400 µg qd	206.6	11	18.4	12	14.4	21
Mometasone 1600 µg qd	199.7	10	19.5	11	13.5	21

[1]CV=Coefficient of Variation, [2]Mometasone administered intranasally.
The prednisone group is not included in the analysis because of cortisol cross-reactivity by RIA.

Review of the plasma and 24 hour urinary free cortisol levels for individual volunteers by line listings in this study failed to reveal significant HPA-axis suppression in all mometasone treated volunteers with the exception of one volunteer (volunteer #04 in the mometasone 400 µg qd group). Nonetheless, this volunteer had normal HPA function in that his pre-cosyntropin plasma cortisol value was 20 µg/dL (normal range 8 a.m. plasma cortisol: 5-23 µg/dL, *Cecil Textbook of Medicine, 20th Edition, Bennett, JC and Plum F., Eds., 20th Edition, 1996, W.B. Saunders, Co., p.2225*) and his 24 hour urinary free cortisol increased from 3 mg/24 hours to 18 mg/24 hours post-cosyntropin (ACTH) stimulation.

Based on data from this study, which is limited in interpretability because of the study flaws previously discussed, no significant difference in plasma cortisol levels (AUC, C_{max} and 8 a.m. plasma cortisol level) on day 28 was nonetheless noted in either the mometasone 400 µg qd or 1600 µg qd treatment group, as compared with placebo.

(3) Study I90-664: Single-dose Comparative Bioactivity of Mometasone vs. Dexamethasone in Healthy Male Volunteers [1.2:13-15]

Study design: This was a randomized, placebo- and positive-controlled (dexamethasone), parallel group, single-, rising-dose study of mometasone nasal spray suspension administered in rising doses of 1000 µg qd, 2000 µg qd, and 4000 µg qd vs. orally administered mometasone administered in rising doses of 2 mg, 4 mg, and 8 mg po qd, vs. dexamethasone elixir administered in rising doses of 0.2 mg, 0.4 mg, and 0.8 mg po qd, and vs. placebo administered to a total of 24

healthy male volunteers.

Volunteers were randomly assigned to the 3 active treatment groups, so that 8 volunteers received intranasal mometasone (1000 µg qd, 2000 µg qd, and 4000 µg qd, and placebo), 8 volunteers received oral mometasone (2 mg, 4 mg, and 8 mg po qd, and placebo), and 8 volunteers received oral dexamethasone (0.2 mg, 0.4 mg, and 0.8 mg po qd, and placebo). Doses were administered at 11 p.m. in a rising progression with the lowest dose administered first. Dose administrations were separated by at least 72 hours.

Plasma cortisol levels were determined at approximately 8 a.m. each day following each 11 p.m. dose; the subsequent 11 p.m. dose in each treatment sequence was not administered until the 8 a.m. plasma cortisol level was not more than 4 µg/dL below the volunteer's designated baseline value and was between 10-25 µg/dL.

In this study cortrosyn (ACTH) stimulation tests were not performed, rather the plasma cortisol area under the curve (AUC_{0-24}) was calculated for the 24-hour period following each treatment based on plasma cortisol levels measured at 11 p.m. prior to treatment administration and at 5 a.m., 6 a.m., 7 a.m., 8 a.m., 9 a.m., 11 a.m., 3 p.m., 6 p.m., and 11 p.m. the following day. Urine for a 24 hour urinary free cortisol assessment was collected as a 24-hour block sample during the 24-hour period prior to the initial treatment administration and during the 48-hour period following each drug administration for subsequent analysis for free cortisol content. Both plasma and urine samples were analyzed for cortisol levels via RIA. Plasma cortisol levels below 2.0 pg/dL were recorded as zero [1.2:15].

Results:

Review of the pooled data and individual volunteer line listings failed to reveal a decrease in the plasma cortisol AUC_{0-24}, 8 a.m. plasma cortisol levels, or 24 hour urinary free cortisol levels in volunteers treated with either intranasal or oral mometasone, as compared with placebo treatment. Conversely, dexamethasone treatment (all doses) resulted in abnormal 8 a.m. cortisol levels (defined as plasma cortisol < 10 µg/dL by the sponsor) and reduced 24 hour plasma AUC values in nearly all volunteers who received dexamethasone treatment, as compared to placebo treatment. Results of the mean AUC_{0-24} for plasma cortisol in all 3 active treatment groups is summarized in Table XVIII. below and confirm a significant adrenal suppression effect only in dexamethasone treated volunteers.

Table XVIII. Mean Plasma Cortisol AUC_{0-24} and Percent Reduction from Placebo for Intranasal Mometasone, Oral Mometasone, and Dexamethasone Treatment Volunteers. Study I90-664. [1.2:15, Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, Study Report I90-664, p. 32]

	Mometasone (Intranasal)			Mometasone (Oral)			Dexamethasone (Oral)		
	1000 µg	2000 µg	4000 µg	2 mg	4 mg	8 mg	0.2 mg	0.4 mg	0.8 mg
Plasma Cortisol AUC_{0-24} (µg·hr/dL)	187.3	169.0	174.8	189.1	166.8	166.1	101.1	32.9	13.0
Change from Placebo (%)	-4%	-13%	-10%	+3%	-9%	-9%	-41%	-81%	-92%

(4) Study C94-052: A long-term safety study of Mometasone furoate aqueous nasal spray vs. Triamcinolone acetonide (Nasacort) in PAR [263:472-473, 264:496-497, Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, Study Report C94-052, p. 1-55].

Study design: While discussed in the individual review of study C94-052 and reiterated in this section on HPA-axis studies, analysis of HPA function in study C94-052 was performed using 2 methods in this study: (1) Cortrosyn testing (cosyntropin (ACTH) stimulation: 250 µg of cosyntropin was administered and plasma cortisol levels were measured 45-60 minutes later) after baseline plasma cortisol levels were obtained and (2) 24 hour urinary free cortisol levels pre- and post-treatment with mometasone and triamcinolone on the baseline (pre-treatment visit) and during weeks 12, 24, and 52 during treatment with either intranasal mometasone or triamcinolone. Of note, if a subject's creatinine value at a given visit was not within 35% of the value at screening, then the subject was excluded from the analyses of urinary free cortisol for that visit [262:32].

Results:

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

in Cortrosyn stimulation testing post-initiation of treatment but no subject had more than one abnormal response [262:78]. Review of the subject line listings submitted 07/14/97 per FDA request by the Sponsor indicates that a total of 10 mometasone treatment group subjects failed to have a > 7 µg/dL increase in plasma cortisol post-cosyntropin stimulation after having received at least 12 weeks (or more) of mometasone treatment (13 triamcinolone treated subjects had similar findings) Schering Plough, Inc. Response to FDA Request-Data Listings, July 14, 1997, Study Report C94-052, p. 1-55]. Nonetheless, in 9 of the 10 mometasone subjects, all plasma cortisol levels were > 18 µg/dL, indicative of adequate adrenal function. In one subject (subject C94-052-16, #008), plasma cortisol levels pre and post-ACTH stimulation were 15.7 µg/dL and 12.9 µg/dL, respectively, indicative of a blunted adrenal response (of note, one triamcinolone subject (subject C94-052-16, #002) also had a blunted adrenal response).

Overall, however, these data indicate that for the majority of subjects, treatment with mometasone 200 µg qd is unlikely to result in either subclinical or clinically significant adrenal suppression.

Table XIX. Cortrosyn Stimulation Test Results for Study C94-052: Mean Plasma Cortisol Levels, Pre- and Post-Treatment with Mometasone and Triamcinolone and Mean Change (Δ) from Screening (ITT Population) [262:78, 263:472]

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

NA=Not applicable, Study performed at sites -01, -05, -06, and -11.
[1]P-value for mometasone vs. triamcinolone (for treatment difference), α=0.05, 2-way ANOVA.

Evaluation of the 24 hour urinary free cortisol levels at study sites -01, 05, 06, and -011 using pooled data from these sites also failed to reveal an effect or a consistent trend post-treatment in decreasing urinary cortisol levels [264:496], although again pooling of data would be less likely to capture abnormal HPA-axis

function in individual subjects. Also of note, a number of subjects failed to have a creatinine value at the respective study visit during which 24 hour urinary free cortisols were collected that was 35% of the value at screening, hence these subjects were excluded from data analysis of the 24 hour urinary free cortisol levels for that visit. As discussed with Ms. Paula Rinaldi, Regulatory Affairs of Schering Plough, Inc. on 08/29/97, the mean screening value for 24 hour urinary free cortisol values was modified to reflect only those subjects that were used in the data analysis for that study visit, i.e. those subjects with a serum creatinine ≥ 35% of the screening value. Results of these modified 24 hour urinary free cortisol levels are summarized in Table XX.

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

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

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

10.4.1.b. Mometasone furoate Plasma Concentration:

Plasma concentrations of mometasone furoate were determined in 3 of the phase II/III studies in NDA 20-762 using an HPLC method with a limit of quantitation of 50 pg/mL [302:110-111].

Results of study C920-011 in which subjects at 2 study sites received either mometasone 50, 100, 200, or 800 µg qd, and had blood samples collected on Day 1 (pre-treatment) and Day 28 (1 and 2 hours post-treatment) indicate that out of 128 samples from 56 subjects, only one plasma mometasone value (77.6 pg/ml) was above the lower limit of quantitation in a 1 hour post-dose sample in a subject

receiving mometasone 800 μg qd.

In study C94-052, where plasma samples were collected at screening, and 1 hour post-dose on weeks 12, 24, and 52 at 4 study sites, only 4 values (out of 169 samples from 45 subjects treated with mometasone 200 μg qd) were above the lower limit of quantitation (58.7 pg/mL in one subject on week 12, 66.1 and 57.1 pg/mL for a second subject on weeks 12 and 24, and 1454 pg/mL for a third subject on week 24). This last plasma value was not felt to represent a true (expected) result and was considered a 'pharmacokinetic outlier'.

In study C94-145, in which subjects received mometasone 200 μg qd, plasma samples were collected at screening, day 1 (5 minutes and 1 hour post-dose) and day 15 (pre-dose and 5 minutes and 1 hour post-dose) at 4 study sites. In this study, all plasma mometasone concentrations in 441 samples from 109 subjects were below the lower limit of quantitation, although an appreciable number of samples were either not obtained or had an insignificant volume to perform HPLC analysis [189:1327, 1345-1349].

10.5. Electrocardiograms

Electrocardiograms (ECGs) performed at baseline (all studies except C93-193 and I94-139) and the endpoint visit (all studies except C93-184, C93-193, C93-215, I92-200, I93-133, I93-180, I94-001, and I94-139) revealed that at the endpoint visit, 77-90% of mometasone treated subjects (mean=80% for all mometasone doses) had a normal ECG recording, as compared with 77% of placebo treated subjects, and 76-91% of active comparator treated subjects.

The proportion of subjects with normal baseline ECGs who had abnormal, but not clinically significant ECGs by the endpoint visit were similar all treatment groups (6 reports (6% incidence) for mometasone 50 μg qd subjects, 7 reports (7% incidence) for mometasone 100 μg qd subjects, 56 reports (4% incidence) for mometasone 200 μg qd subjects, 11 reports (2% incidence) for mometasone 'variable group' or 100-400 μg qd subjects, 8 reports (9% incidence) for mometasone 800 μg qd subjects, 0 reports (0% incidence) for mometasone 200 μg qd + loratadine 10 mg po qd (combination treatment) subjects, and 36 reports (4% incidence) for placebo subjects) [302:112].

A comparison of endpoint visit ECGs with baseline for 'clinically significant' ECG changes revealed no significant difference in incidence between mometasone treated subjects and placebo. Only one mometasone 'variable-dose' subject (I93-211-15, #07) had a normal baseline ECG and was found 3 weeks later when she discontinued the study from urticaria and angioedema, to have left anterior hemiblock and an incomplete right bundle branch block on ECG [302:111-112] on her endpoint visit ECG. One active comparator group subject (subject C93-014-04, #21, a 44 year old female who was receiving beclomethasone 336 μg qd) was also found to have a 'clinically significant' abnormality on endpoint visit ECG (new onset anterior wall myocardial infarction) which was not present at baseline. Given the large number of subjects who had ECGs performed in the different treatment groups (n=1246 for mometasone 200

µg qd, n=363 for beclomethasone 336 µg qd, and n=986 placebo subjects) these individual cases (1 for mometasone, 1 for beclomethasone) are too few in number. do not show a dose response, and are thus unlikely to be related to either study drug treatment.

10.6. Vital Signs and Weight

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) were monitored in all clinical studies at screening, baseline, and at each visit, and weight was recorded at the screening and final (endpoint) evaluation.

Review of the vital sign database failed to reveal any clinically relevant change from baseline observed in mean values for the pooled safety population as well as via stratification by age, (<12 , 12-17 , 18-64, ≥ 65 years), gender, or race (Caucasian and non-Caucasian) [302:115-119, 311:2913-2918, 3029-3052]. Flag shift distributions showed that the distribution of subjects by % change from baseline were similar among the different mometasone doses, other active comparators, and placebo [311:2920-2946, 3054-3080]. The proportion of subjects with changes in blood pressure or heart rate ≥ 30% (i.e. outliers) were also similarly distributed among the different treatment groups 311:3082-3259]. As expected, comparison of weight differences at baseline and endpoint between the different demographic groups showed a mean lower weight for subjects age 12-17 years (baseline mean weight=62.4 kg, endpoint mean weight=63.1 kg) than the other age groups, and in female (baseline mean weight=67.4 kg, endpoint mean weight=67.4 kg) vs. male subjects (baseline mean weight=79.7 kg, endpoint mean weight=80.0 kg) [302:118]. In summary, no clinically relevant difference in vital signs or weight was observed for the different treatment groups, the different doses of mometasone, or the different demographic groups [312:3262-3585, 313:3587-3895].

10.7. Physical Examination and Ophthalmic Examination for Glaucoma and Cataracts

Physical examinations performed on mometasone subjects at screening/baseline and at the endpoint visit overall did not reveal any discernable abnormalities, as compared with placebo; with the exception of nasal ulcer formation in a small percentage of mometasone treated subjects which was greater in frequency (1.3%) than in placebo subjects (0.5%, discussed in Section) [302:120]. In addition, a slightly higher frequency of punctate blood was noted the nasal vault in PAR mometasone treatment subjects (5-6%) as compared with SAR mometasone treatment subjects (3%), or placebo subjects (2-4%) [313:3897-3900]. These findings are consistent with the higher incidence of epistaxis in the longer duration PAR studies (12-52 weeks), as compared with SAR studies that were no longer than 4 weeks in duration.

In terms of glaucoma and cataract formation, 2 studies (C92-280 and C93-014) were specifically designed to evaluate subjects for development of these complications via measurement of intraocular pressures and via slit lamp

examination.

While cataract formation was not detected in any mometasone treated subjects, one subject in the mometasone 200 µg qd treatment group developed several scattered punctate cortical opacities in the right eye > left eye by week 12 of treatment [228:6609]. Regarding the incidence of glaucoma in mometasone treated subjects, in study C92-280, mean and median intraocular pressures at screening and week 12 of the study failed to show any significant difference in measurements for all 3 treatment groups, including the mometasone group [220:839]. Evaluation of individual study subject intraocular pressure measurements revealed only 1 subject in the mometasone (200 µg qd) treatment group who at week 12 had a 3 mm Hg increase in intraocular pressure (to a total pressure of 24 mm Hg) in the right eye [228:6597]. This difference was not felt to represent a significant change from baseline (daily fluctuations of up to 4 mm Hg are acceptable variations in intraocular pressure).

In study C93-014, a 1 year follow-up study of C92-280, one mometasone subject (variable dose group, mometasone dose not specified in submission) was noted to have a significant elevation in intraocular pressures in both eyes post-screening [260:2728], although again, mean intraocular pressures for the screening and week 52 visits were similar for all 3 treatment groups (mometasone, active comparator, and placebo) and ranged from 14.8 mm Hg-15.7 mm Hg [254:533].

10.8. Four Month Safety Update

The 4 month safety update for mometasone was submitted 01/31/97 (Vol 7.1-7.5) and comprised safety results for the adult PAR study I94-078 which was individually reviewed in the clinical study section of the medical officer review, along with 3 ongoing phase III and phase IV trials (C96-195, C95-219, P96-017/J96-017) and safety data from 3 completed pediatric trials (C94-140, C95-136, and C95-161). No new or unusual safety findings were evident in these studies.

For study I94-078, again the most frequent adverse events for all treatment groups consisted of headache, viral infection, epistaxis, and pharyngitis [4 Month Safety Update, Schering Plough, Inc., 01/31/97, Vol. 7.1:12-23, 50-117]. There were no reports of nasal perforation, although several subjects in the mometasone and budesonide (the active comparator treatment group) developed nasal ulcerations post-treatment. The only notable ADRs for mometasone treated subjects in this study were the following: (1) one report of a spontaneous abortion in a 32 year female subject (subject I94-078-21, #19, [290:10, A51.1:95. A51.3:636]) in the mometasone treatment group > 30 days after completion of the 13 week study (12 weeks of mometasone treatment) who was using an IUD throughout the study and at the time of conception, (2) one report of an increase in SGPT from 12 IU/L at screening to 92 IU/L by week 12 of mometasone treatment (subject I94-078-07, #01, [A51.1:97, A51.3:640]), and (3) one report of a decrease in the WBC from a screening value of 4.04 to 2.5 x 10^3/mm^3 by week 12 of mometasone treatment (subject I94-078-09, #08, [A51.1:97, A51.3:640, 4

Month Safety Update, Schering Plough, Inc., 01/31/97, Vol. 7.1:44]). These adverse event reports do not add any substantial new information to the pooled safety database discussed in previous sections of the integrated summary of safety (ISS). No significant patterns of laboratory test abnormalities, abnormalities in vital signs, or physical exam were noted in the study.

A review of the sponsor's update on ongoing phase III studies (C96-195-a 52 week sinusitis study in adult subjects, P95-219-a 2 week randomized, double-blind, single center study comparing mometasone to placebo using nasal function, nasal cytology studies, and biochemical markers, and P96-017/J96-017-a 6 week randomized, double-blind, multi-center trial comparing mometasone and placebo for the treatment of subjects with increased asthma symptoms in conjunction with SAR) confirmed the safety findings (e.g. increased incidence of headache in mometasone and placebo treatment groups) of the other SAR and PAR studies in this submission and did not reveal any new, untoward effects of mometasone treatment.

Three studies were likewise completed in pediatric subjects; two of which were phase I studies and one of which was a phase II dose-ranging study. In these studies doses of mometasone ranging from 25 μg qd to 200 μg qd in subjects age 3-12 years were administered to > 500 pediatric subjects for a duration of 7-28 days (all studies combined) and overall showed a similar incidence of adverse events, as compared with frequencies previously discussed in adult subjects. Again, the most common adverse event reported was headache [4 Month Safety Update, Schering Plough, Inc., 01/31/97, p. 30, 34]. Other more frequent adverse events in mometasone treated pediatric subjects, as compared with placebo included epistaxis, pharyngitis, and coughing [4 Month Safety Update, Schering Plough, Inc., 01/31/97, Vol. 7.1:36].

Thirty (30') minute Cortrosyn stimulation tests performed in 36 pediatric subjects (C95-136) before and after treatment with doses of mometasone ranging from 50, 100, to 200 μg qd for 14 days, failed to reveal any significant decrease in plasma cortisol levels on day 14 compared with baseline in any individual subjects and did not significantly change the mean plasma cortisol levels for pooled subjects at each mometasone dose, as compared with placebo treatment [7.1: Study Report for C95-136, p.28-30].

No serious adverse events in pediatric subjects clearly associated with mometasone use were identified in the 4 month safety update, although one 10 year old female subject in study C95-161 (subject C95-161-12, #48) receiving mometasone 200 μg qd for 2-3 weeks developed an upper respiratory infection, and sinusitis, which progressed to pneumonia with nausea and vomiting [4 Month Safety Update, Schering Plough, Inc., 01/31/97, Vol 7.1:47]. The subject was subsequently treated with I.V. antibiotics and the pneumonia resolved. The relationship of this adverse event to mometasone use in this subject is not likely to be related given the short duration of mometasone use.

10.9. CONCLUSIONS:

A review of the integrated summary of safety (ISS) for controlled and all (controlled, uncontrolled, phase I) studies of mometasone for the treatment of SAR, prophylaxis of SAR, and treatment of PAR; along with the 4 month safety update for mometasone, indicates that mometasone furoate nasal spray is safe and well tolerated at the to-be-marketed dose of 200 µg qd in adult subjects.

Adverse events were generally low in frequency, the most common being headache, viral infection, epistaxis, pharyngitis, and upper respiratory infection. With the exception of a small increase in the frequency of epistaxis with increasing doses of mometasone, no significant dose response in adverse events was seen with mometasone treatment. No significant demographic difference in adverse events reporting was appreciated with the exception of a slightly greater number of adverse events reported in older subjects (age ≥ 65 years), in particular, nasal ulcers. Serious adverse events associated with mometasone use were rare and no deaths were reported.

Except for rare reports of a mild increases in liver function tests (SGOT, SGPT, bilirubin, and alkaline phosphatase) and a mild decrease in the total white blood cell count (WBC) for individual subjects, no significant laboratory abnormalities were reported with mometasone administered in a dose of 200 µg qd. No increased risk for glaucoma or cataract formation with intranasal mometasone use was detected in any of the long-term (1 year) safety studies. HPA-axis suppression with long-term (≥ 1 year) mometasone use was not demonstrable, and the number of rare subject outliers of decreased plasma cortisol levels was not significantly different between the mometasone and placebo treatment group. In summary, mometasone furoate nasal spray appears to be safe for the treatment of SAR, prophylaxis of SAR, and for the treatment of PAR at the recommended dose of 200 µg qd.

11.0. CONCLUSION: Executive Summary of Efficacy and Safety

The three pivotal trials, C93-013 (seasonal allergic rhinitis (SAR)), C93-215 (Prophylaxis of SAR), and C92-280 (perennial allergic rhinitis (PAR)), and nine supplementary trials (five supplementary SAR trials, one supplementary prophylaxis of SAR trial, and three PAR trials), evaluated the efficacy of intranasal mometasone furoate spray (NASONEX), 200 µg, given once daily for treatment and prophylaxis of seasonal allergic rhinitis (SAR) and treatment of perennial allergic rhinitis (PAR). The primary efficacy variable in the pivotal trials (with the exception of the prophylaxis trial), was the subject rated mean change in the total nasal symptom score from baseline for the initial 15 day interval of treatment for combined a.m. and p.m. scores. The total nasal symptom score was defined as a 12 point symptom score comprised by the addition of 4 component nasal symptoms: rhinorrhea, nasal congestion, sneezing, and nasal itching which were each individually rated on a 4 point scale (0-3). Symptoms were assessed reflectively over the previous 12 hours in the a.m. and p.m. by study subjects. Instantaneous symptom scores were not recorded.

The three pivotal trials of greater than 1100 adult subjects age 12 and over demonstrated that mometasone nasal spray administered at 200 µg qd produced a decrease in the mean total nasal symptom score for the initial 15 day study interval that was statistically significantly lower than placebo. For the pivotal prophylaxis trial, a statistically significant increase in the proportion of 'minimal' (i.e. total nasal symptom score was ≤ 2) SAR symptom days, which was defined a priori as the primary efficacy variable, was seen in those subjects treated with mometasone nasal spray 200 µg qd, compared with placebo treated subjects. Although subjects were pre-treated with mometasone from 2-4 weeks prior to the anticipated onset of the pollen season in the pivotal (C93-215) and supportive (I93-133) prophylaxis studies, based on the onset of action of mometasone, one (1) week of pre-treatment with intranasal mometasone 200 µg qd appears to be a reasonable prophylaxis period prior to the anticipated onset of a given patient's allergy season.

Mometasone treatment demonstrated an adequate 24 hour duration of activity, supporting once a day dosing of 200 µg via nasal spray. Onset of action (Study C93-184 and C93-013) was shown to be between 2.0-2.5 days, with a statistically significant and consistent decrease in total nasal symptoms demonstrable in mometasone treated subjects at approximately this time point post-initiation of mometasone treatment. The most appropriate dose of mometasone for the treatment of rhinitis in adult subjects was shown to be 200 µg qd (Study C92-011), although lower doses of mometasone (50 µg and 100 µg qd) also demonstrated a statistically significant decrease in rhinitis symptoms, compared with placebo. At the 50 µg qd and 100 µg qd doses of mometasone, the decrease in rhinitis symptoms were not as consistent during the first few days of treatment as with the 200 µg qd dose of mometasone. Conversely, a higher dose of mometasone, given as 800 µg qd intranasally, did not provide a statistically or

consistently numerically greater efficacy response in reducing rhinitis symptoms, than the 200 µg dose. For the majority of clinical studies reviewed in NDA 20-762, mometasone treatment was less efficacious in the treatment of the non-nasal symptoms of rhinitis (eye redness, eye itch, eye tearing, and ear and/or palatal itch), than in the treatment of the nasal symptoms of rhinitis. A number of studies for the three clinical indications in this NDA submission allowed rescue antihistamine use and results of these studies indicate that treatment with mometasone nasal spray decreased rescue medication use, compared with placebo patients.

No significant demographic differences, based on age, gender, or race, were seen in the SAR, prophylaxis of SAR, or PAR studies with mometasone. In summary, mometasone furoate nasal spray administered at 200 µg qd is effective for the treatment of symptoms due to SAR and PAR, and for the prophylaxis of symptoms of SAR.

The adverse event database consisted of over 3000 subjects internationally, the youngest of which (one subject) was < 12 years of age, though this subject's exact age was not specified in the NDA. Of these, 2266 subjects received at least one dose of mometasone furoate nasal spray ≥ 200 µg qd. The exposure ranged from one dose to greater than 1 year (52 weeks).

Adverse events were generally low in frequency, the most common being headache, viral infection, epistaxis, pharyngitis, and upper respiratory infection. With the exception of a small increase in the frequency of epistaxis with increasing doses of mometasone, no significant dose response in adverse events was seen with intranasal mometasone treatment. No significant demographic difference in adverse event reporting was noted with the exception of a slightly greater number of adverse events, (in particular, nasal ulcers), reported in older subjects (age ≥ 65 years). Serious adverse events associated with intranasal mometasone use were rare and no deaths were reported.

Except for rare reports of a mild increase in liver function tests (SGOT, SGPT, bilirubin, and alkaline phosphatase) and a mild decrease in the total white blood cell count (WBC) for individual subjects, no significant laboratory abnormalities were reported with mometasone administered intranasally at a dose of 200 µg qd. No increased risk for glaucoma or cataract formation with intranasal mometasone use was detected in any of long-term (1 year) safety studies (PAR indication) and HPA-axis suppression with long-term (≥ 1 year) mometasone use was not demonstrable. The number of rare subject outliers of decreased plasma cortisol levels was not significantly different between the mometasone and placebo treatment group. In summary, mometasone furoate nasal spray appears to be safe for the treatment of SAR, prophylaxis of SAR, and for the treatment of PAR at the recommended dose of 200 µg qd.

11.1. Reviewer Recommendation

Mometasone furoate nasal spray 200 µg qd is shown to be safe and effective for the treatment of symptoms of seasonal and perennial allergic rhinitis

and for the prophylaxis of symptoms of seasonal allergic rhinitis in adults ≥ 12 years of age. The recommended prophylaxis period for a given patient's seasonal allergies, based on the mometasone onset of action study and the two SAR prophylaxis studies should be ≥ 1 week. The medical reviewer of NDA 20-762 recommends approval of mometasone furoate nasal spray (NASONEX) 200 µg qd for these three clinical indications.

12.0. Division of Scientific Investigation (DSI) Review:

Clinical investigator audits were conducted by the Division of Scientific Investigation (HFD-344, FDA) on 3 individual principal investigators for the pivotal studies for the 3 proposed clinical indications for mometasone furoate nasal spray. For the pivotal SAR study C93-013, Dr. Andrew Pedinoff (site C93-013-07) underwent study audit, for the pivotal prophylaxis of SAR study C93-215, Dr. Donald Aaronson (site C93-215-01) underwent study audit, and for the pivotal PAR study C92-280, Dr. Harold Kaiser (site C92-280-07) underwent study audit.

In addition to checking the protocol used on site, the signed consent forms for each subject, the investigator's brochure, all adverse event source records, case report forms, and correspondence between the study site, the sponsor(s), and the IRB; per request of the medical reviewer, a number of additional clinical parameters were checked for each study site.

For the SAR study C93-013, allergy skin test results (screening visit), total nasal symptom scores (at baseline and on day 15), and concomitant medication use (on day 15) in the source records were checked on select study subjects and compared to the study reports submitted to NDA 20-762. For the prophylaxis study C93-215, the allergy skin test results (screening visit), total nasal symptom scores (at baseline, at day 29, and day 57), and concomitant medication use (on day 57) were checked on select subjects. Finally, for the PAR study C92-280, ophthalmic exam results which included an assessment of intraocular pressures for both eyes and presence/absence of cataract formation (at screening and at week 12), the Water's view X-ray (at screening), total nasal symptom scores at baseline, day 15, and day 29 were checked on select subjects.

Based on these reviews, Drs. Pedinoff and Aaronson were found to have minor problems with their consent forms but otherwise unremarkable audits. No data discrepancies were noted between the source records and the study reports for the clinical parameters listed above. Audit of Dr. Kaiser's study site revealed several data discrepancies (5 out of 22 study subjects) between case report form. data and the source data but no trend in reporting (i.e. either favoring or disfavoring mometasone treatment) was detected. Furthermore, exclusion of this study site from data analysis for study C92-280, did not change results of the primary efficacy variable and in general made minimal impact on the overall study results. This investigator was only involved in 3 additional studies in NDA 20-762 (4 out of 21 studies total), and hence would not be anticipated to make a significant impact on overall data findings for the entire NDA. The recommended classification for all 3 investigators was NAI (no action indicated)