CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20762

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

JUL 14 1997

NDA #: 20-762

Applicant: Schering-Plough Corporation

Name of Drug: Nasonex (mometasone furoate monohydrate) Nasal Spray

Indication: Seasonal and Perennial allergic rhinitis

Documents Reviewed: Volumes 1.1, 1.320-1.323, 1.328-1.333, 1.367-377 dated September 30,1996

This review pertains to three placebo and active controlled studies. One was in patients with perennial allergic rhinitis. The other two were in patients with seasonal allergic rhinitis. One of these seasonal allergic trials was a prophylaxis trial while the other was a treatment trial.

The medical officer for this submission was A. Worobec, M.D., HFD-570, with whom this review was discussed.

I. Study C93-013

A. Study Description and Method of Analysis

This was a multi-center, double-blind, active- and placebo-controlled study of mometasone 200 mcg QD, vs BDP (Vancanese AQ) 168 mcg BID vs placebo in patients 12 years or older with seasonal allergic rhinitis. There was a two-day to seven-day period between screening and baseline. The treatment period was 30 days.

The following symptoms were evaluated by the patient in daily diaries:

Nasal Symptoms	Non-nasal Symptoms
Rhinorrhea	Itching/burning eyes
Stuffiness/congestion	Tearing/watering eyes
Nasal itching	Redness of eyes
Sneezing	Itching of ears or palate

The severity of these symptoms were rated using the following scale:

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

The diary symptoms were assessed in the AM and PM. The derived variables of Nasal symptoms, Non-Nasal symptoms and Total symptoms were calculated by summing the 4 nasal symptom scores, the 4 non-nasal symptom scores and all 8 symptom scores, respectively. If a symptom was missing on a day, the corresponding total symptom score and either nasal or non-nasal score were left as missing for that day. The sponsor calculated for each patient an AM symptom score for Days 2-15 by averaging the nonmissing AM symptom scores for that two week period. The sponsor calculated for each patient a PM symptom score for Days 1-15 by averaging the nonmissing symptom scores for that two week period. The sponsor calculated for each patient a Nasal symptom score as the average of the AM and PM Nasal scores for the two week period. This average was calculated even if the AM average or PM average was missing for that patient.

The patients recorded their symptomatology twice daily at the same time of day (each morning and evening) before dosing.

The sponsor had the patient take only the PM dose if the patient came to the clinic after 2 PM at the beginning of treatment. [This slightly favors BDP since it is a twice a day drug (the PM dose of BDP is active, whereas the PM dose of Mometasone is a vehicle).]

Chlorpheniramine was provided for rescue. The patient was to fill out a rescue medication card rating his/her symptoms prior to the use of chlorpheniramine.

Patients were to have at least moderate nasal congestion and one other moderate nasal symptom at baseline. The combined score of nasal symptoms was to be at least 6. The patient's overall condition of rhinitis had to be moderate, i.e. a score of at least 2. The combined scores were to be satisfied at both the screening and baseline visit.

The sponsor did not define in the protocol how baseline would be defined for diary data. In the study report, the sponsor defined the AM baseline as the average score on the day of baseline visit and the AM scores from the 3 consecutive days prior to the day of baseline visit. The baseline PM score was the average of the PM scores of the 3 days prior to the baseline day. The AM & PM combined baseline was the average of the baseline AM and PM scores.

The primary efficacy variable was defined in the protocol as the average change in total nasal symptom score over the initial 15 day study period.

Although the study report states that the evaluable patient population would be primary, this reviewer did not find such a statement in the protocol. This review will focus upon the intent-to-treat analysis. As very few patients were considered unevaluable, the results of the evaluable patient analyses are not much different.

The primary analysis on the changes from baseline for the diary variables is an analysis of variance with factors treatment, investigators and treatment-by-investigator interaction. The sponsor included additional factors, such as gender, in supplementary, exploratory analyses.

B. Results

There were 345 patients randomized into this study at 10 centers. One patient received the first dose of medication and then immediately dropped out with no follow-up efficacy or safety data. This patient was excluded from the intent-to-treat analysis. The intent-to-treat population , therefor, included 344 patients (112 mometasone, 116 BDP and 116 placebo).

The treatment groups were comparable at baseline in demographic variables, except for gender (p=0.03). The placebo group had more females (62%) compared to the other groups (46% and 45%). This difference in gender made the groups nearly significantly different in weight (p=0.07).

Twenty-three patients (10 mometasone, 7 BDP and 6 placebo) did not complete the study.

Table 1 shows the AM and PM averaged nasal symptom score mean changes from baseline for days 1-15, days 16-30 and endpoint. Mometasone is significantly different from placebo for all three analyses. The significant differences between the raw treatment

means shows that baseline definition probably had little effect on the significance of the mometasone vs placebo comparison.

Significant differences of mometasone from placebo in Days 1-15 Averaged AM & PM changes from baseline were seen in all 4 components of the nasal symptom.

Table 2 shows the mean changes for the AM nasal symptom score. Mometasone was significantly different from placebo for Days 2-15 and nearly significantly different for Days 16-30 and endpoint. This comparison is important because it demonstrates that Mometasone has an effect at the end of its dosing interval.

Table 3 provides the mean changes from baseline for the non-nasal AM and PM averages. BDP was significantly better than mometasone for endpoint and nearly significantly better for Days 1-15 and Days 16-30. Mometasone had no effect on the non-nasal symptoms.

The sponsor found a significant (P=.05) treatment-by-investigator interaction for AM and PM average nasal symptom score for Days 1-15, Days 16-30 and endpoint. Significant treatment-by-investigator interaction was found also for other analyses. The sponsor found that 7 centers favored mometasone over placebo, 2 favored placebo over mometasone and 1 was neutral. The ordering of the BDP means compared to mometasone and placebo means also varied. Some of the treatment-by-investigator interaction is caused by BDP. Therefore not much weight should be given to treatment-by-investigator interaction in this analysis. Overall the data favored mometasone over placebo for nasal symptoms.

In an exploratory analysis, the sponsor found a significant treatment-by-gender interaction. Mometasone had more effect in females than males. There was almost no effect over placebo in the males for mometasone.(The two centers above that favored placebo over mometasone had a large number of males in the mometasone group.) This reviewer would attribute this difference to sampling variation as the medical officer indicates that there is no gender differences in nasal mucosa that would account for such a difference (most of the effect of mometasone is topical).

The sponsor did other analyses that could be considered confirmatory. Two worthy of discussion are the use of baseline as a covariate, and the substitution of rescue medication diary card assessments, if the patient used rescue medication. The baseline is highly significant, as is usual in allergic rhinitis symptom assessments. The treatment comparisons were more highly significant for the analysis of covariance of the primary variable, changes in nasal symptom scores. The substitution of

rescue scores when patients took rescue medication had negligible effect on the changes from baseline and p-values.

II. Study C92-280

A. Study Description and Method of Analysis

This was a multi center, double-blind, active- and placebo-controlled, parallel group study of mometasone 200 mcg QD, vs BDP (Vancanese AQ) 168 mcg BID vs placebo in patients 12 years or older with perennial allergic rhinitis. There was a 7 day to 14 day period between screening and baseline. The treatment period was 12 weeks.

The diary variables and analyses were similar to those of study C93-013 above, with the following exceptions. For patients who took rescue medication between visits, the last set of symptom scores recorded in their rescue medication diary prior to using rescue medication were considered as the appropriate evaluation of symptoms for the next 12-hour period. The symptom scores in the diary replaced the corresponding scores in the regular diary for the appropriate 12-hour period in all analyses and summaries of symptom scores (and in their calculation of all composite or total symptom scores). The baseline was calculated from the AM scores at the baseline visit and the 7 days prior, as opposed to 3 days, as in Study C93-013.

Patients had to have congestion and/or rhinorrhea each at least moderate at both Screening and Baseline visit and be at least moderate on the diary entries for 4 of the last seven days (AM, PM or rescue medication diary) of the run-in period, and a total nasal score of at least 5 at both Screening and Baseline visit in order to qualify for entry into the study.

B. Results

There were 491 patients enrolled in the study. One patient on placebo was excluded from all analyses. She took her first dose of medication at the study center and then was an immediate dropout and had no follow up safety or efficacy data. The intent-to-treat population had therefore 490 patients (164 on mometasone, 163 on BDP and 163 on placebo). These patients were in 19 centers.

The treatment groups were comparable at baseline in demographic variables.

Sixty four patients did not complete the study (20 mometasone,

19 BDP and 25 placebo). Treatments were fairly balanced with respect to the reasons for not completing.

Table 4 shows the AM and PM averaged nasal symptom score mean changes from baseline for 15 day averages and endpoint. Mometasone is significantly different from placebo in changes from baseline for all time intervals and endpoint. The significant differences between the raw treatment means suggest that the definition of baseline would have little effect on the significance of the mometasone placebo comparison.

Significant differences were seen in some of the components of the nasal symptom. Significant differences of mometasone from placebo in 15 Day Averaged AM & PM changes from baseline were seen in nasal discharge and sneezing for all but one 15 day period. Nasal stuffiness showed significant differences between mometasone and placebo for only 2 of the 15-day time periods. Nasal itch was not significantly different from placebo for any of the 15 day intervals.

This study demonstrated comparable effects for mometasone in males and females.

Table 5 shows the mean changes for the AM nasal symptom score. Mometasone was significantly different from placebo for all 15 day averages and endpoint. This comparison is important because it demonstrates that Mometasone has an effect at the end of its dosing interval.

Table 6 provides the mean changes from baseline for the non-nasal AM and PM averages. Neither BDP or Mometasone had an effect on the non-nasal symptoms. Some significance was seen in the analyses of raw data but these are effected by differences at baseline (lower mean for BDP) .

III. Study C93-215

A. Study Description and Method of Analysis

This was a multi center, double-blind, active- and placebo-controlled, parallel group study of 8 weeks duration comparing mometasone 200 mcg QD, BDP 168 mcg BID, and placebo in patients with seasonal allergic rhinitis. They received treatment up to four weeks prior to and four weeks after the anticipated onset of the first significant ragweed season in the respective geographical vicinity of each study center. Patients within each center were enrolled as a cohort within a five day-period. If the onset of the pollen period was later than anticipated an

additional visit was scheduled.

Because the mometasone and BDP bottles were not of identical appearance a double-dummy approach was used.

At the end of the study, prior to data analysis, the investigator provided the dates for onset of the appearance of ragweed pollen, the peak dates to include the two weeks of highest counts, and offset of the ragweed season (unless still going).

The prophylactic period was the period from the start of treatment to the day before the start of the ragweed season. The pollen season was the time period from the start of the pollen season through the last day of treatment.

The diary data was handled similarly to that in Study C93-013 with the exception that averages were calculated over the whole prophylactic period and 15 day intervals over the pollen period. Baseline was handled the same as in Study 93-013 (using the AM baseline day values and 3 days of diary before the Baseline visit.) However, the primary efficacy analysis, defined below, was different.

The primary efficacy variable was defined as the proportion of minimal symptom days (days when the total nasal symptom score ≤ 2 based on the average of the AM and PM diary evaluations.) This was analyzed by an analysis of variance with factors treatment, investigators and treatment-by-investigator interaction.

There was an inconsistency in the protocol with respect to the definition of "minimal symptom days". The definition given above was used in the Statistics section. The Synopsis section said it was as above with the additional requirement that all nasal and nonnasal symptoms had to be rated as mild or absent. The sponsor said this latter definition was inadvertently carried over from a early version of the I93-133 study protocol. The sponsor also did an analysis not discussed here using that version of the definition and got similar results.

B. Results

There were 349 patients randomized into the study. Two placebo patients had no follow up visits and were excluded from the intent-to-treat analysis.

The treatment groups were comparable in baseline demographic variables.

Eleven patients (8 placebo, 2 mometasone and 1 BDP) withdrew for treatment failure. In all 37 patients withdrew (19 placebo, 13 BDP and 5 mometasone).

Table 7 contains the results of the analysis of the proportion of minimal symptom days (Total Nasal AM & PM average ≤2) for the ragweed season, the total season and the prophylactic period. Both BDP and mometasone were significantly different from placebo during the ragweed season and the total treatment period. Mometasone was significantly better than placebo during the prophylactic period with Vancanese being nearly significantly different from placebo.

Table 8 shows the AM and PM averaged nasal symptom score mean changes from baseline for the prophylactic period, 15 day averages during the pollen season and endpoint. Mometasone is significantly different from placebo in changes from baseline for endpoint and all time intervals except days 46-61. (The results for days 31-45 were not estimable with the model fit but significant if treatment-by-investigator effect is taken out of the model.) The significant differences between raw treatment means shows that how baseline was defined most probably would have little effect on the significance of the mometasone placebo comparison. Significant differences from placebo were seen in each of the four components of AM & PM average Nasal scores at days 1-15, 16-30 and endpoint.

This study demonstrated comparable effects for mometasone in males and females.

Table 9 shows the mean changes for the AM nasal symptom score. Mometasone was significantly different from placebo for endpoint and all 15 day averages except days 46-61 where sample size is small. This comparison is important because it demonstrates that Mometasone has an effect at the end of its dosing interval.

Table 10 provides the mean changes from baseline for the non-nasal AM and PM averages. Mometasone was significantly different from placebo for endpoint and all 15 day averages except days 31-45 and 46-61. Significant differences of mometasone from placebo were seen in the four components at some of these time points.

IV. Reviewer's Comments

Mometasone has adequately demonstrated efficacy in the three studies reviewed. Significant differences for mometasone from placebo were seen in diary combined AM & PM nasal score in all of the three studies at most of the on-treatment 15-day time

intervals in all three studies. Significant differences favoring mometasone over placebo were also seen in the AM nasal score which indicates that mometasone demonstrates once a day efficacy (significance at end of dosing interval.)

The combined AM & PM non-nasal symptom score was only significant in the prophylactic trial C93-215.

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Concur: Dr. Wilson EW 7/14/97

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This review contains 9 pages of text and 9 pages of tables.

cc:
Orig NDA 20-762
HFD-570
HFD-570/Dr. Worobec
HFD-570/Ms. Toyer
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TABLE 1

C93-013

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

INTENT-TO-TREAT POPULATION

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

	(A) MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO				ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	POOLED SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	112	7.6	2.2	116	7.3	2.2	116	7.6	2.0	2.0	0.47	<.01	0.02	0.25	0.6	0.36
1-15 RAW	112	5.3	2.2	116	4.5	2.1	116	6.1	2.0	2.0	<.01	<.01	0.11	<.01	<.01	<.01
CHG	112	-2.3	2.6	116	-2.9	2.1	116	-1.5	2.1	2.2	<.01	0.09	0.05	0.08	<.01	<.01
%CHG	112	-25	38.2	116	-37	25.6	116	-16	29.2							
16-30 RAW	108	4.4	2.5	112	3.6	2.3	112	5.2	2.6	2.3	<.01	<.01	0.02	0.01	0.03	<.01
CHG	108	-3.2	3.0	112	-3.7	2.6	112	-2.4	2.7	2.6	<.01	0.01	0.01	0.16	0.03	<.01
%CHG	108	-36	50.4	112	-49	31.1	112	-30	36.7							
ENDPT RAW	112	4.5	2.6	116	3.7	2.3	116	5.2	2.6	2.3	<.01	<.01	0.02	<.01	0.03	<.01
CHG	112	-3.1	3.0	116	-3.7	2.6	116	-2.3	2.7	2.6	<.01	0.01	<.01	0.1	0.04	<.01
%CHG	112	-35	50.0	116	-48	31.3	116	-29	37.0							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL
@ SUM OF 4 NASAL SYMPTOMS FROM AVERAGED AM AND PM DIARIES -- RUNNY NOSE, STUFFINESS, SNEEZING AND NASAL ITCH
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM AND PM BASELINEVALUES
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

TABLE 2

C93-013

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

INTENT-TO-TREAT POPULATION

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

	(A) MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO				ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	POOLED SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	112	7.7	2.2	116	7.3	2.2	116	7.7	2.0	2.0	0.3	<.01	0.02	0.18	0.98	0.18
2-15 RAW	112	5.4	2.3	116	4.5	2.1	116	6.1	2.1	2.0	<.01	<.01	0.11	<.01	0.01	<.01
CHG	112	-2.2	2.7	116	-2.8	2.1	116	-1.6	2.1	2.2	<.01	0.06	0.05	0.05	0.02	<.01
%CHG	112	-25	36.2	116	-36	27.3	116	-18	26.3							
16-30 RAW	108	4.5	2.6	112	3.7	2.4	112	5.2	2.6	2.3	<.01	<.01	0.02	0.01	0.04	<.01
CHG	108	-3.2	3.1	112	-3.6	2.6	112	-2.5	2.6	2.6	0.01	<.01	0.01	0.25	0.06	<.01
%CHG	108	-37	44.6	112	-47	32.6	112	-31	35.3							
ENDPT RAW	112	4.6	2.7	116	3.7	2.4	116	5.3	2.6	2.4	<.01	<.01	0.02	0.01	0.05	<.01
CHG	112	-3.1	3.1	116	-3.6	2.6	116	-2.4	2.7	2.6	<.01	<.01	<.01	0.14	0.07	<.01
%CHG	112	-35	45.0	116	-47	32.6	116	-29	35.6							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF 4 NASAL SYMPTOMS FROM AM DIARY -- RUNNY NOSE, STUFFINESS, SNEEZING AND NASAL ITCH
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF THE 4 AM DIARY ENTRIES FROM DAY1 (BASELINE VISIT DAY) AND 3 PRIOR CONSECUTIVE DAYS
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

TABLE 3

C93-013

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

INTENT-TO-TREAT POPULATION

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

	(A) MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO				ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	POOLED SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	112	5.5	2.7	116	5.3	2.7	116	5.5	2.6	2.6	0.85	0.01	0.17	0.65	0.95	0.61
1-15 RAW	112	4.1	2.5	116	3.4	2.1	116	4.2	2.3	2.3	0.02	0.01	0.93	0.02	0.72	0.01
CHG	112	-1.4	2.2	116	-1.9	2.2	116	-1.3	2.0	2.1	0.05	0.64	0.09	0.06	0.75	0.03
%CHG	112	-13	77.3	116	-24	71.2	114	-16	43.8							
16-30 RAW	108	3.3	2.5	112	2.6	2.3	112	3.2	2.5	2.4	0.04	<.01	0.97	0.02	0.71	0.04
CHG	108	-2.1	2.6	112	-2.8	2.6	112	-2.3	2.5	2.6	0.13	0.05	0.21	0.05	0.63	0.14
%CHG	108	-23	95.5	112	-46	54.3	110	-38	44.1							
ENDPT RAW	112	3.5	2.6	116	2.6	2.3	116	3.3	2.5	2.5	0.02	0.01	0.93	0.01	0.66	0.03
CHG	112	-2.0	2.6	116	-2.7	2.7	116	-2.2	2.6	2.6	0.1	0.06	0.14	0.04	0.63	0.12
%CHG	112	-21	95.5	116	-44	54.4	114	-35	50.5							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL
@ SUM OF 4 NON-NASAL SYMPTOMS FROM AVERAGED AM AND PM DIARIES -- EYE ITCH, EYE TEAR, EYE REDNESS, AND EAR ITCH
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM AND PM BASELINEVALUES
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

TABLE 4

C92-280

EFFICACY AND SAFETY OF SCH 32088 VS VANCENASE AQ AND PLACEBO IN PERENNIAL RHINITIS

INTENT-TO-TREAT POPULATION

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

	(A) MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	163	6.6	2.2	163	6.7	2.0	162	6.9	2.0	2.0	0.34	0.01	0.06	0.69	0.16	0.31
1-15 RAW	163	5.1	2.2	163	5.0	2.3	162	5.9	2.1	2.2	<.01	<.01	0.57	0.75	<.01	<.01
CHG	163	-1.5	2.0	163	-1.7	2.0	162	-1.0	1.6	1.9	0.01	0.07	0.6	0.43	0.02	<.01
%CHG	163	-20	32.2	163	-23	32.9	162	-13	26.1							
16-30 RAW	159	4.4	2.3	157	4.2	2.4	157	5.3	2.2	2.2	<.01	<.01	0.54	0.51	<.01	<.01
CHG	159	-2.2	2.3	157	-2.4	2.5	157	-1.6	2.1	2.2	<.01	<.01	0.37	0.37	0.02	<.01
%CHG	159	-30	34.9	157	-33	40.5	157	-18	59.4							
31-45 RAW	152	4.2	2.5	157	4.0	2.5	153	5.1	2.4	2.4	<.01	<.01	0.34	0.58	<.01	<.01
CHG	152	-2.5	2.7	157	-2.7	2.6	153	-1.8	2.3	2.5	<.01	0.01	0.22	0.52	0.01	<.01
%CHG	152	-33	41.6	157	-37	41.1	153	-19	85.9							
46-60 RAW	147	3.8	2.4	157	3.8	2.5	148	4.9	2.4	2.4	<.01	<.01	0.47	0.95	<.01	<.01
CHG	147	-2.8	2.7	157	-2.9	2.6	148	-2.0	2.4	2.5	0.01	0.02	0.52	0.86	0.01	<.01
%CHG	147	-38	40.5	157	-40	38.5	148	-22	86.9							
61-75 RAW	144	3.7	2.3	150	3.7	2.4	142	4.5	2.4	2.3	<.01	<.01	0.91	0.76	<.01	<.01
CHG	144	-2.9	2.5	150	-3.0	2.5	142	-2.3	2.5	2.4	0.06	<.01	0.5	0.87	0.05	0.03
%CHG	144	-41	35.3	150	-43	35.1	142	-26	90.4							
76-90 RAW	142	3.7	2.3	145	3.6	2.4	139	4.6	2.5	2.3	<.01	<.01	0.88	0.74	<.01	<.01
CHG	142	-2.9	2.5	145	-3.0	2.5	139	-2.3	2.7	2.5	0.04	<.01	0.36	0.75	0.05	0.02
%CHG	142	-42	36.0	145	-43	35.1	139	-25	95.1							
ENDPT RAW	163	3.9	2.5	163	3.9	2.6	162	4.8	2.7	2.5	<.01	<.01	0.96	0.92	<.01	<.01
CHG	163	-2.7	2.7	163	-2.8	2.5	162	-2.1	2.7	2.6	0.03	0.01	0.61	0.83	0.03	0.02
%CHG	163	-38	40.5	163	-41	35.6	162	-24	89.3							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF 4 NASAL SYMPTOMS FROM AVERAGED AM AND PM DIARIES -- RUNN Y NOSE, STUFFINESS, SNEEZING AND NASAL ITCH
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM AND PM BASELINE VALUES
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT
SYMPTOMS ADJUSTED FOR RESCUE MEDICATION

TABLE 5

C92-280

EFFICACY AND SAFETY OF SCH 32088 VS VANCENASE AQ AND PLACEBO IN PERENNIAL RHINITIS

INTENT-TO-TREAT POPULATION

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

	(A) MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO				ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	POOLED SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	163	6.8	2.2	163	6.8	2.1	162	7.0	2.1	2.1	0.4	0.03	0.07	0.73	0.34	0.19
2-15 RAW	163	5.2	2.3	163	5.0	2.3	162	6.0	2.2	2.2	<.01	<.01	0.56	0.46	<.01	<.01
CHG	163	-1.6	2.0	163	-1.7	2.1	162	-1.0	1.6	1.9	<.01	0.11	0.58	0.64	0.01	<.01
%CHG	163	-21	32.7	163	-23	33.0	162	-13	25.0							
16-30 RAW	159	4.5	2.3	157	4.3	2.5	157	5.4	2.3	2.3	<.01	<.01	0.67	0.38	<.01	<.01
CHG	159	-2.2	2.3	157	-2.4	2.5	157	-1.5	2.1	2.3	<.01	<.01	0.31	0.62	<.01	<.01
%CHG	159	-31	34.4	157	-32	38.4	157	-17	51.5							
31-45 RAW	152	4.3	2.5	157	4.1	2.5	153	5.2	2.5	2.4	<.01	<.01	0.45	0.45	<.01	<.01
CHG	152	-2.5	2.7	157	-2.7	2.6	153	-1.8	2.3	2.5	<.01	0.01	0.33	0.78	<.01	<.01
%CHG	152	-34	41.0	157	-36	41.4	153	-19	75.6							
46-60 RAW	147	3.9	2.4	157	3.9	2.6	148	5.0	2.5	2.4	<.01	<.01	0.45	0.87	<.01	<.01
CHG	147	-2.9	2.7	157	-2.8	2.7	148	-2.0	2.4	2.6	<.01	0.02	0.41	0.76	<.01	0.01
%CHG	147	-39	39.1	157	-39	40.9	148	-21	88.5							
61-75 RAW	144	3.8	2.3	150	3.7	2.5	142	4.7	2.4	2.3	<.01	<.01	0.92	0.63	<.01	<.01
CHG	144	-3.0	2.4	150	-3.0	2.6	142	-2.3	2.6	2.5	0.04	<.01	0.52	0.81	0.02	0.03
%CHG	144	-41	35.8	150	-42	37.3	142	-24	92.8							
76-90 RAW	142	3.8	2.4	145	3.7	2.4	139	4.7	2.5	2.4	<.01	<.01	0.93	0.57	<.01	<.01
CHG	142	-3.0	2.4	145	-3.0	2.6	139	-2.3	2.7	2.5	0.03	<.01	0.5	0.96	0.02	0.02
%CHG	142	-42	36.8	145	-42	37.1	139	-25	83.7							
ENDPT RAW	163	4.0	2.5	163	3.9	2.6	162	4.9	2.7	2.5	<.01	<.01	0.97	0.87	<.01	<.01
CHG	163	-2.8	2.6	163	-2.8	2.6	162	-2.1	2.7	2.6	0.02	<.01	0.65	0.9	0.01	0.02
%CHG	163	-39	40.4	163	-40	37.1	162	-24	79.3							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF 4 NASAL SYMPTOMS FROM AM DIARY -- RUNNY NOSE, STUFFINESS , SNEEZING AND NASAL ITCH
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 8 AM DIARY ENTRIES (DAY -6 THROUGH DAY 1)
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES

ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT
SYMPTOMS ADJUSTED FOR RESCUE MEDICATION

TABLE 6

C92-280

EFFICACY AND SAFETY OF SCH 32088 VS VANCENASE AQ AND PLACEBO IN PERENNIAL RHINITIS

INTENT-TO-TREAT POPULATION

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

	(A) MOMETASONE			(B) VANCENASE AQ			(C) PLACEBO				ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	POOLED SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	163	4.3	2.8	163	3.8	2.5	162	4.2	2.6	2.5	0.16	0.01	0.04	0.08	0.77	0.13
1-15 RAW	163	3.5	2.5	163	3.0	2.3	162	3.5	2.4	2.3	0.03	<.01	0.16	0.04	0.81	0.02
CHG	163	-0.8	1.8	163	-0.9	1.7	162	-0.7	1.7	1.7	0.6	0.03	0.08	0.84	0.45	0.34
%CHG	158	16.1	319	158	-3.8	105	161	1.9	95.6							
16-30 RAW	159	3.1	2.5	157	2.5	2.3	157	3.0	2.4	2.3	0.03	<.01	0.3	0.01	0.68	0.04
CHG	159	-1.2	2.2	157	-1.4	2.1	157	-1.1	2.1	2.1	0.61	<.01	0.22	0.55	0.69	0.32
%CHG	154	-15	106	152	-16	151	156	-17	78.6							
31-45 RAW	152	2.9	2.5	157	2.4	2.3	153	2.8	2.5	2.3	0.05	<.01	0.13	0.03	0.88	0.04
CHG	152	-1.4	2.3	157	-1.5	2.3	153	-1.3	2.3	2.2	0.72	0.01	0.16	0.8	0.59	0.43
%CHG	147	-24	107	152	-19	136	152	-17	125							
46-60 RAW	147	2.7	2.4	157	2.2	2.4	148	2.7	2.5	2.3	0.1	<.01	0.09	0.07	0.94	0.06
CHG	147	-1.6	2.4	157	-1.6	2.2	148	-1.5	2.2	2.3	0.73	0.09	0.36	0.97	0.48	0.5
%CHG	142	-29	92.9	152	-33	89.4	147	-27	112							
61-75 RAW	144	2.6	2.3	150	2.2	2.3	142	2.4	2.3	2.2	0.27	<.01	0.21	0.11	0.54	0.33
CHG	144	-1.8	2.3	150	-1.6	2.1	142	-1.7	2.4	2.2	0.91	0.02	0.41	0.68	0.89	0.78
%CHG	139	-38	61.6	145	-34	115	141	-32	94.6							
76-90 RAW	142	2.7	2.4	145	2.2	2.3	139	2.4	2.5	2.3	0.19	<.01	0.61	0.07	0.45	0.3
CHG	142	-1.7	2.4	145	-1.7	2.2	139	-1.7	2.4	2.3	0.95	0.06	0.17	0.98	0.79	0.77
%CHG	137	-30	77.6	140	-29	148	138	-31	93.7							
ENDPT RAW	163	2.7	2.4	163	2.3	2.3	162	2.7	2.6	2.4	0.17	<.01	0.42	0.09	0.85	0.12
CHG	163	-1.6	2.5	163	-1.6	2.2	162	-1.6	2.5	2.4	0.99	0.05	0.39	0.87	0.91	0.96
%CHG	158	-5.2	319	158	-27	144	161	-28	91.8							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF 4 NON-NASAL SYMPTOMS FROM AVERAGED AM AND PM DIARIES -- EYE ITCH, EYE TEAR, EYE REDNESS, AND EAR ITCH
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM AND PM BASELINE VALUES
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT
SYMPTOMS ADJUSTED FOR RESCUE MEDICATION

TABLE 7

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

PROPORTION OF DAYS WITH AM & PM AVERAGED TOTAL NASAL SYMPTOMSCORE @ <= 2

	(A) MOMETASONE			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
RAGWEED	115	0.84	0.25	112	0.79	0.29	109	0.63	0.36	0.29	<.01	<.01	0.02	0.17	<.01	<.01
TOTAL	116	0.89	0.19	116	0.85	0.22	115	0.75	0.26	0.22	<.01	<.01	0.19	0.15	<.01	<.01
PROPHYL	116	0.95	0.16	116	0.93	0.17	115	0.88	0.23	0.19	0.02	<.01	0.9	0.35	0.01	0.06

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 4 NASAL SYMPTOMS FROM THE AVERAGED AM & PM DIARIES - RUNNY NOSE, STUFFINESS, SNEEZING AND ITCH
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE

TABLE 6

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM & PM AVERAGED NASAL SYMPTOM SCORE - POOLED DIARY DATA

	(A) MFNS			(B) VANCENASE			(C) PLACEBO				ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	POOLED SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	116	0.3	0.5	115	0.4	0.5	115	0.4	0.5	0.4	0.19	<.01	0.48	0.41	0.07	0.32
PRE RAW	116	0.4	0.7	115	0.6	1.0	115	0.7	0.9	0.8	0.01	<.01	0.65	0.13	<.01	0.13
CHG	116	0.1	0.6	115	0.2	1.0	115	0.3	0.8	0.8	0.12	<.01	0.32	0.29	0.04	0.32
%CHG	66	14.0	127	65	56.6	206	65	97.9	234							
1-15 RAW	114	0.7	1.0	111	1.0	1.3	109	2.0	2.0	1.4	<.01	<.01	<.01	0.10	<.01	<.01
CHG	114	0.4	0.9	111	0.6	1.4	109	1.6	2.0	1.4	<.01	<.01	<.01	0.2	<.01	<.01
%CHG	65	86.6	237	63	216	432	59	367	713							
16-30 RAW	114	1.2	1.3	107	1.4	1.7	103	2.4	2.3	1.7	<.01	0.03	0.04	0.21	<.01	<.01
CHG	114	0.8	1.3	107	1.0	1.6	103	1.9	2.3	1.6	<.01	<.01	0.02	0.27	<.01	<.01
%CHG	65	184	322	60	225	369	56	442	656							
31-45 RAW	76	1.4	2.0	67	1.7	2.2	61	2.4	2.4	2.2	<.01	0.54	0.54	N/E	N/E	N/E
CHG	76	1.0	2.0	67	1.3	2.3	61	2.0	2.4	2.2	<.01	0.04	0.49	N/E	N/E	N/E
%CHG	40	173	361	33	223	611	30	404	960							
46-61 RAW	16	1.4	1.5	14	2.0	2.6	13	1.8	1.9	2.2	0.69	0.83	0.7	0.5	N/E	N/E
CHG	16	1.0	1.5	14	1.7	2.9	13	1.6	2.0	2.2	0.53	0.62	0.62	0.38	N/E	N/E
%CHG	11	281	384	8	602	1267	4	118	281							
ENDPT RAW	116	1.2	1.7	115	1.5	1.9	115	2.6	2.5	2.0	<.01	0.02	0.08	0.26	<.01	<.01
CHG	116	0.9	1.7	115	1.1	2.0	115	2.1	2.5	2.0	<.01	<.01	0.06	0.35	<.01	<.01
%CHG	66	184	344	65	256	573	65	507	906							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
PRE : PRE-SEASON TREATMENT INTERVAL -- OTHERS ARE DAYS POST-ONSET OF SEASON
@ SUM OF THE 4 NASAL SYMPTOMS FROM THE AVERAGED AM & PM DIARIES - RUNNY NOSE, STUFFINESS, SNEEZING AND ITCH
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM & PM DIARY BASELINE VALUES
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

TABLE 9

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM NASAL SYMPTOM SCORE - POOLED DIARY DATA

		(A) MFNS			(B) VANCENASE			(C) PLACEBO			POOLED	ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS		N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE		116	0.4	0.5	115	0.5	0.6	115	0.5	0.6	0.5	0.49	<.01	0.34	0.39	0.25	0.[illegible]
PRE	RAW	116	0.5	0.8	115	0.6	1.0	115	0.8	0.9	0.8	0.02	<.01	0.56	0.16	<.01	0.14
	CHG	116	0.1	0.7	115	0.2	1.1	115	0.3	0.9	0.8	0.09	<.01	0.2	0.37	0.03	0.19
	%CHG	63	2.4	124	57	0.5	140	60	106	272							
1-15	RAW	114	0.8	1.0	111	1.0	1.4	109	2.0	2.0	1.4	<.01	<.01	0.01	0.16	<.01	<.01
	CHG	114	0.4	0.9	111	0.6	1.4	109	1.5	2.1	1.5	<.01	<.01	<.01	0.26	<.01	<.01
	%CHG	62	47.9	174	55	115	355	55	307	622							
16-30	RAW	114	1.2	1.3	107	1.5	1.7	103	2.4	2.3	1.7	<.01	0.02	0.05	0.18	<.01	<.01
	CHG	114	0.7	1.3	107	1.0	1.9	103	1.9	2.3	1.6	<.01	<.01	0.03	0.26	<.01	<.01
	%CHG	62	119	251	52	103	244	54	400	731							
31-45	RAW	76	1.4	2.0	67	1.6	2.3	61	2.4	2.3	2.2	<.01	0.43	0.56	N/E	N/E	N/E
	CHG	76	1.0	2.0	67	1.3	2.4	61	1.9	2.4	2.2	<.01	0.02	0.48	N/E	N/E	N/E
	%CHG	39	120	286	30	125	343	28	209	383							
46-61	RAW	18	1.4	1.6	14	2.2	3.1	13	1.8	2.1	2.4	0.58	0.8	0.57	0.41	N/E	N/E
	CHG	18	0.9	1.5	14	1.8	3.2	13	1.5	2.2	2.4	0.4	0.63	0.46	0.29	N/E	N/E
	%CHG	11	170	319	6	474	762	4	19.7	147							
ENDPT	RAW	116	1.3	1.7	115	1.6	2.0	115	2.6	2.5	2.0	<.01	0.01	0.14	0.23	<.01	<.01
	CHG	116	0.9	1.7	115	1.1	2.1	115	2.1	2.6	2.1	<.01	<.01	0.11	0.33	<.01	<.01
	%CHG	63	117	261	57	141	403	60	378	700							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 4 NASAL SYMPTOMS FROM THE AM DIARY - RUNNY NOSE, STUFFINESS, SNEEZING AND ITCH
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF 4 AM DIARY ENTRIES - 3 CONSECUTIVE DAYS PRIOR TO AND INCLUDING DAY 1
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

TABLE 10

C93-215

PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS WITH MOMETASONE FUROATE AQUEOUS NASAL SPRAY

INTENT-TO-TREAT POPULATION

AM & PM AVERAGED NON-NASAL SYMPTOM SCORE - POOLED DIARY DATA

	(A) MFNS			(B) VANCENASE			(C) PLACEBO				ANOVA P-VALUES #			PAIRWISE COMPARISONS #		
DAYS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	POOLED SD	TRT	INV	T X I	A-B	A-C	B-C
BASELINE	116	0.1	0.3	115	0.2	0.4	115	0.2	0.4	0.4	0.47	<.01	0.07	0.6	0.22	0.49
PRE RAW	116	0.3	0.4	115	0.3	0.6	115	0.3	0.6	0.6	0.79	<.01	0.56	0.67	0.49	0.8
CHG	116	0.1	0.4	115	0.1	0.8	115	0.1	0.4	0.6	0.99	<.01	0.43	0.91	0.94	0.87
%CHG	33	86.2	315	26	-20	132	42	26.7	154							
1-15 RAW	114	0.6	0.6	111	0.7	1.0	109	1.0	1.5	1.1	<.01	0.04	0.1	0.86	<.01	<.01
CHG	114	0.4	0.9	111	0.5	1.0	109	0.9	1.5	1.1	<.01	0.01	0.06	0.66	<.01	<.01
%CHG	33	132	423	26	91.1	264	37	207	364							
16-30 RAW	114	0.6	1.3	107	1.1	1.7	103	1.3	2.0	1.6	0.03	0.01	1.09	0.17	0.01	0.01
CHG	114	0.7	1.3	107	0.9	1.7	103	1.2	1.9	1.6	0.04	<.01	0.08	0.2	0.01	0.01
%CHG	33	130	267	25	137	383	37	295	463							
31-45 RAW	76	0.9	1.7	67	1.2	2.0	61	1.2	2.1	1.9	0.26	0.06	0.91	N/E	N/E	N/E
CHG	76	0.8	1.8	67	1.1	2.1	61	1.0	2.0	1.9	0.41	0.01	0.96	N/E	N/E	N/E
%CHG	26	143	300	18	203	490	22	280	560							
46-61 RAW	18	1.0	1.5	14	1.9	3.1	13	0.7	1.0	2.1	0.66	0.79	0.49	0.62	N/E	N/E
CHG	18	0.6	1.5	14	1.8	3.0	13	0.7	1.0	2.0	0.69	0.6	0.37	0.63	N/E	N/E
%CHG	7	349	749	3	802	756	3	294	460							
ENDPT RAW	116	0.8	1.5	115	1.1	1.8	115	1.4	2.1	1.8	0.04	<.01	0.06	0.13	0.01	0.3
CHG	116	0.6	1.5	115	0.9	1.9	115	1.2	2.0	1.7	0.06	<.01	0.08	0.16	0.02	0.36
%CHG	33	176	438	28	150	440	42	239	430							

SD = STANDARD DEVIATION T X I = TREATMENT BY INVESTIGATOR INTERACTION N/E = NON-ESTIMABLE
# P-VALUES ARE FROM 2-WAY ANALYSIS OF VARIANCE AND LSMEANS PAIRWISE COMPARISONS (NO ADJUSTMENT FOR OVERALL ALPHA-LEVEL)
@ SUM OF THE 4 NON-NASAL SYMPTOMS FROM THE AVERAGED AM & PM DIARIES - EYE TEAR, EYE REDNESS, EYE ITCH AND EAR/PALATE ITCH
BASELINE FOR EACH SUBJECT WAS THE AVERAGE OF AM & PM DIARY BASELINE VALUES
SYMPTOMS ARE SCORED AS 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE
SUBJECTS WITHOUT BASELINE AND AT LEAST 1 POST-BASELINE VALUE WERE EXCLUDED
SOME PERCENT CHANGE VALUES MAY NOT BE AVAILABLE DUE TO 0 BASELINE VALUES
ENDPT = LAST AVAILABLE POST-BASELINE VALUE FOR EACH SUBJECT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20762

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-570

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review #1 of NDA 20-762
January 06, 1997

A. 1. **APPLICATION NUMBER:** NDA 20-762

APPLICANT: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

2. **PRODUCT NAME:** Nasonex (mometasone furoate) Nasal Spray

3. **DOSAGE FORM:** Mometasone furoate monohydrate (0.05% w/w) in 20 mL plastic spray bottles

4. **METHOD OF STERILIZATION:** None (non-sterile product). The product is preserved with benzalkonium chloride (0.2 mg/g) and phenylethyl alcohol (2.5 mg/g)

5. **PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION:** The proposed indication for the drug product is for the treatment of the symptoms of seasonal/perennial allergic rhinitis in adults and adolescents 12 years and older.

6. **DRUG PRIORITY CLASSIFICATION:** 3S

B. 1. **DATE OF INITIAL SUBMISSION:** Sept. 30, 1996

2. **DATE OF CONSULT:** Nov. 25, 1996

3. **RELATED DOCUMENTS:** (none)

4. **ASSIGNED FOR REVIEW:** Dec. 2, 1996

C. **REMARKS:** In addition to the microbial limits and preservative effectiveness testing review requested by HFD-570, this review addresses the microbiology content of the stability section.

APPEARS THIS WAY
ON ORIGINAL

D. CONCLUSIONS:

Preservative effectiveness testing, microbial limits testing, and the respective specifications are adequate for the drug product. The application is recommended for approval for issues concerning microbiology.

Neal Sweeney 1/6/97

Neal Sweeney, Ph.D.

PHC 1/13/97

cc:

Original NDA 20-762
HFD-570/ Division File
HFD-570/D. Toyer/C. Bertha/G. Poochikian/C. Schumaker
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, January 06, 1996
R/D initialed by P. Cooney January 06, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20762

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology & Biopharmaceutics Review

NASONEX™ Nasal Spray
(50 µg/Actuation mometasone furoate monohydrate suspension)
NDA 20-762

Type of Submission: New NDA, 1S

Submission Date:
9/30/96

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Reviewer:
Brad Gillespie, PharmD

Synopsis Intended for once daily intranasal administration, each actuation of NASONEX is designed to deliver 50 µg of mometasone furoate. The proposed daily dosage is 2 sprays in each nostril (200 µg) for the prophylaxis and treatment of symptoms associated with seasonal and perennial allergic rhinitis.

In support of this application, the sponsor has submitted the results of eight pivotal clinical trials and 2 human pharmacokinetic studies.

Two pharmacokinetic trials were evaluated and excerpts are included from the Pharmacology/Toxicology (Dr. T. Du) review of *in vitro* metabolism. The *in vitro* metabolism study showed that mometasone is extensively metabolized by rat and mouse S9 liver fraction to 6-hydroxy mometasone (≈40%) and two minor unidentified metabolites (≤2%). The mass balance study demonstrated that when administered as an intranasal suspension, mometasone absorption is minimal (≈2% of administered radioactivity recovered in the urine). When given as intravenous and oral solutions, mometasone is extensively metabolized and excreted mainly in the feces. When given as an intranasal suspension, most of the administered dose is recovered in the feces, probably as unabsorbed drug. Plasma mometasone concentrations after intranasal administration of this product were inadequate to assess its bioavailability. After intravenous administration of mometasone, females were found to have a longer elimination half-life (16.6 versus 7.7 hours in males). After administration of an oral solution, mometasone bioavailability was higher in females then males (C_{max}: +105%; AUC: +51%). Part of these observed differences are probably due to differences in subject volume of distribution (mean subject weights - males: 171.0 lbs; females: 147.8 lbs → male/female = 1.16). The remaining difference is not explained by the data presented. While mometasone bioavailability was inadequate to assess this effect when administered as the intranasal product, the possibility of increased bioavailability in females should be considered when evaluating the safety of this product.

TABLE OF CONTENTS

Page Number

Background..... ii
Summary of Clinical Pharmacology & Biopharmaceutics..... iii
Comments..... iv
Recommendation..... v

Appendix I (Study Summaries)

Study I Mass Balance Study..... 1
Study II Absolute Bioavailability Study..... 6
Study III *In vitro* Metabolism 9

Background Mometasone furoate has been marketed as a topical lotion, ointment and cream since the late 1980s. In this application, the sponsor has submitted the results of eight pivotal clinical trials and 2 human pharmacokinetics studies to support marketing of a metered-dose, manual spray unit containing an aqueous suspension of mometasone furoate monohydrate.

NASONEX's proposed indication is for the prophylaxis and treatment of symptoms associated with seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis in adults and children 12 years of age and older. The proposed recommended dose is two sprays (50 μg of mometasone furoate/spray) in each nostril once daily (total daily dose of 200 μg).

APPEARS THIS WAY
ON ORIGINAL

Summary of Clinical Pharmacology & Biopharmaceutics

I. METABOLISM/MASS BALANCE

In vitro metabolism experiments demonstrated that while mometasone is not metabolized by rat lung S9 fractions, extensive metabolism occurred with liver S9 fractions. In rat liver S9 incubation, SCH 32088 was extensively metabolized. Approximately 40% of SCH 32088 (0.05mM substrate) was converted to 6-hydroxy SCH 32088. Smaller proportions of mometasone and two unknown metabolites were also detected. In mouse liver, 6-hydroxylation, ester hydrolysis and metabolism to an unidentified product were observed.

Drug derived radioactivity was minimally absorbed (~ 2% of administered radioactivity recovered in the urine) when mometasone was administered as a nasal spray. Mometasone was extensively metabolized after administration of intravenous and oral solutions. It appears that the major route of excretion is fecal elimination of metabolized drug. When given as the nasal spray, most of the administered radioactivity is eliminated in the feces, probably as unabsorbed drug.

II. BIOAVAILABILITY

Plasma mometasone concentrations observed after intranasal administration of this product were inadequate to assess its bioavailability.

III. PHARMACOKINETICS

After administration of a 1.0 mg single dose of an intravenous solution, the mean mometasone $AUC_{0-\infty}$ for males and females were: 17557 (CV-30%) pg·hr/mL and 18742 (CV-19%) pg·hr/mL, respectively. The elimination half lives for males and females were 7.73 (CV-48%) and 16.6 (CV-78%) hours, respectively.

IV. SPECIAL POPULATIONS

Gender The effect of gender on mometasone disposition was evaluated by stratifying the volunteers by sex in the Absolute Bioavailability study (C95-050). In the intravenous arm of this study, terminal elimination rates were higher in females versus males (16.6 versus 7.7 hours). After administration of an oral solution, mometasone bioavailability was higher in females then males (C_{max}: +105%; AUC: +51%). Part of these observed difference are probably due to differences in subject volume of distribution (mean subject weights - males: 171.0 lbs; females: 147.8 lbs → male/female = 1.16). The remaining difference is not explained by the data presented. While mometasone bioavailability was inadequate to assess this effect when administered as the intranasal product, the possibility of increased bioavailability in females should be considered when evaluating the safety of this product.

V. FORMULATIONS

The pivotal clinical efficacy and safety trial batches were of full production scale and represent the final, to-be marketed formulation. The batch used for the bioavailability study was of one-half production-scale and used a packaging system different from the to-be-marketed. It is not expected that these differences would have a major effect on bioavailability

COMMENTS (From Study C95-050)

1. Relatively sporadic and transient mometasone plasma concentrations were observed in four female subjects (Subjects 13, 16, 21 and 22) participating in the intranasal arm of this study. The sponsor is requested to provide an explanation for these findings.

2. If the sponsor elects to develop additional mometasone furoate products with bioavailability adequate to permit quantification, a complete human pharmacokinetic program would be necessary for approval. Please contact the Office of Clinical Pharmacology & Biopharmaceutics for further details.

3. Markedly higher bioavailability was observed in female versus male subjects after administration of mometasone furoate as an oral solution. Weight adjustments of C_{max} and AUC were not performed by the sponsor. Based on mean subject weights (males: 171.0 lbs; females: 147.8 lbs → male/female = 1.16) only part of the difference observed is probably derived from differences in volume of distribution. Thus, the possibility of increased mometasone bioavailability in females should be considered when evaluating the safety and efficacy of this product.

Labeling Comments

1. In the *Absorption* portion of the **Pharmacokinetics** section:
   --The last sentence in the first paragraph: "The systemic bioavailability is negligible (≤0.1%)," is not supported by the data and should be removed.
   --The second paragraph should be replaced with: "Studies in normal volunteers have shown that mometasone furoate monohydrate, when administered as the nasal spray is poorly absorbed. A study with radiolabeled drug administered intranasally showed about 2% of the radioactivity excreted in the urine. In the fecal fraction, the 78% of radioactivity recovered probably represented unabsorbed, unchanged drug.
2. The *Distribution* portion of the **Pharmacokinetics** section should be omitted.
3. In the *Metabolism* portion of the **Pharmacokinetics** section:
   --The first sentence should be replaced with: "Mometasone furoate studies have shown that any portion of the mometasone dose which may be swallowed and absorbed undergoes extensive metabolism."
   --The second sentence (The multiple metabolites....) should be omitted.
   --The fourth sentence (After intravenous administration....) should be omitted.
4. The **Special Populations** section should be changed to read: "The effect of special populations on mometasone pharmacokinetics have not been adequately investigated."

Recommendation The Human Pharmacokinetics portion of this submission has been reviewed by the Office of Clinical Pharmacology & Biopharmaceutics and has been found acceptable to support approval of NDA 20-762.

Please forward Comments 1 - 2, Labeling Comments 1 - 4 and the Recommendation, above, to the sponsor.

Bradley K Gillespie 9/11/97
Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

Clin Pharm/Biopharm Briefing: 9/10/97: Drs Conner, ChenM, Worobec and Hunt

RD Dale P. Conner, PharmD, Team Leader

FT 9/11/97 Dale P. Conner, PharmD, Team Leader

cc:
HFD-570 (NDA 20-762, Divisional File, Toyer, Worobec, Himmel)
HFD-870 (ChenME, Conner, Hunt)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)

SCH 32088: Absorption, Metabolism and Excretion of ^{3}H-SCH 32088 Administered by Oral Swallow as a Solution, Oral Inhalation and Nasal Spray as Suspensions (C91-101-01), Intravenous as Solution (C91-103-01), Oral Inhalation by Gentlehaler (C91-102-01) or Oral Swallow (C91-328-01) as Suspensions in Male Volunteers

Investigator

Study Dates C91-101-01: 06/25/91 - 11/12/91
C91-102-01: 11/18/91 - 11/26/91
C91-103-01: 09/09/91 - 09/17/91
C91-328-01: 06/22/91 - 06/30/92

Analytical Facility Schering Plough Research Institute (SPRI)

OBJECTIVE To determine the absorption, metabolism and excretion of ^{3}H-SCH 32088 in healthy male volunteers following single-dose administration by oral swallow as a solution and suspension, by oral metered dose inhaler (MDI) and intranasal inhalation.

BACKGROUND Four separate studies were conducted by the sponsor. The results of these four studies are compiled into a single report, which is the subject of this review.

FORMULATIONS Six subjects were assigned to each of the following six treatment groups:

			Dose		
Study No.	Treatment	Dosage Form	mg/Subject	µCi/Subject	Mode of Administration
C91-101-01	A	Oral Solution	1.03	209	Oral Swallow
C91-101-01	B	MDI	0.86	163	MDI Inhalation
C91-101-01	C	Nasal Spray	0.19	197	Nasal Inhalation
C91-102-01	—	Gentlehaler	0.40	79	MDI w/spacer device
C91-103-01	—	IV Solution	1.03	204	1 minute infusion
C91-328-01	—	Oral Suspension	0.99	195	Oral Swallow

STUDY DESIGN Approximately 12 hours prior to dosing, all volunteers were confined to the study site. Ten hours prior to dosing, a standard light snack was served, and an overnight fast was maintained. On the following morning, subjects were administered the above treatments. After dosing, volunteers remained fasting and ambulatory for an additional 4 hours. After this time, regular meals were served. Subjects were confined at the testing facility from Day 0 until the final urine and fecal samples were collected. Blood samples were obtained just prior to (zero hour), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144 and 168 hours after study drug administration. Urine samples were collected prior to dosing and at the following post-dose intervals: 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Stool samples were collected up to 168 hours after dosing and then pooled into 24 hour blocks for assay. Expired air was collected for

two ten minute periods: immediately after dosing and one hour following drug administration. Gauze pads used to collect any overflow material and filters used to trap exhaled drug after inhalation were extracted with an isopropanol-acetone mixture. All samples were analyzed for radioactivity. Additionally, the sponsor performed profiling of plasma, urine and fecal extracts. Hydrolysis of selected plasma and urine samples were performed using an enzyme preparation containing β-glucuronidase and aryl sulfate. Tritium exchange determinations were conducted by comparing the percent of radioactivity in the urine to a distilled fraction.

ASSAY

DATA ANALYSIS

Plasma (from total radioactivity): - C_{max}, T_{max}, AUC_{t}[1], AUC_{0-24}, $AUC_{0-\infty}$, k_{el} and $t_{1/2}$
Urine (from total radioactivity): U_{0t} (amount excreted during a collection interval)
Feces: Total radioactivity in pooled fecal samples up to 168 hours after dosing

RESULTS The mean percent of radioactivity administered in the body as tritiated water at 168 hours was estimated to be less than 4%, suggesting only a minor fraction of the tritium label had exchanged with body water. Thus, ^{3}H-SCH 32088 is relatively stable in humans. All subjects completed the study with no dropouts.

Quantifiable plasma radioactivity was detected in subjects after receiving the intravenous, oral solution, MDI and gentlehaler formulations. The mean ng eq TR/mL versus time profiles for the first 36 hours after dosing are presented in Figure 1. Mean plasma TR pharmacokinetic parameters are presented and compared in Table 1. The results of the /radio-flow monitoring analyses demonstrated that following intravenous (IV) and oral (PO) administration of ^{3}H-SCH 32088, plasma radioactivity was primarily associated with metabolites more polar than the available standards. After IV dosing, approximately 39% of the 3-hr post-dose radioactivity was associated with parent drug compared to 1.5% of the 3-hr post-dose plasma radioactivity after oral dosing. Approximately 12% and 33% of the 3-hr plasma radioactivity was associated with parent drug following administration of the MDI and Gentlehaler, respectively. After administration of the nasal and oral suspension formulations, plasma radioactivity was too low to permit profiling. Plasma sample hydrolysis showed modest changes in profiles suggesting some hydrolytic release of conjugated metabolites.

The mass balance of ^{3}H-SCH 32088 in urine and feces is presented in Table 2.

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[1] Area under the plasma concentration vs. time profile to the last quantifiable concentration

The metabolite profiles of both urine and fecal samples following intravenous and oral solution administration demonstrated that all of the radioactivity observed was associated with metabolites more polar than the parent drug. As with the plasma samples, enzymatic hydrolysis of the urine showed modest changes in the radioactive profiles. Analysis of fecal extracts from the MDI, Gentlehaler, nasal spray and oral suspension routes, demonstrated the presence of unchanged SCH 32088, probably due to unabsorbed drug.

DISCUSSION Mass balance data obtained after intravenous administration of radiolabel drug suggests that approximately 2/3 of systemic radioactivity is eliminated in the feces and 1/3 of systemic radioactivity is eliminated in the urine. When dosed as an oral or intranasal suspension 73% and 78%, respectively was recovered in the feces. It is not clear to what extent biliary excretion is contributing to this radioactive fraction.

CONCLUSION Drug derived radioactivity was completely absorbed when given orally as a solution but only minimally (~ 2% of administered radioactivity recovered in the urine) when administered as a oral suspension or nasal spray. When administered as an oral inhalation by the MDI and Gentlehaler, moderate absorption was observed (23-30% and 67-69%, respectively). Systemic SCH 32088 was extensively metabolized regardless of the route of administration. Based on observations after administration of intravenous and oral solutions, it appears that the major route of excretion is fecal elimination of metabolized drug. When given as the nasal spray or the oral suspension, most of the administered radioactivity is eliminated in the feces.

Figure 1. Mean Plasma Radioactivity (ng eq/mL) After Administration of ^{3}H-SCH 32088 to Male Volunteers

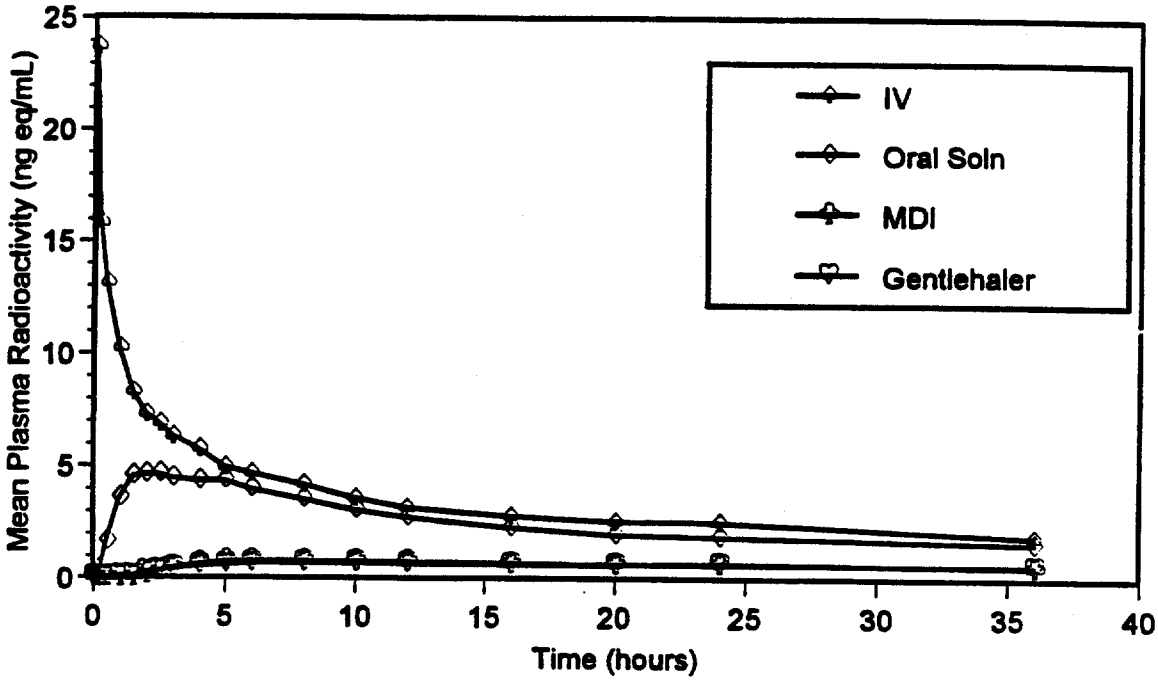

Table 1. Mean (%CV) ^{3}H SCH 32088 Pharmacokinetic Parameters (based on ng eq/mL)

Parameter	(unit)	Intravenous	Oral Solution	MDI	Gentlehaler
C_{max}[2]	(ng eq/mL)	23.7 (26)	4.83 (19)	0.803 (17)	0.685 (18)
T_{max}[3]	(hours)	—	2 (1.5 - 5)	9 (6 - 24)	9 (8 - 48)
AUC_{0-24}	(ng eq·hr/mL)	100.7 (14)	68.7 (13)	14.6 (21)	12.9 (23)
AUC_{tf}[4]	(ng eq·hr/mL)	280.7 (23)	251.7 (26)	45.0 (90)	69.5 (22)
$AUC_{0-\infty}$	(ng eq·hr/mL)	401.1 (41)	438.4 (44)	80.7 (107)	110.2 (41)
$t_{1/2}$	(hours)	100.0 (39)	164.6 (27)	55.4 (96)	90.6 (53)

[2] Maximum Plasma Concentration observed except for IV, which is $C_{5\ min}$
[3] Central tendency described as the *median* and variability as the *range*
[4] Area under the plasma concentration vs. time curve from time zero until last quantifiable timepoint

Table 2. Excretion of Radioactivity Following Administration of ^{3}H-SCH 32088 to Male Volunteers

Parameter	Intravenous	Oral Solution	MDI	Gentlehaler	Nasal Spray	Oral Suspension
Urine[5] (% of Dose)	24	25	7	16	2	2
Feces[6] (% of Dose)	54	62	86	89	78	73
U+F[7] (% of Dose)	78	87	93	105	80	75

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[5] Percent of administered radioactivity excreted in the urine through 168 hours
[6] Percent of administered radioactivity excreted in the feces through 168 hours
[7] Total percentage of radioactivity recovered in the urine and feces through 168 hours

SCH 32088: Singe-Dose Absolute Bioavailability Study of Mometasone Furoate Administered as an Intravenous Solution, Oral Solution, Oral Suspension and Nasal Spray- A Four-Way Crossover Design

Study No. C95-050-01 **Volume** 1.155-7 **Pages** 1 - 1113
Investigator

Study Dates 5/10/95 - 6/8/95
Analytical Facility
Analysis Dates 7/19/95 - 10/3/95

OBJECTIVES To determine the absolute bioavailability of mometasone furoate (SCH 32088) administered intranasally as a suspension, orally as a suspension and orally as a solution

FORMULATIONS

Treatment A: Intravenous (IV) solution - 1.0 mg of mometasone furoate administered as 1.0 mL of a 1.0 mg/mL solution via an IV injection

Treatment B: Oral (PO) solution - 1 mg of mometasone furoate administered as 33.3 mL of a 0.03 mg/mL solution

Treatment C: Oral suspension - 1 mg of mometasone furoate administered as 2.0 mL of a 0.5 mg/gm suspension

Treatment D: Nasal Suspension - 400 µg of mometasone furoate administered as 8 sprays from a nasal pump spray bottle delivering 50 µg/spray

STUDY DESIGN A total of 24 healthy, non-smoking adult subjects (12 male and 12 female) were included in this open-label, randomized, single-dose, 4-treatment, 4-period crossover study. At least twelve hours prior to dosing, all subjects were confined to the study site, and volunteers completed a practice session to ensure proper dosing technique for the nasal sprayer. After an overnight fast, subjects received a single dose of study medication. Volunteers continued fasting and remained ambulatory for 4 hours after study drug administration. At this time, a light lunch was served. Eight hours after dosing, regular meals resumed. A washout interval of seven days separated the dosing periods. Subjects were confined throughout each study phase and abstained from the consumption of grapefruit juice, alcohol and xanthine containing foods and beverages. Blood samples were obtained for plasma SCH 32088 determinations just prior to (zero hour), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36 and 48 hours after study drug administration.

ASSAY

DATA ANALYSIS
Pharmacokinetic: C_{max}, T_{max}, AUC_{tf}[8], $AUC_{0-\infty}$, CL, F, $t_{1/2}$ and $t_{1/2,eff}$[9]
Statistical: Descriptive statistics were provided for all parameters. Analysis of variance (ANOVA) was used to assess the effect of gender on drug disposition.

RESULTS All 24 subjects completed the study in accordance with the protocol. After dosing the oral and intranasal suspension, observed SCH 32088 concentrations were low, and transient. Only when given as an intravenous or oral solution were useful plasma concentration data obtained. The mean plasma concentration versus time profiles for males and females for the first 12 hours after intravenous dosing are presented in Figure 2. Pharmacokinetic parameters following dosing of intravenous and oral solution are presented in Tables 3 and 4, respectively.

COMMENT Mometasone is biotransformed to multiple metabolites. The activity and/or toxicity of these moieties is unknown. Radioalabel mass balance studies demonstrated that when mometasone is administered as a nasal or oral suspension, respectively, only minimal quantities of the drug are systemically absorbed. When given as an oral solution, complete absorption occurs and when mometasone is inhaled, moderate absorption can be expected. Thus, this study, which assessed only the bioavailability of the parent compound, may be inadequate for some of the more bioavailable dosage forms.

DISCUSSION Markedly higher bioavailability was observed in female versus male subjects after administration of mometasone furoate as an oral solution. Weight adjustments of C_{max} and AUC were not performed by the sponsor. Based on mean subject weights (males: 171.0 lbs; females: 147.8 lbs → male/female = 1.16) part of the difference observed is probably derived from differences in volume of distribution. Additionally, high variability observed in both sexes should be considered as a possible source of estimation error.

CONCLUSION This study documented that the absolute bioavailability of the oral mometasone solution is approximately 2%. The source(s) of difference(s) in bioavailability between males and females is/are not clear from the data presented. Thus the possibility of increased mometasone bioavailability in females should be considered when evaluating the safety and efficacy of this product. Plasma mometasone concentrations observed after dosing of the oral suspension and the intranasal suspension were too low to permit a determination of bioavailability.

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[8] Area under the plasma concentration versus time profile to the final quantifiable timepoint
[9] Effective half-life, to estimate potential for accumulation (*J Clin Pharmacol* 1995;35:763-766)

Figure 2. Mean Plasma SCH 32088 Concentrations for the First 12 Hours After Dosing 1.0 mg Intravenous Mometasone Furoate to Males and Females

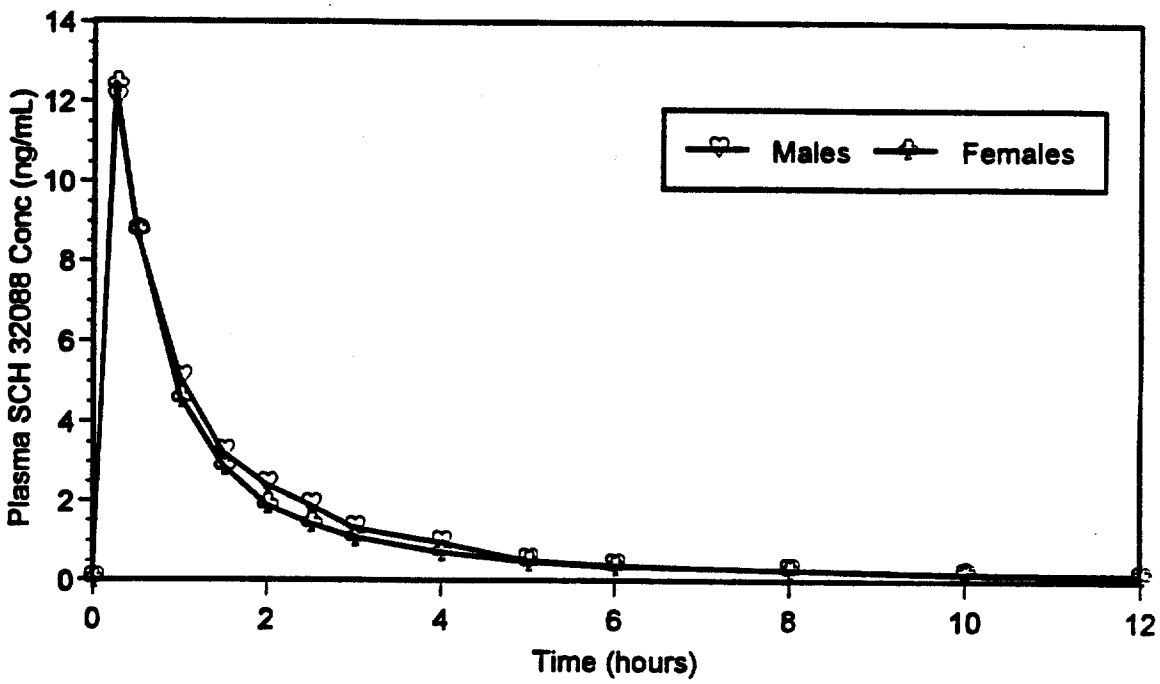

Table 3. Mean (%CV) SCH 32088 Pharmacokinetic Parameters for Male and Female Volunteers After Intravenous Dosing of 1 mg Mometasone Furoate

	AUC_{tf}[10] (pg·hr/mL)	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hours)	$t_{1/2,eff}$[11] (hours)
Males	17287 (27)	17557 (30)	7.73 (48)	5.04 (10)
Females	16933 (20)	18742 (19)	16.6 (78)	6.93 (46)

Table 4. Mean (%CV) SCH 32088 Pharmacokinetic Parameters for Male and Female Volunteers After Oral Dosing of 1 mg Mometasone Furoate as an Oral Solution

	C_{max} (pg/mL)	T_{max}[12] (hours)	AUC_{tf}[10] (pg·hr/mL)	F[13] (%)
Males	187 (64)	0.5 (0.25-20)	272 (70)	1.93 (67)
Females	385 (100)	0.5 (0.25-12)	413 (68)	1.99 (74)

[10] Area under the plasma concentration vs. time profile to the last quantifiable timepoint
[11] Effective half-life
[12] Central tendency described as the *median* and variability as the *range*
[13] Mean of individual subject absolute bioavailability

In vitro metabolism in pulmonary and hepatic tissues (P-5642, 8/92; Vol. 152)
(Excerpted from Dr. Du's Pharmacology/Toxicology Review)

To determine SCH 32088 metabolisms in rat or mouse pulmonary and hepatic tissues, ^{3}H-SCH 32088 (Batch #: 23650-49-7) was incubated in vitro with the supernatant of lung and liver fractions. After the culture, the supernatant was analyzed using
Each incubation was divided into three groups. Group I represented the live protein, 30 min incubations which were analyzed to identify metabolic products. Groups II (Live protein + 0 min incubation) and III (denatured protein + 30 min incubation) were used as the controls. Only peaks presented in Group I (but not in other groups) were identified as the metabolites. If metabolic product appeared in all groups, it was considered as an artifact.

Results showed that no metabolism of ^{3}H-SCH 32088 was found in both rat and mouse lung S9 incubations. Since SCH 32088-9, 11-epoxide was found in all mouse incubation groups, it was considered to be an artifact. (See table below.)

LUNG S9 METABOLIC PROFILE
(Mean (%CV) percent of total peak area)

Incubation	Epoxide*	SCH 32088
Rat Lung		
Ia**	–	99.02 (1.7)
Ib	–	100
IIa	–	100
IIb	–	100
IIIa	–	100
IIIb	–	100
Mouse Lung		
Ia	2.5 (12)	97.5 (0.3)
Ib	1.2 (21)	98.8 (0.3)
IIa	2.9 (75)	97.1 (2)
IIb	1.1 (25)	98.9 (0.3)
IIIa	2.8 (4)	[illegible]
IIIb	1.2 (3)	98.8 (0)

Epoxide*: SCH 32088-9,11-epoxide
a**: 0.05 mM substrate concentration
b: 0.50 mM substrate concentration
I: live protein, 30 min incubation
II: live protein, 0 min incubation
III: denatured protein, 30 min incubation

In rat liver S9 incubation, SCH 32088 was extensively metabolized. Approximately 40% of SCH 32088 (0.05mM substrate) was converted to 6-hydroxy SCH 32088. Mometasone and two unknown metabolites (UK1 and UK2) were also detected. In mouse liver, 6-hydroxylation, ester hydrolysis and metabolism to an unidentified product were observed. (See table below)

LIVER S9 METABOLIC PROFILE

(Mean (%CV) percent of total peak area)

Incubation	6-OH*	UK1	Mometasone	Epoxide	UK2	SCH 32088
Rat Liver						
Ia**	98.5 (3)	0.8 (24)	0.7 (42)	1.9 (20)	2.1 (16)	55.9 (3)
Ib	5.1 (4)	0.3 (16)	0.3 (9)	0.7 (6)	0.3 (16)	93.5 (0.3)
IIa	–	–	–	0.7 (12)	–	99.3 (0.1)
IIb	–	–	–	0.5 (4)	–	99.5 (0.02)
IIIa	–	–	–	2.2 (8)	–	97.8 (0.2)
IIIb	–	–	–	0.9 (15)	–	99.1 (0.1)
Mouse Liver						
Ia	3.2 (6)	1.0 (31)	0.8 (5)	1.9 (2)	–	93.0 (0.6)
Ib	1.4 (17)	0.3 (26)	0.5 (12)	1.5 (16)	–	96.2 (0.4)
IIa	–	–	–	2.6 (76)	–	97.4 (2)
IIb	–	–	–	1.3 (12)	–	98.7 (0.2)
IIIa	–	–	–	2.7 (23)	–	97.3 (0.6)
IIIb	–	–	–	1.2 (5)	–	98.8 (0.1)

6-OH*: 6β-Hydroxy Mometasone Furoate
UK1: unknown 1
Epoxide: SCH 32088-6,11-epoxide
UK2: unknown 2
a**: 0.05 mM substrate concentration
b: 0.50 mM substrate concentration
I: live protein, 30 min incubation
I: live protein, 0 min incubation
II: denatured protein, 30 min incubation

The above results showed that SCH 32088 in rats or mice was extensively metabolized by liver S9, but no by lung S9 system in vitro. This result can be attributed to low concentrations of metabolic enzymes in the lungs in comparison with the livers.

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Clinical Pharmacology & Biopharmaceutics Review

NDA 20-762

Mometasone Furoate Nasal Spray (NASONEX™)

Schering, Corporation
2000 Galloping Hill Road
Kenilworth, NJ

Submission Date:
9/30/96
Submission Type:
New NDA, 1S
Review Type:
Suitability for filing
Reviewer:
Brad Gillespie, PharmD

Background NASONEX Nasal Spray is a metered-dose, manual spray unit containing an aqueous suspension of mometasone furorate (MF) monohydrate (equivalent to 0.05% w/w MF anhydrous) in an aqueous medium. Each actuation of the device is designed to deliver the equivalent of 50 µg MF anhydrous.

NASONEX Nasal Spray is a glucocorticosteroid claimed to demonstrate anti-inflammatory properties in the nasal mucosa without systemic activity. In an *in vitro* model, MF was shown to be at least 10 times more potent than other steroids tested, to include, beclomethasone, betamethasone and dexamethasone. In support of this application, the sponsor has conducted 18 clinical safety and efficacy trials. Additionally, the sponsor has submitted 5 clinical pharmacology studies. The first study report is actually a compilation of 4 separate radiolabel mass balance studies. The second study is a four-way crossover study comparing the bioavailability of MF when administered as an intravenous (IV), oral suspension, oral solution or nasal spray. The remaining 3 clinical pharmacology studies were designed to assess the safety of the formulation by measuring suppression of the hypothalamic pituitary adrenocortical (HPA)-axis.

Discussion Originally, the sponsor proposed using an to quantify plasma mometasone concentrations. A second review of the assay validation data determined that this assay was inappropriate. At this time, the sponsor developed a

. The lower limit of quantitation for this method is 50 pg/mL. Even at this level of sensitivity, only sporadic plasma mometasone concentrations were observed after the administration of therapeutic doses of MF intranasal. Therefore, the sponsor has submitted an abbreviated Human Pharmacokinetic package in support of this NDA.

Comments

1. The physical and chemical properties of the drug substance/product were adequately described.

2. The proposed package insert was annotated, allowing identification of source studies for data verification.

3. The sponsor proposes marketing a single 0.5 mg/g formulation. The to-be-marketed fomulation was used for all of the pivotal clinical studies.

4. The sponsor has performed radiolabeled mass balance studies to characterize the ADME of this product.

5. As described in the discussion section, above, bioavailability studies are limited by assay sensitivity. In this case of a topical steroid, local bioavailability can be assured by clinical efficacy, while systemic bioactivity can be assessed by evaluating HPA-axis suppression.

6. The sponsor has included an evaluation of gender effect in their proposed package insert. These data will need to be reviewed carefully, in the absence of reliable pharmacokinetic data.

7. Assay validation data for the bioavailability study has been provided by the sponsor.

8. The plasma assay used in the radiolabel mass-balance study was the un-validated method. Therefore, only radioactivity, without plasma concentration data are available in this report.

9. At a July 15, 1995 pre-NDA meeting, the sponsor assured FDA that they were currently conducting *in vitro* studies to characterize the metabolism of mometasone. None of these data are present in this submission. The sponsor is requested to submit these data.

Recommendation This submission has been reviewed in a cursory fashion. and has been found acceptable to permit filing from the Office of Clinical Pharmacology & Biopharmaceutics' (OCPB) perspective.

Please forward Comment 9 to the sponsor in the form of an information request (IR) letter.

Bradley K. Gillespie 10/17/96
Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

FT 10/16/96
Dale P. Conner, PharmD, Team Leader

cc:
HFD-570 (NDA 20-762, Divisional File, Toyer)
HFD-870 (Chen, Conner, Hunt, Gillespie)
HFD-870 (Drug, Chron, Reviewer)
HFD-850 (Lesko)
HFD-340 (Viswanthan)