The protocol's stated lower limit of detection for the cortisol assay is [redacted] This is probably a typo since the lowest value for normal serum cortisol is 5 μg/dl.

It was clarified on the telecon with the sponsor (2/23/96), that the normal values and ranges included in this protocol probably refer to [redacted] method that was going to be used by [redacted] The sponsor will provide us with the information on [redacted] method used.

The protocol does not specify what will be the rescue medication's handling instructions or who will review the patient's records regarding their use. This could lead to unblinding in the placebo group.

The study protocol does not specify what would be the preferred or chosen assay to evaluate HPA-axis suppression.

It is not stated in the study protocol how and when patients will be randomized.

The protocol does not specify when clinical labs will be repeated after screening.

RESULTS

Reviewer's comments:

Patients enrolled/analyzed

The principal investigator was [redacted] and the investigational site: [redacted]

The first patient was enrolled on May 5, 1991 and the last patient completed on September 16, 1991.

After the baseline period, patients were randomly assigned to treatment. Of the 28 patients that were enrolled in the study: 6/8 placebo, 5/5 Trinasal 400, 4/5 Trinasal 800 and 5/5 Trinasal 1600, completed the study. Table 1, vol 15. The report does not specify how patients were randomized to treatment groups and a randomization code is not provided. It is noted in the protocol that there would be 2 placebo patients assigned to each treatment group. The placebo patients that completed the study (6/8) have been grouped as one study group for all tables and analyses.

The majority of the patients enrolled were males (20/28, 71%). All but one patient was Caucasian. Patients ranged from 19-44 years of age. There were no significant

differences among treatment groups with regards to medical history, including smoking. All treatment groups had patients with history of smoking, 30-60%, without any significant differences between groups. Table 3, vol 15. Treatment groups did not differ significantly at baseline, with regards to height, weight, frame size, and vital signs.

Study medication

Triamcinolone acetonide: Lot 10901, expiration date 7/92

Placebo: Lot 11001, expiration date 7/92

According to the Table of Investigational formulations (page 056, in vol 1), the Triamcinolone acetonide lot used in this study used the investigational formula #39-050-2, the same as the NDA formulation.

The to be marketed unit pump, a [redacted] nasal actuator is not the same pump that was used in this study [redacted]

Study discontinuations

Two placebo patients and one Trinasal 800 treated patient discontinued the study.

Pt #2 (placebo)- discontinued the due to adverse events: headache, nausea and vomiting.

Pt. #25 (placebo)- discontinued due to personal reasons.

Pt. #20 (Trinasal 800)- did not return for dosing and was considered to be non-compliant.

Assessment of Adrenal Function

As it was clarified in a telephone conversation with the sponsor on 2/26/96, all results for serum cortisol levels reported in the study report have been obtained using [redacted] method.

The protocol's planned statistical analyses for this study was modified before data analysis, (vol 15, p036) and some analyses that are described in the protocol's statistical plan were not done, i.e. repeated measure analyses.

According to the study report, a retrospective power calculation was done using data from this study for the AUC 0-8 hrs of the serum cortisol-by-time plot, at the final evaluation. The observed mean difference between the results for Trinasal 1600 and Prednisone was 89.4 and the pooled standard deviation was 56.3. Using 56.3 as the estimated standard deviation, a difference of 89.4 would be detectable with approximately 60%

power, using an alpha level of 0.05. Therefore the study was not underpowered to detect important differences.

Biometrics was asked to discuss the two power calculations mentioned in the previous paragraph. The Biometrics reviewer could not verify the power calculation in the original protocol because the standard deviation used was not included in the text. The retrospective power calculation could be considered as an exercise to find out what the power would be if the comparison of the AUC of the serum cortisol-by-time plot at the final evaluation between Tri-Nasal 1600 μg and Prednisone were to be done, given the sample size of 5 used in each group. A planned study with a 60% power would not be acceptable. If the second analysis is used in planning a study, the desired sample size would be at least 8 per group to guarantee an 80% power.

The parameters that were used to evaluate HPA-axis function were:

1) peak and AUC of serum cortisol concentrations following maximal stimulation of adrenal cortisol secretion by cosyntropin at baseline and end of treatment.

2)baseline, cosyntropin stimulated, and weekly 24-hour excretion of urinary cortisol (UFC) and 17-hydroxycorticosteroids (17-OHCS)

3)weekly a.m. serum cortisol concentrations

Serum Cortisol Analyses

1. **Cosyntropin-stimulated serum cortisol concentrations**

Descriptive statistics were calculated for AUC by treatment group, for Day 1 and Day 43. Treatment groups were compared at each day using ANOVA or ANCOVA methods. Changes in AUC from Day 1 to Day 43 were calculated for each patient. Paired t-tests were used to assess whether there were significant changes in AUC within treatment groups, from Day 1 to Day 43.

The peak concentration of cortisol from zero to eight hrs was also determined for each patient on Days 1 (baseline) and 43 (final evaluation). The statistical analyses used were the same as for AUC.

Area under the Curve (mcg*h/dl) for serum cortisol - 0 to 8 hours

To calculate AUC 0-8 hrs, the sponsor used the pre-stimulation serum cortisol at 0 hrs.

Mean Area under the Curve (mcg*h/dl) for serum cortisol at Baseline on Day 1- 0 to 8 hours from Table 5A, vol 15.

	Placebo	Prednisone 10 mg	Tri-nasal 400	Tri-nasal 800	Tri-nasal 1600
Baseline Day 1	341.2 N=8	298.9 N=5	310.1 N=5	347.8 N=5	311.3 N=5

AUC for serum cortisol (mean)- Treatment comparison analysis, Table 5C, vol 15.

Day	overall p value	P vs Pred	P vs 400	P vs 800	P vs 1600	Pred vs 400	Pred vs 800	Pred vs 1600	400 vs 800	400 vs 1600	800 vs 1600
1	0.247 *	0.088	0.203	0.785	0.220	0.674	0.076	0.642	0.166	0.964	0.179

* P value based on ANOVA model with effect for treatment

Baseline (Day 1): There were no statistically significant differences between treatment groups; Table 5A, vol 15. The mean range in values was 299 to 347 mcg*h/dL.

Mean Area under the Curve (mcg*h/dl) for serum cortisol on Day 43- Final Day- 0 to 8 hours from Table 5A, vol 15.

	Placebo	Prednisone 10 mg	Tri-nasal 400	Tri-nasal 800	Tri-nasal 1600
Final Day Day 43	332.9 N=6	189.2 N=5	289.7 N=5	332.4 N=4	278.6 N=5

AUC for serum cortisol (mean)- Treatment comparison analysis, Table 5C, vol 15.

Day	overall p value	P vs Pred	P vs 400	P vs 800	P vs 1600	Pred vs 400	Pred vs 800	Pred vs 1600	400 vs 800	400 vs 1600	800 vs 1600
43	0.005 **	<.001	0.281	0.647	0.142	0.004	0.003	0.010	0.604	0.685	0.382

**p value based on an ANCOVA model with baseline covariate and effect for treatment.

On **Day 43**, the baseline used as a covariate for each patient was the value of AUC 0-8 hrs for Day 1 (teleconference with sponsor dated 7/22/96. There were statistically significant differences between the prednisone treated group and placebo, as well as between prednisone and

all active treatments; Table 5C, vol 15. However, no significant differences were observed between placebo and the Trinasal groups.

Area under the curve for serum cortisol 0-8 hrs, from Table 5B, vol 15. **Change from baseline** analysis. (AUC Day 1-AUC Day 43)

	Placebo	Prednisone 10 mg	Tri-nasal 400	Tri-nasal 800	Tri-nasal 1600
Change from baseline	0.2	-109.7	-20.4	-25.1	-32.7
Within-group P value*	0.990	0.014	0.292	0.405	0.285

* Based on a paired t-test

There was no analysis reported that compares between group differences for the change in AUC from baseline. If the values for the changes in AUC were calculated by subtracting the mean AUC value in Day 43 from Day 1, there must be an error in the calculations or in the reported values for the placebo and Tri-nasal 800 μg AUC's change from baseline. According to the reported value it should be -8.1 instead of 0.2 μg*hr/dl for placebo and -15.4 instead of -25.4 μg*hr/dl for the Tri-nasal 800 μg.

No obvious mean decreases in serum cortisol were observed at baseline for Day 43, except for the prednisone treated group. Figure 2-Day 43, vol 15 (attached) and Fig 1-Day 1, vol 15 (attached).

All the individual patients graphs for serum cortisol post-stimulation were reviewed. On Day 43 all patients had values at 0 hrs that were within the limits of normal used for ——— assay in this study. Two patients in the Prednisone treated group (#3 and #7) and one placebo treated patient (#9), had values <10 μg/dL at 0 hrs. Patient #3 had a serum cortisol max change post stimulation of <20 μg/dL (but the other two patients had maximal changes of about 23 for #7 and 44 for #9. One patient (#23-TAA 1600 μg)had a 0 hrs of — μg/dL but after stimulation the max change was approx. 6 μg/dL.

As pointed out in the study report, two patients treated with Trinasal 1600 had lower than expected AUCs during the treatment period. These AUCs approached levels seen in the prednisone treated groups and suggests that in some patients this dose could cause HPA-axis suppression. Although these patients were not specifically identified in the report, the two patients that would fit this description are patients #23 and #24 (see attached Figure 3, for these patients. Both of these patients were 24

y/o, Caucasian, males, with a baseline weight of 144 and 152 lb respectively and they were both smokers.

In telephone facsimile dated 3/6/96, the sponsor confirmed that patients #23 and #24 were the two patients treated with Trinasal 1600 that had the reduced serum cortisol levels following cosyntropin stimulation after 42 days of treatment. In the same telephone facsimile a listing of the AUCs for individual patients along with the changes from baseline was provided (attached). After looking at this table, the individual patient results for AUCs in patient #17 (Trinasal 800) when compared to the corresponding Figure (attached) show an irregular response to cosyntropin stimulation. However, the peak value for serum cortisol during cosyntropin stimulation is not lower than the mean peak level for the treatment or the placebo group.

Peak serum cortisol

The following results of peak serum cortisol post-stimulation do not take into account the pre-stimulatory values of the individual patients for the specific day, i.e. the pre-stimulatory serum cortisol level was not subtracted from the peak serum cortisol level.

Peak serum cortisol (mean) on Baseline Day 1- 0-8 hours from Table 6A, vol 15

	Placebo	Prednisone 10 mg	Tri-nasal 400	Tri-nasal 800	Tri-nasal 1600
Baseline Day 1	55.4 N=8	49.7 N=5	48.8 N=5	58.1 N=5	50.3 N=5

Peak serum cortisol- Treatment comparison analysis from Table 6C, vol 15.

Day	overall p value	P vs Pred	P vs 400	P vs 800	P vs 1600	Pred vs 400	Pred vs 800	Pred vs 1600	400 vs 800	400 vs 1600	800 vs 1600
1	0.052 *	0.090	0.054	0.408	0.126	0.811	0.028	0.872	0.016	0.690	0.039

* P value based on ANOVA model with effect for treatment

Baseline (Day 1): Treatment groups differed at baseline, p=0.052, using an ANOVA model with effect for treatment. The Trinasal 800 group had the highest value in peak serum cortisol; the Tri-nasal 400 group had the lowest one.

Peak serum cortisol (mean) on Day 43 - 0-8 hours from Table 6A, vol 15

	Placebo	Prednisone 10 mg	Tri-nasal 400	Tri-nasal 800	Tri-nasal 1600

Final Day Day 43	57.1 N=6	34.7 N=5	49.1 N=5	57.6 N=4	45.8 N=5

Peak serum cortisol- Treatment comparison analysis from Table 6C, vol 15.

Day	overall p value	P vs Pred	P vs 400	P vs 800	P vs 1600	Pred vs 400	Pred vs 800	Pred vs 1600	400 vs 800	400 vs 1600	800 vs 1600
43	0.001 **	<.001	0.116	0.919	0.031	0.010	<.001	0.040	0.130	0.526	0.041

**p value based on an ANCOVA model with baseline covariate and effect for treatment.

Final evaluation (Day 43): The baseline used as a covariate for each patient was the Day 1 peak serum cortisol value (teleconference with Sponsor dated 7/22/96). There were significant differences between treatments, p=0.001, Table 6C, vol 15. The prednisone treated group had the lowest peak serum cortisol value, Table 6A, vol 15. When the treatment groups were compared at final evaluation (Day 43) for peak serum cortisol, in addition to the prednisone group, the Tri-nasal 1600 treated group also showed significant differences versus placebo and versus the Trinasal 800 treated group, Table 6C, vol 15.

Peak Serum Cortisol (μg/dl) from Table 6B, vol 15. **Change from baseline** analysis. (Peak serum cortisol Day 1-Peak serum cortisol Day 43)

	Placebo	Prednisone 10 mg	Tri-nasal 400	Tri-nasal 800	Tri-nasal 1600
Change from baseline	2.9	-15.0	0.2	-0.8	-4.5
Within-group P value*	0.210	0.045	0.940	0.717	0.534

* Based on a paired t-test

The within group difference from baseline for Day 43 was statistically significant in the prednisone treated group (-15.0 mcg/dl). A statistical analysis was not reported for between group comparisons. For the above table, if the mean for both Day 43 and Day 1 were used to calculate the change from baseline then there are errors in the calculations: it should be 1.7 instead of 2.9 for the placebo group, 0.3 instead 0.2 for Tri-nasal 400 μg and -0.5 instead of -0.8 in the Tri-nasal 800 μg. These

corrections do not appear to be large enough to change the sponsor's conclusions.

2. 24-Hour urinary free cortisol with and without cosyntropin stimulation.

There were no differences between treatment groups at baseline for urinary free cortisol. The unstimulated 24 hr urinary free cortisol values obtained in the prednisone treated group post baseline, are not valid. Prednisolone levels from oral prednisone interfered with _____ assay used, producing artificially high urinary free cortisol.

Significant mean decreases (within group) in free urinary cortisol from baseline were observed for Days 7, 28 and 42 for Tri-nasal 800 and on Day 42 for Tri-nasal 1600, Table 8B, vol 15. The large standard deviations for some of the values may reflect the variability of either the assay, the unmonitored 24 hr urine collections or low patient numbers.

Mean urinary free cortisol (mcg/24 hrs)- 0-8 hours from Table 8A, vol 15.

Day	Placebo	Prednisone	Trinasal 400	Trinasal 800	Trinasal 1600
1	99.3 N=8	88.4 N=5	112.2 N=5	89.7 N=5	104.0 N=5
7	108.1 N=6	264.5 N=5	65.5 N=5	38.3 N=4	72.2 N=5
28	97.1 N=6	327.1 N=5	71.0 N=5	45.8 N=4	63.0 N=5
35	83.8 N=6	371.5 N=5	80.2 N=5	49.2 N=4	54.9 N=5
42	77.9 N=6	262.1 N=5	88.9 N=5	52.1 N=4	58.1 N=5

None of the Trinasal groups differed from each other or the placebo group for Days 7, 28, 35, and 42, Table 8C, vol 15.

Cosyntropin stimulated urinary free cortisol

There were no statistically significant differences between treatment groups at baseline for urinary free cortisol after cosyntropin stimulation. On Day 43, the prednisone group had a significantly lower mean stimulated urinary free cortisol than the placebo group and each of the Trinasal groups. None of the Trinasal group means were significantly different from each other

or the placebo group on Day 43, Table 9C, vol 15.

3. 24-hr urinary 17-hydroxycorticosteroids(17-OHCS) with and without Cosyntropin stimulation

There were no statistically significant differences between treatment groups at baseline for 24 hr urinary 17-OHCS (Table 10A, vol 15).

Mean Urinary 17-OHCS (mg/24 hr) from Table 10A, vol 15

Day	Placebo	Prednisone	Tri-nasal 400	Tri-nasal 800	Tri-nasal 1600
Baseline	6.8 N=8	6.4 N=5	6.6 N=5	6.4 N=5	7.6 N=5
Day 7	5.2 N=6	3.7 N=5	2.9 N=5	2.4 N=4	4.7 N=5
Day 28	6.8 N=6	4.1 N=5	3.7 N=5	1.7 N=4	N=3.5 N=5
Day 35	5.4 N=6	4.8 N=5	4.1 N=5	2.3 N=4	3.3 N=5
Day 42	5.0 N=6	3.6 N=4	3.2 N=5	3.0 N=4	3.5 N=5

However, in terms of differences from baseline within treatment groups (Table 10B, vol 15), for the Trinasal 400 group, the difference from baseline was statistically significant on Days 7, 28 and 42. For the Tri-nasal 800 group, the difference from baseline was significant on Days 7, 28, 35, and 42, for the Trinasal 1600, only on Day 35, and for the Prednisone group also only on day 35, Table 10B, vol 15.

The difference between the active Trinasal treated groups and placebo were significant for Trinasal 400 group on Days 7 and 28, for Trinasal 800 on Days 7, 28 and 35 and for Trinasal 1600 on Day 28, Table 10C, vol 15. There were no statistical significant differences between the Trinasal treated groups and placebo on Day 42. There were no differences between the prednisone treated group and placebo, Table 10C, vol 15.

These results could reflect variability or validity of the assay or problems in the unmonitored 24hr urine sample collection, since the results do not seem to get lower or worse with the highest Trinasal dose used, and Day 35 was the only time that the prednisone group had a statistical significant difference from baseline. However, even though the results may indicate detectable suppression of endogenous cortisol production by the

Trinasal doses used, since the results in the positive control group do not show a consistent significant difference from placebo, the validity of the assay or methods is in question.

Cosyntropin stimulated 24-hr urinary 17-OHCS

Mean decreases from Day 1 to Day 43, were observed in all groups but these results were significant only in the prednisone treated group, Table 11B, vol 15. On Day 43, the prednisone group had a significantly lower baseline adjusted mean stimulated 17-OHCS value than the placebo and each of the Trinasal treatment groups, Table 11C, vol 15.

4. Morning serum cortisol concentrations

For Day 1, there were no differences at baseline between treatment groups, Table 7A, vol 15. At the end of the treatment phase, on Day 43, only the prednisone treated group had a statistically significant change (within group) from baseline ($p=0.038$), Table 7B, vol 15. The prednisone treated group was different from the placebo group only on Day 36 (Table 7C, vol 15).

SAFETY

Changes in physical examination parameters

There were no significant clinical changes in the physical examination parameters reported at final evaluation with respect to baseline (Tables 18A, 18B and 18C in vol 15). [redacted] was not part of the study protocol.

Nasal examination results

Four patients were reported to have clinical changes (nasal congestion or rhinorrhea) in the nasal exam during the treatment phase. In 2 of the 4 patients the changes did not persist. Two (1 placebo, 1 Trinasal 400) patients had their first abnormal report at the end of treatment (Data Listing 4, vol 59).

Adverse events

Two of the 28 patients did not report any adverse events during the study (1 placebo, 1 Trinasal 800-Table 13A, vol 15). Headache was the most frequent adverse event reported. Among the adverse events reported by two or more patients were: asthenia, rhinitis, pharyngitis, epistaxis, nausea, vomiting, mouth ulceration, dizziness, rash and conjunctivitis. Treatment groups were not significantly different with respect to the frequency of patients reporting these adverse events.

No patient treated with Trinasal had an adverse event that was

classified as severe, Table 13B-vol 15. Of those adverse events classified to be of moderate severity other than headache were: rhinitis (1, Trinasal 400), vomiting (1, Trinasal 800), dizziness (1, Trinasal 800) and CNS depression (1, Trinasal 800).

From the number of adverse events (occurrences), that were considered to be related to study medication that were also reported at a higher frequency in the active groups than in placebo were: epistaxis (5 in Trinasal 1600, dizziness (5 in Trinasal 800), CNS depression (2 in Trinasal 800), dry mouth (2 in Trinasal 1600), Table 13C, vol 15.

One patient in the Trinasal 800 group was reported to have mild burning on the nostril at one time, and it was considered to have a highly probable relation to study drug.

After reviewing the individual data for adverse events (Data Listing 15, vol 61), the following questions were clarified in a telephone conversation with the sponsor on 2/29/96: There were no suspected lesions on the study for which fungal cultures were obtained. It was also clarified in this telephone conversation, that although patient #26 (Trinasal 1600), had the following progression of adverse events: asthenia, abdominal pain, pharyngitis, chills, fever, body aches, and small blisters in both hands, the CRF did not have any investigator comments. The adverse events were not classified as intercurrent illness.

The clinical implications of the adverse event data collected in this study has to be seen in the perspective of the limited number of patients, and the fact that patients did not keep a daily diary of adverse events.

Clinical Laboratory Parameters

There were statistically significant mean increases in WBC from baseline (within group) for all treatment groups except for the Trinasal 1600 treatment group. Placebo (1.93 per cubic mm, p=0.008), Trinasal 400 (1.07 per cubic mm, p=0.040) and Trinasal 800 (2.72 per cubic mm, p=0.010), prednisone (1.61 per cubic mm, p=0.053), Table 14B, vol 15. The prednisone treated group did not have a change that was greater than the placebo group.

There were significant differences in the changes in cholesterol and triglycerides from baseline to final evaluation (Table 15A, vol 15). For the prednisone treated group the within-group mean increases from baseline of 16.2 mg/dl for cholesterol and 65 mg/dl for triglycerides were not statistically significant different but were in direction of the expected clinical laboratory changes.

There were other small, statistically significant changes in other clinical labs including urine analysis, but these changes are not considered to be clinically significant.

Concomitant Medication

Patients were allowed to use Bromfed as a rescue medication. Its use was more prevalent in the placebo, prednisone and Trinasal 400 treatment groups. Concomitant medications for headache were frequently used among treatment groups (Data Listing 16, vol 61).

Summary and conclusions

In this study, between treatment groups comparisons were done for both baseline (Day 1) and final day (Day 43) and changes between Day 43 and Day 1 were compared within treatment groups. The values for AUC and peak serum cortisol post cosyntropin stimulation on Day 43 were significantly lower than those of the placebo treated group. Trinasal 400 μg (200μg bid) and Trinasal 800 (400 μg bid) did not suppress the HPA-axis as measured by cosyntropin-stimulated serum cortisol (AUC and peak). Although the values in the Trin-nasal 1600 μg for AUC on Day 43 were not significantly lower than those patients on placebo, the stimulated peak serum cortisol was significantly lower than placebo.

Two patients (#23 and #24) treated with Trinasal 1600 μg (800 μg bid), had lower than expected AUCs 0-8 hrs during the treatment period, suggesting that in some patients this dose could cause HPA-axis suppression.

For the parameter of peak serum cortisol levels following cosyntropin stimulation, the Tri-nasal 1600 treated group showed significant differences against placebo (p=0.031) and versus the Trinasal 800 treated group (p=0.041).

The to be marketed unit pump, a [redacted] nasal actuator is not the same pump that was used in this study. The characteristics of the to be marketed pump need to be supported by comparative data from the unit pump used in this and other pivotal clinical studies.

From the review of individual data provided by the sponsor in a telephone facsimile dated 3/6/96, for serum cortisol AUCs after cosyntropin stimulation, one patient (#17) from the Trinasal 800 treatment group had a decreases in serum cortisol AUC comparable to patient #23. The Figure shows an irregular response but the individual peak value for patient #17 (from Figure 3) was not lower than the mean peak for that group or for the placebo group. This treatment group did not show significant mean decreases in either AUCs or peak responses to cosyntropin stimulation.

There were no significant differences between the Trinasal treated groups and placebo in the measured morning serum cortisol samples. The prednisone treated group was different from the placebo group only on Day 36 (Table 7C, vol 15). The difference in morning serum cortisol level from baseline (within-group) was

statistically significant only for Day 43 (Table 7B, vol 15), suggesting that the test may not be valid or sensitive enough to detect differences in HPA-axis suppression for daily doses of prednisone of 10 mg or under.

The results of the assay used to measure the unstimulated 24 hr urine free cortisol excretion are not validated in the study because the concurrent use of prednisone in this group (positive control group) interfered with the assay.

During the treatment phase, the results of the unstimulated 24 urines for 17-OHCS for the Trinasal treated groups, showed lower levels than baseline, at different time intervals. The difference between the active Trinasal treated groups and placebo were significant for Trinasal 400 group on Days 7 and 28, for Trinasal 800 on Days 7, 28 and 35 and for Trinasal 1600 on Day 35, Table 10C, vol 15. These values do not get lower as the dose of Trinasal increases and the fact that the prednisone treated group was found to be significantly different from placebo only on Day 35 puts in question the significance of these results for unstimulated urine for 17 OHCS. When urine for 17-OHCS was measured after cosyntropin stimulation, the results show mean decreases (within group) from Day 1 to Day 43, observed in all groups, but these results were significant only in the prednisone treated group, Table 11B, vol 15. On Day 43, the prednisone group had a significantly lower baseline adjusted mean stimulated 17-OHCS value than the placebo and each of the Trinasal treatment groups, Table 11C, vol 15.

The clinical parameters measured, clinical laboratories and adverse events observed did not show clinically significant differences between treatment groups, including the prednisone treated group when they were compared to the patients receiving placebo. There were no severe adverse events reported in the Trinasal treated group. In particular, in terms of adverse events, due to the small number of patients per treatment group, and to the fact that the number of adverse events for placebo patients were pooled and compared to the other active groups, it is difficult to estimate what would be the specific clinical relevance and importance of a difference between the active treated group and placebo in this study.

Therefore, this study supports the conclusion that Trinasal 400 µg (200µg bid) and Trinasal 800 (400 µg bid) do not suppress the HPA-axis by mean data on cosyntropin stimulation of serum cortisol (AUC-0-8 hrs and peak values) after 42 days of treatment.

10.f. Other Efficacy Studies

A total of fourteen studies have been completed by the sponsor. Of these, ten contain efficacy data: three were considered by the sponsor to be adequate and well controlled studies (100-309, 100-204, and 100-305). There are in addition three other placebo controlled studies (0501, 3-0501, and 4-0501); two active controlled studies (38-050 and 0485) and two open-labeled studies (3-0501-OL and 100-307). The other four studies completed by the sponsor consist of three human PK/Bioavailability studies: 100-104, 100-105 and 100-106 and one study reviewed in the previous section, that evaluates the HPA-axis (1-0501).

A detailed review of the following efficacy studies was included in the previous sections of this review : 100-309, 100-204, 100-305,and 0501.

A reviewer's summary of the other efficacy studies submitted to the NDA follows. These studies were not considered by the reviewer to be adequate, well controlled studies in support of efficacy.

Placebo controlled studies:

Study 3-501

Title: A double-blind, randomized study of triamcinolone acetonide nasal solution, 200 µg administered once daily vs placebo in patients with perennial allergic rhinitis.

Summary: from Pages 125-127, vol 4.1, vol 4.47, 1995; pages 2.29-2.30, vol 2.1, 1992.

This was one of the three clinical studies originally submitted in the NDA application dated January 17, 1992. The objective of this study was to compare the safety and efficacy of Trinasal 200 µg qd to placebo in the treatment of perennial allergic rhinitis in patients 18-65 yrs of age. The study was a double-blind, randomized, placebo controlled study conducted at a single center. A minimum of one week baseline period was used. A total of 30 patients (12 male, 18 female) were randomized into the study, 29 had post baseline evaluations and 27 patients completed the study. Patients received treatment for 6 weeks. They were allowed to use chlorpheniramine maleate 4 mg as a rescue medication. Patients used daily diary evaluations to assess symptoms. Symptoms were to be recorded at 7PM daily and patients were supposed to evaluate the presence and severity of the symptoms during the preceding 24 hr period. Patients were also asked to assess symptoms at clinic visits for the previous week. Physicians assessed allergy symptoms and recorded adverse events at weeks 2, 4 and 6. Safety assessments included physical exam and clinical lab evaluations at screening and final evaluation.

The primary endpoints of efficacy were the severity and duration of nasal congestion and runny nose from the patient diary. Duration was rated using a 0-4 scale:

0=symptoms did not recur since last treatment
1=symptoms recurred more than 18 hours after last treatment
2=symptoms recurred within 12-18 hrs after last treatment
3=symptoms recurred within 6-12 hrs after last treatment
4=symptoms recurred within 6 hours after last treatment

There was a significant interaction between baseline disease severity ratings and treatment for the primary efficacy variables. In the intent to treat population, no statistical significant differences were demonstrated between treatments for the severity of nasal congestion, runny nose or sneezing, Table 4A and 4B, vol 4.47. In the patient diary evaluation of symptom duration, the Tri-nasal 200 μg group had a significant decrease in the duration of nasal congestion but not on runny nose, Table 2, vol 4.47. There were no significant differences between treatments for the mean rating of number of chlorpheniramine tablets used, Table 2, vol 4.47.

A secondary analysis was submitted. In it the patients were stratified into patients with symptom scores above or below the median value. Changes from baseline ratings were compared within strata using the Wilcoxon Rank Sum test.

In the strata of patients whose baseline symptoms were above the baseline median value, Tri-nasal 200 μg was found to be more effective than placebo in improving patient's scores for severity of nasal congestion and runny nose. For patients with symptoms at baseline that were lower than the baseline median value a significant improvement was not observed. For these two symptoms, the symptom scores remained at about the same level after treatment as they were pretreatment, Table 3, vol 4.47.

Using this secondary analysis, no statistically significant improvement versus placebo were demonstrated in the patient's daily scores for severity of the individual symptoms of sneezing, itchy N/T/P or itchy R/W/ eyes, Table 14 in page 127, vol 4.1.

The small number of patients, the significant baseline-treatment interactions for the primary efficacy endpoints, and the lack of ability for the study to demonstrate efficacy in the primary endpoints selected for the intent-to-treat population, make the results of this study inadequate to support the efficacy of this dose of Tri-nasal (200 μg bid), for the indication of perennial allergic rhinitis.

Study 4-0501

Title: A double-blind, randomized, comparative dose study of

triamcinolone acetonide nasal solution, administered once daily vs placebo in patients with seasonal allergic rhinitis.

Summary: from pages 117-119, in vol 4.1, page 039 in vol 4.9 and vol 4.48.

The objective of the study was to compare the safety and efficacy of 100 and 200 μg of Tri-nasal administered once daily vs placebo for the treatment of seasonal allergic rhinitis (oak pollen) in patients 18-65 years of age. This was a 4 week, double-blind, randomized study, conducted at a single site. There was a baseline period of at least 4 days. A total of 80 patients were enrolled and 70 patients completed the study. Patients used symptom scores to assesses symptom severity and duration in a daily diary at 7PM, for the preceding 24 hr period. Physicians assessed symptoms at weekly visits. Safety assessments included adverse event recording at weekly visits and physical examination and clinical laboratory evaluation at baseline and at the final visit. Chlorpheniramine 4 mg was allowed as rescue medication.

The primary efficacy parameters were the symptoms of rhinorrhea (including runny nose and post nasal drainage) and nasal congestion.

There were no statistically significant differences between treatments for the severity or duration of the individual symptoms of nasal congestion or rhinorrhea, Table 9F and 10F vol 4.48. An analysis of the SSI scores was also done. There were not statistically significant differences between treatments.

The results of this study do not support the efficacy of either the 100 μg or ~~20~~ 200 μg versus placebo for the treatment of seasonal allergic rhinitis.

Active controlled studies

The following two studies were not placebo controlled and are not considered to be adequate to support the efficacy of the drug.

Study 38-050 (pp. 128-131 vol 4.1)

Title: Comparative study of triamcinolone acetonide 200 μg bid and flunisolide 100 μg bid in patients ages 12 to 40 years with seasonal allergic rhinitis (ragweed hay fever).

This study compared the efficacy and safety of Tri-nasal 200 μg bid with flunisolide 100 μg bid for the treatment of seasonal allergic rhinitis in patients with ragweed hay fever that were 12-40 years of age. The study was conducted in a single center, it was double-blind, and randomized. It enrolled 25 patients and all patients completed the study. The baseline period lasted 3 weeks and patients received treatment for 4 weeks. The primary endpoint was patients' diary scores

of individual symptom severity. Physicians made efficacy and safety assessments at weekly clinic visits. Physical exam, clinical labs and early morning serum cortisol assays were obtained at baseline and at the final visit.

In the overall repeated measures analysis of the 4 weeks of treatment, patients in both treatment groups had significant improvement from baseline in sneezing, nasal congestion and eye symptoms, Table 15, vol 4.1. Only patients on the flunisolide group had significant improvement in the severity of nasal secretions. There were no significant overall between-treatment group differences involving any of the allergy symptoms. However, for the flunisolide treatment group there were statistical significant differences from baseline at week 1 for sneezing, nasal congestion and nasal secretions. For the Tri-nasal treatment, statistical significant differences from baseline were first observed at week 2, for sneezing and nasal congestion. This may suggest a difference in the onset of action for the two formulations.

Study 0485 (pp.132-136 vol 4.1)

Title: A double-blind, randomized comparative study of triamcinolone acetonide in subject ages 12-65 years with seasonal allergic rhinitis.

This study compared the efficacy and safety of Tri-nasal 200 µg bid with flunisolide 100 µg bid for the treatment of seasonal allergic rhinitis in patients with grass pollen sensitivity that were 12-65 years of age. The study was conducted in 5 centers, it was double-blind, and randomized. It enrolled 127 patients and 122 patients completed the study. The baseline period lasted 2 weeks and patients received treatment for 4 weeks. Chlorpheniramine maleate 4 mg was allowed as a rescue medication. The primary endpoint of efficacy was the daily diary patients' scores of individual symptom severity. Physical exam, clinical labs and early morning serum cortisol assays were obtained at baseline and at the final visit.

The repeated measures analysis showed a significant improvement of symptoms from baseline over the 4 weeks of therapy for both treatments for sneezing, nasal congestion, nasal secretions, itchy nose/throat/palate and eye symptoms. Patients in both treatments consumed less rescue medication compared to baseline. The improvement on the individual symptom of sneezing was significantly greater for patients treated with flunisolide than for those patients treated with Tri-nasal, there were no overall between group changes for the other individual symptoms, Table 16, vol 4.1. The between group comparisons were made on the differences in the intensity-severity of symptoms from baseline values.

Open labeled studies:

The following two studies are open-labeled studies and are not adequate to support the efficacy of Tri-nasal for the perennial allergic

rhinitis indication but are of value from the safety standpoint.

Study 3-05010L (pp.141-144 in vol 4.1)

Title: A double-blind, randomized, comparative study of triamcinolone acetonide nasal solution, 200 μg, administered once daily versus placebo in patients with perennial allergic rhinitis: long-term, open-label segment.

The objective of this study was to evaluate the safety and efficacy of 200 μg triamcinolone acetonide nasal solution administered once daily over a 6 month period. Patients with confirmed diagnosis of perennial allergic rhinitis who had completed the double-blind segment of the study were eligible to enter the open-label segment. This was a single center study. Chlorpheniramine maleate 4 mg up to 4 times per day was allowed as a rescue medication to control severe allergy symptoms. A total of 21 patients, 19-65 years of age entered the study. Patient kept daily diaries and physician evaluation of symptoms were performed at monthly visits.

The patient derived symptom severity index score (sum of symptom severity index scores for nasal congestion, runny nose and sneezing) averaged per month was the primary endpoint of efficacy. Descriptive statistics were used to report the efficacy results, p. 143, vol 4.1. The mean of these scores (both for patients and physicians) as well as the mean number of tablets of rescue medication used decreased from the beginning of this open-label segment to the end of the study.

One patient was lost to follow up at the 3 month visit. No patients were discontinued due to adverse events. There were no serious adverse events reported. All patients reported adverse events. Severe headache was reported by 3 patients, severe pharyngitis by 2 patients and severe flu syndrome, pain, application site reaction, ear pain and diarrhea were reported by one patient each. The rest of the adverse events are classified as mild or moderate in severity, vol 4.51. Pt. #108 had the surgical removal of a L posterior cervical lymph node that was a benign cyst of the L parotid gland during the study, it was classified as mouth neoplasia (vol 4.102). Twenty patients experienced an adverse event of the respiratory system: 15 had pharyngitis, 11 rhinitis and 3 epistaxis. Seven patients had application site reactions, 12 reported headaches and 7 a flu-syndrome.

Title: A chronic use study of nasal triamcinolone acetonide solution (Tri-nasal) in patients with perennial allergic rhinitis.

The objective of this study was to evaluate the safety of the Tri-nasal spray over a 6 month period starting with an initial dose of 400 μg qd with subsequent titration between 400 μg (4 actuations per nostril once daily), 200 μg qd (2 sprays/nostril once daily) and 100 μg (1 spray/nostril) depending on the degree of symptom control. A total of 355 patients (146 male, 209 female) initiated treatment and 260 (73.2%) completed the study. All patients were instructed to administer 400 μg

qd at visit 2. At visit 3-9, the dose was reduced to 200 μg depending on the patient response to treatment. A further reduction to 100 μg was also allowed. Increases in dosage from 100 μg to 200 μg and from 200 μg to 400 μg was also allowed if symptoms were not controlled with the lower dosages. The safety assessments and results from this study will be discussed in the integrated safety summary section.

For efficacy, the study evaluated: patient diary assessment of symptom severity and physician assessment of symptom control, as well as use of rescue medication. There were significant reductions in symptom severity from final evaluation to baseline for the symptom severity index score and for each individual symptom in both patient diaries and physician evaluation, Table 19, vol. 4.1. There was no obvious relationship between length of treatment with Tri-nasal and use of rescue medication, p.053, vol 4.52

The improvement in allergy symptoms was accompanied by a decrease in the average daily dose of Tri-nasal used by patients from 400 μg to between — μg and 250 μg, p.145. vol 4.1.

The mean daily dose of Tri-nasal decreased from 400 μg initially to 321.5 ± 101.1 μg by week 3 and 247.0 ± 110.6 μg by week 10. The mean daily dose was between 220 and 242 μg per day through week 26 of the study.

A total of 77 patients (21.7%) remained on the 400 μg dose for the duration of the study; 99 patients (27.9%) titrated down to 200 μg and remained on that dose for the rest of the study; 45 patients (12.7%) titrated downward to 200 μg followed by 100 μg qd and remained at that dose through the end of the study. All other dosing frequencies occurred in less than 10% of the patients, Table 9, vol 4.52.

For the entire study the percentage of patients using the selected doses most frequently were: 100 μg qd, (N=61), 18.1%; 200 μg qd (N=136), 40.4%; 400 μg qd (N=140), 41.5%, Table 10, vol 4.52.

11. OVERVIEW OF EFFICACY

Seasonal allergic rhinitis

The efficacy of the Tri-nasal solution for the indication of seasonal allergic rhinitis was studied in the following placebo controlled clinical trials: 100-309, 100-305, 100-204 and 0501. In studies: 100-309, 100-305 and 100-204 the primary efficacy endpoint selected was the patient's Symptom Severity Index (SSI) score. This score was calculated as the sum of three individual symptom severity scores (nasal congestion, rhinorrhea, and sneezing). The SSI scale had a minimum rating of 0 and a maximum of 12 points. Treatment group comparisons for each treatment week were made using an ANCOVA model, adjusting for study site, with the corresponding baseline as a covariate. For study 0501 the primary endpoint selected were patient's individual symptom scores. Secondary efficacy parameters usually evaluated included: patient derived symptom severity scores for individual symptoms, physician assessments of SSI at weekly clinic visits, patient rated duration of symptoms, nasal exams at weekly clinic visits by the physician, use of rescue medication when allowed, and physician and patient global severity scores. Both adult males and females were studied. The studies had baseline periods of at least 4-7 days. The efficacy of the drug was studied for 2 weeks in 100-309, to 4 weeks in studies 100-305, 100-204 and 0501.

These four studies were double-blind, multicenter, parallel, randomized, and placebo controlled. The results of these studies were reviewed in detail in the previous sections of this review. Only the results in the intent-to-treat population were considered adequate to support efficacy.

The formulation that was used in these four studies was the same as the to be marketed formulation, 39-050-2. The µg/volume to be delivered by actuation, 50 µg/spray was the same for studies 100-309, 100-305 and 100-204 for the 100 and 200 µg doses. The dosing was adjusted by varying the number of actuations used in these three studies for the 200 and 400 µg doses. The weight/volume delivered per actuation was different for the 50 µg dose in study 100-305. In this case the actuation was ——— µg/spray.

The to be marketed unit pump is not the same pump used in any of these four studies. The same pump with a different actuator, was used for study 0501. A ——— pump was used for the other three studies. Chemistry is aware of these issues and is in communication with the sponsor. The characteristics of the to be marketed pump need to be supported by comparative data from the unit pumps used in these clinical studies.

Assuming that the chemistry issues are appropriately resolved and that the delivery of the nasal spray units are comparable to the to be marketed one, the efficacy of the Tri-nasal formulations for the relief of nasal symptoms is supported as follows:

Studies 100-309 and 100-305 support the efficacy of Tri-nasal 200 μg versus placebo.

Studies 100-309 and 100-204 support the efficacy of Tri-nasal 400 μg versus placebo.

Study 100-305 supports the efficacy of Tri-nasal 50 μg versus placebo.

Study 0501 supports the efficacy of Tri-nasal 200 μg bid versus placebo.

In general the results of the following four studies do not support the efficacy of the Tri-nasal formulations for the relief of the eye symptom complex: itchy, red, teary eye.

Study 100-309 (grass pollen-13 centers-Tri-nasal 200 μg qd, Trinasal 400 μg qd, and Nasacort 440 μg qd vs placebo qd) did not have statistically significant baseline differences in the SSI score for patients randomized to receive active treatment and those on placebo. In this study patients needed to have had moderate symptoms during 4/7 days of their baseline period before randomization to active treatment. No rescue medication was used. The Nasacort treatment was not blinded. All active treatments had comparable efficacy and they all showed superiority to placebo for two weeks of treatment in the primary efficacy endpoint. Sneezing was significantly improved for both weeks in patients receiving all active treatments versus those on placebo. Rhinorrhea and nasal congestion showed a significant improvement for week 1 in all active treated groups versus those patients on placebo (except for the Tri-nasal 200 treatment group) and for week 2 of treatment. Both Tri-nasal 400 μg and Nasacort 440 μg showed statistical significant improvement over placebo in the SSI scores by day 2 of treatment. The improvement in the SSI scores for these two days for Tri-nasal 200 μg treated patients was not different from placebo, even though there was a numerical improvement in the SSI scores for the Tri-nasal 200 μg treated group. A statistical significant difference was also demonstrated between the patient group that received Nasacort 440 μg and those patients treated with Tri-nasal 200 μg. It could therefore take patients treated with Tri-nasal 200 μqd longer than two days to achieve demonstrable efficacy. In general, the secondary efficacy endpoints also support the efficacy of the active treatments versus placebo for two weeks of treatment.

Study 100-305 (grass pollen-6 centers- Tri-nasal 400 μg qd, Tri-nasal 200 μg qd, Tri-nasal 50 μg qd vs placebo qd-rescue medicine allowed:chlorpheniramine 4 mg). There were statistically significant baseline differences for the primary endpoint (patient's SSI scores) at baseline. Both the Tri-nasal 400 μg and placebo groups had statistically significant lower symptom scores than the other two active treatments. Patients receiving the Tri-nasal 50 and 200 μg treatment had a statistically significant improvement over placebo for all treatment weeks. No statistically significant improvements were demonstrated between the Tri-nasal 400 μg treatment group and placebo until week 4. Significant improvement was demonstrated for sneezing

for patients treated with Tri-nasal 200 μg compared to those patients treated with placebo for all treatment weeks and for weeks 1-3 for patients treated with Tri-nasal 50 μg. A statistical improvement was demonstrated for nasal congestion in patients treated with Tri-nasal 50 and 200 μg versus those patients receiving placebo for all weeks of treatment. Significant improvement versus placebo in nasal congestion was demonstrated for week 4 in patients treated with Tri-nasal 400 μg. Rhinorrhea improved significantly versus placebo on weeks 1 and 4 for Tri-nasal 50 μg, on week 1 for Tri-nasal 200 μg and for week 4 for Tri-nasal 400 μg. There were no statistically significant differences between the mean chlorpheniramine (mg) use per week during the study for patients on active treatment versus placebo, except for the Tri-nasal 400 μg treated group. This effect was considered to be a treatment site interaction that could be eliminated by removing one patient from the analysis. It was noted that the number of placebo patients using rescue medication during treatment phase remained about the same as in week 1 and the number of active treated patients using rescue medication by the end of the treatment phase was less than at week 1. No significant overall treatment differences were shown for physician rated SSI scores between active treated groups and placebo. In view of the discrepancy in results of the higher dose formulation and the lower dose formulations in terms of efficacy versus placebo (SSI scores and individual symptoms) we asked the statistical reviewer for his opinion on the adequacy of the statistical analysis used. The assessment at the time of the team meeting of 3/16/96 was that the analyses used were adequate to differentiate whether the significant differences found in the study between the 50 and 200 μg formulation and placebo were real drug effects and not a carry over effect from significant baseline differences.

Study 100-204 [mountain cedar pollen-5 centers-Tri-nasal 50 μg qd, Tri-nasal 400 μg qd, Kenalog 40 (4 mg IM q week) versus placebo-chlorpheniramine 4 mg was allowed as a rescue medication]. Patients needed to have a score of at least 8 of a possible 16 for 4 individual symptoms, on 4/7 days during the baseline period before randomization to active treatment. There were statistically significant baseline differences in the patients' SSI scores for patients randomized to active treatments versus those that would receive placebo. The scores in the patients randomized to the placebo group were higher. Patients receiving Tri-nasal 400 μg had a statistical significant improvement over placebo for SSI scores for all treatment weeks. Patients on Kenalog 4 mg IM demonstrated a statistical significant improvement in SSI scores versus placebo for weeks 2 and 3. No significant improvement in SSI scores was demonstrated between patients receiving Tri-nasal 50 μg and those receiving placebo except for week 3 of treatment. For patients receiving Tri-nasal 400 μg, significant improvement versus placebo was demonstrated during all study weeks for sneezing and rhinorrhea, and during weeks 1-3 for nasal congestion. For patients receiving Kenalog 4 mg IM q. week, significant improvement versus placebo was demonstrated for sneezing, during weeks 3 and 4, rhinorrhea during week 3 and for nasal congestion during weeks 2, 3, and 4. Patients receiving Tri-nasal 50 μg had significant improvement over placebo demonstrated for sneezing during week 3,

rhinorrhea during weeks 2 and 3 and nasal congestion during week 2.

Study 0501 (spring-5 centers- Tri-nasal 200 μg bid vs placebo-rescue medication allowed:Seldane 60 mg qd, Opcon-A, Afrinol and Afrin prn). The primary endpoint for efficacy was the patient evaluation of individual symptom severity. Of the five symptom/symptom complexes evaluated only nasal congestion was statistically significantly different at baseline for Tri-nasal 200 μg bid and placebo. The patients treated with Tri-nasal 200 μg bid had an significant improvement of sneezing, nasal secretions, and itchy nose/throat/palate during the 4 weeks of treatment versus those treated with placebo. There were no significant differences in the eye symptom scores for patients receiving active treatment and those that were on placebo. There were no statistical differences in the mean number of Seldane tablets that patients took during baseline or during the first week of active treatment. Thereafter the Tri-nasal treated group took significantly less Seldane than the placebo group. Although the study report does not include an analysis of the use of the other concomitant medication between treatment groups, the individual patient data listing suggests that the use of Afrin and Afrinol in the third and fourth week of the study is more prevalent in placebo treated patients. The investigator evaluation of symptom severity followed the same pattern as the patient symptom scores except for the fact that no statistical significant differences were demonstrated between the effect of the Tri-nasal 200 μg treatment and placebo for the first week of treatment. Both treatment improved the individual symptom scores for all symptoms during the first week compared to baseline. The overall effect of the Tri-nasal 200 μg bid treatment on the patients' eye symptoms was not significantly different from placebo.

Perennial allergic rhinitis

One placebo-controlled clinical trial was submitted in the NDA in support of the efficacy of Tri-nasal for the indication of perennial allergic rhinitis. Study 3-501 (single center-double-blind-randomized study of Tri-nasal 200 μg qd vs placebo in patients with perennial allergic rhinitis, rescue medication allowed: chlorpheniramine 4 mg). A total of 30 patients (12 male, 18 female) were randomized into the study, 29 had post baseline evaluations and 27 patients completed the study. Patients received treatment for 6 weeks. There were significant baseline-treatment interactions for the primary efficacy endpoints, the study had a small sample size, and it did not demonstrate efficacy in the primary endpoints selected for the intent-to-treat population. Therefore, the results of this study are not adequate to support the efficacy of this dose of Tri-nasal for the indication of perennial allergic rhinitis.

In terms of efficacy, the sponsor could choose to reference Nasacort's approved indication of perennial allergic rhinitis, since triamcinolone acetonide has been approved for this indication and the bioavalability of the Tri-nasal solution is greater than the one of Nasacort (Biopharm reviewer's opinion at team meeting dated 5/16/96, based on the data provided by Dr. C. Kwong from the Nasacort AQ NDA). However, the higher

bioavalability of Tri-nasal compared to Nasacort (CFC) via the nasal route poses a safety concern. The data supporting the use of the reference of the Nasacort's(CFC) to support the perennial allergic rhinitis indication for Tri-nasal would not adequate to support safety in terms of systemic effects, for the ——— use of Tri-nasal on a ——————— basis, because the systemic exposure to triamcinolone from Tri-nasal is higher than that of Nasacort (CFC). The Azmacort data could be referenced if the systemic exposure of the approved doses is higher than the one with Tri-nasal and an assessment of risk-benefit ratio is made. However, these considerations may be less favorable for an indication of ——————— than it would be for the treatment of asthma.

Topical Effect

A topical effect for Tri-nasal 400 μg vs Kenalog 4 mg IM was not demonstrated in study 100-204. The selected dose and route of administration of 4 mg Kenalog IM q week is not considered to be an adequate comparator to assess the topical effect of the Tri-nasal solution. Blood levels for the drug were not obtained in study 100-204, but the results of the single dose pharmacokinetic study, 100-104, comparing Tri-nasal 400 μg to Kenalog 4 mg IM, suggest that a weekly dose of Kenalog 4 mg would produce much lower systemic levels than what would be expected with daily doses of Tri-nasal 400 μg in terms of Cmax and AUCs, according to the Biopharm reviewer's opinion in the 5/16/96 team meeting. Therefore, the efficacy of Tri-nasal could be considered to be secondary to higher systemic exposure rather than to a local topical effect.

In study 100-204, a 4 week SAR study, patients on Kenalog 4 mg IM demonstrated a statistical significant improvement in SSI scores (primary endpoint) versus placebo only for weeks 2 and 3. Kenalog 4 mg improved the following individual symptoms compared to placebo: sneezing (week 3 and 4), rhinorrhea (week 3), nasal congestion (week 2, 3, and 4), itchy nose/throat/palate (weeks 2 and 3), itchy red/watery eyes (weeks 2 and 3). Tri-nasal 400 μg qd was superior to placebo for all weeks of treatment (SSI scores) and significant improvement versus placebo was demonstrated during all study weeks for sneezing and rhinorrhea, and during weeks 1-3 for nasal congestion. Trinasal —— μg was superior to Kenalog 4 mg IM q week for the first 2 weeks of treatment in terms of SSI scores. It was also superior to Kenalog improving sneezing during week 1; rhinorrhea during week 1 and 2; itchy nose/throat/palate during week 1; and it was not found to be different from Kenalog for nasal congestion or itchy/red/watery eyes.

In the 100-204 study the difference in onset of action for Tri-nasal versus Kenalog, could be related to early exposure to higher systemic triamcinolone levels with Tri-nasal 400 μg than with Kenalog 4 mg IM once a week.

Dose response

A definite dose response in terms of the efficacy primary endpoint in

seasonal allergic rhinitis was not demonstrated between Tri-nasal 400 μg and Tri-nasal 200 μg in 100-309, between Tri-nasal 200 μg and Tri-nasal 50 μg in 100-305, or between Tri-nasal 400 and 50 μg in 100-204. However, in Study 100-309, efficacy versus placebo (SSI scores) was demonstrated for Tri-nasal 400 μg on Days 1 and 2 and no statistically significant differences were demonstrated for Tri-nasal 200 μg on these two days. This difference in onset of action could be interpreted as a dose response.

In the team meeting dated 5/16/96 the statistical reviewer expressed his opinion on the meaning of the dose-response analysis reported in study 100-305 for patient diary evaluation of SSI scores, Fig 3A, vol 4.31. He did not considered that the results of the analysis could be used in favor of a dose response based on the statistical significance for a linear trend for weeks 1,3 and 4 and a cubic trend for weeks 1 and 2, when the lines are almost flat and there is an increase in the mean SSI scores with an increase in Tri-nasal dose from 200 to 400 μg.

12. Integrated Safety Summary

The integrated safety summary (ISS) of all conducted clinical studies in the NDA, with the exception of study 100-309, is found in volume 4.10.

The supplement to the NDA dated March 7, 1996 includes the Division's requested integrated safety information for Study 100-309. This supplement updates the sections on demographics and background characteristics, adverse event frequency by body systems and preferred term, drop-outs due to adverse events, deaths and other serious adverse events. Only the following tables were updated:

> Table 9.1 (vol 4.10, pages 130-136) adverse events by body systems and preferred terms, Trinasal vs Placebo in the All Studies population
>
> Table 9.2 (vol 4.10, pages 137-142) adverse events by body systems and preferred terms, Trinasal vs Active Controls in the All Studies population
>
> Table 9.15 (vol 4.10, pages 303-306) adverse events in seasonal allergic rhinitis placebo controlled trials by body system and preferred terms, Trinasal vs Placebo and Nasacort
>
> Table 9.16 (vol 4.10, pages 307-308) adverse events at least possibly related to drug in seasonal allergic rhinitis placebo controlled trials by body system and preferred terms, Trinasal vs Placebo and Nasacort

In telephone facsimile dated 6/25/96 the sponsor states that as a result of examining the programs and data of the laboratory analysis presented in the ISS, they found discrepancies. These were generated by their contracted research organization, [redacted] The laboratory values for some of the interim visits were being erroneously assigned to the screening visit. "This error affects approximately 20 patients from studies 100-305, 100-1 and 100-104." " The changes in the descriptive statistics for lymphocytes, platelet count, CPK and cholesterol were negligible and did not affect any conclusions". The sponsor will check the rest of the labs and will inform FDA any significant changes in the results.

The adverse event database in this ISS and in this review does not exclude adverse events prior to randomization to study drug, i.e. those adverse events that were reported during the baseline period. The sponsor provided the adverse event database for placebo controlled studies post randomization on the submission dated July 1, 1996.

Extent of exposure

Exposure by Dose

A total of 1,768 patients were enrolled in 14 studies. Of these, 1187 received various doses of Tri-nasal, 345 received placebo and 278 received an active comparator (some patients received more than one treatment, page 17 SU 3/7/96).

From the updated Tables 9.1 and 9.2 (Tables 2 and 3 in SU 3/7/96), a listing of the number of patients receiving the individual treatment follows. It should be noted that the sum of the individual patients listed as receiving Tri-nasal treatment (Table 2 SU 3/7/96) exceeds the number of patients quoted in page 17 of the SU 3/7/96. The sum of patients receiving individual Tri-nasal treatments is 1,251 and the listed number is 1,187. The difference, 64 patients, is the number of patients that received more than one treatment in cross-over studies, as per telephone facsimile dated 6/17/96.

All Trinasal: N=1187				**Placebo:N=345**
50 μg	100 μg	200 μg	≥400 μg	
N=142	N=55	N=250	N=804	

Active controls:			
Nasacort	Kenalog 4 mg	Kenalog 8 mg	Flunisolide 200 μg
N=116	N=83	N=8	N=74

Prednisone 10 mg
N=5

The sponsor also clarifies the difference of 8 patients in the number of patients listed as been the total of patients receiving active controls (SU 3/7/96 page 17) and the total number of patients from the sum of those receiving individual active controls in Table 3 in SU 3/7/96) in the same telephone facsimile (6/17/96).

From the 804 patients listed as having received ≥400 μg of Tri-nasal, 794 received 400 μg, 5 received 800 μg and 5 received 1600 μg. From those 794 patients that are listed as having received 400 μg, 355 participated in the dose titration study 100-307. These patients are counted as having received 400 μg even though they may titrated down their dose during the study duration.

The sponsor was requested to clarify the extent of exposure to treatment for the 200 μg and 400 μg dose groups. In the sponsor's response, telephone facsimile dated 7/18/96, it is stated that it was agreed between Muro and FDA to assign all patients in study 100-307 to the 400 μg dose; the dose at study initiation. The tables provided in this communication do not clarify the issue of actual exposure to study drug dose. It is very probable that the cited agreement between Muro and FDA for study 100-307 had to do with the assignment of adverse event by dose. It is important in terms of safety to know the actual extent of exposure to the 400 μg and 200 μg dose in this study. The sponsor should be asked again to clarify this issue in terms of the actual doses received.

Exposure by duration of treatment

Most patients that were exposed to Tri-nasal, did so for 28-42 days (Tri-nasal 400 μg (253), Tri-nasal 200 μg (77), Tri-nasal 100 μg (23), and Tri-nasal 50 μg (117), page 021 vol 4.10 and Table 8 in vol 4.10.

The 3/7/96 SU submission does not update the ISS Table 8 in vol 4.10, exposure by duration, with the data from study 100-309. This study was a 2 week SAR study that enrolled 377 patients. These patients were randomized as follows: Tri-nasal 200 μg (94), Tri-nasal 400 μg (95), Nasacort 440 μg (92),in Table 1A, vol 6.1. If the numbers of patients for the study 100-309 are included with those of the NDA database, the total number of patients exposed to Tri-nasal for >1 to 14 day period is still less than the number of patients exposed to the >28 to 42 day period.

A total of 352 patients received Trinasal for > 42 days. Most patients exposed to Tri-nasal for > 42 days [Tri-nasal 200 μg (24) and Tri-nasal 400 μg (319), ISS Table 8, vol 4.10] were from Study 100-307. The study 100-307 was an open 6 month titration study, that enrolled 355 patients. However, even though all the patients in study 100-307 are listed as having received Tri-nasal at a dose of 400 μg for more than 42 days, they may have been titrated to a lower dose before the 42 days were over, refer to the report from study 100-307, Table 9 vol 4.52. According to this table only 77 patients in this study received 400 μg of Tri-nasal for >42 days consecutively. The report states that for the first month of the study, 234 patients (69.4%) used 400 μg qd for most days in the month. In subsequent months, the percentage of patients predominantly using the 400 μg dose decreased to 47.2%, 32.9 %, 28.3%, 26.1% and 27.4% for months 2 through 6 respectively. During the first month of the study, 87 patients (25.8%) used the 200 μg dose for most days of the month, increasing to 39.5 % during Month 2. For Months 3-6 the frequency of patients using the 200 μg dose remained between 49% and 50%, page 044 in volume 4.52.

Exposure by gender

There were 637 female patients (53.7%) and 550 male patients (46.3%) that received Tri-nasal (all doses), page 17, SU 3/7/96.

Exposure by age

The mean age for patients that received Tri-nasal was 34 ± 10.67 years with a range of 12 to 65 years of age, page 17, SU 3/7/96.

12-16 yrs of age

The reviewer could not find a table or direct information in the NDA, of exposure by age groups, especially for the 12-16 yrs of age group. After looking at Table 1.1, vol 10, listing the individual studies, only two studies list sites at which patients 12-18 yrs of age were enrolled. These were the SAR studies 0485

and 38-050, neither of which were placebo controlled studies. The total number of patients enrolled in Study 0485 receiving Tri-nasal 200 μg bid was 65, and in study 38-050, there were 13 patients enrolled that received Tri-nasal 200 μg bid. A total of twenty one patients 12-16 yrs of age, were exposed to a total dose of 400 μg of Tri-nasal, as listed in a table of Adverse events by duration of exposure in the telephone facsimile dated 6/17/96.

>55 yrs of age

There is information regarding the dose received by the > 55 y/o population when the adverse event database is presented by age groups (<55 and ≥55 yrs) in Table 9.8.2, vol 4.10. There were a total of 53 patients that received Tri-nasal (all doses) and 11 that received placebo. Of the 53 patients, 8 received 50 μg, 1 received 100 μg, 12 received 200 μg and 32 received ≥400 μg.

The reviewer could not find a discussion of the extent of exposure by duration of treatment in the >55 y/o group of patients in the ISS or in the 3/7/96 SU. This information was requested and provided by the sponsor on telephone facsimile dated 6/17/96. There is a discrepancy in these tables. The total number of Trinasal patients listed as >55 y/o in the table Incidence of increased cough and rhinitis is 49. However the sum of all Trinasal patients >55 y/o is 35 in the tables of adverse events by duration of exposure. These differences were clarified in the sponsor's telephone facsimile dated 7/18/96. In the telephone facsimile dated 6/17/96 the table of adverse events by duration of exposure did not present the data of patients >55 years of age exposed to >42 days to study drug. According to the table provided in page 22 of the sponsor's 7/18/96 telephone facsimile there were 14 patients >55 yrs of age that were exposed to study drug for >42 days, making 35+14= 49, the total number of patients that are >55 in the database.

Total Number of Tri-nasal Patients			
	Age <55	Age=55	Age>55
All studies except 100-309	945	8	45
Study 100-309	185	0	4

Exposure by race

The majority of the patients, 1031 (87.1%), were Caucasian. There were 4.8% Black, 4.6% Hispanic, 3.1% Asian and 0.4% others, page 17 SU 3/7/96.

In conclusion, from the available information and the size of the population enrolled at the specific study sites it appears that the general population studied under-represents races other than Caucasians, is adequate for gender and under represents the 12-16 and ≥ 55 y/o age groups.

Incidence of adverse events

Adverse events were counted only in the dose group to which the patient was assigned immediately prior to or at the time of the event. The adverse events which occurred prior to receiving study medication were not separated from those which occurred while on study drug. On teleconference with the sponsor dated 6/4/96, the reviewer learned that this meant that all NDA and SU adverse event databases included the adverse events that were recorded prior to randomization to study drug. At a later date the sponsor clarified that this was the way that the adverse events were also reported for study 100-307 in the individual study report. It had been the sponsor's understanding that this was the way that the Division wanted this information reported. It was noted by Dr. Susan Johnson, the Medical Officer at the time, that the intent was to initially look at the whole adverse event database picture before asking for post randomization data. It was felt that because of the way that the adverse event data had been collected, there would be a high possibility of missing important safety data if it was not done in this way.

The sponsor was asked to provide us with adverse event data post randomization in all placebo controlled studies. This information was provided by the sponsor in the correspondence N(AM) dated 7/1/96. In this review the adverse event data post randomization in all placebo controlled studies follows the tables and discussion of the adverse events in the All Studies population.

The All studies adverse event data reported in this review is data that includes adverse events reported prior to randomization to study drug.

Patients did not record the adverse events in their daily diary. Adverse events were recorded in the case report forms at the clinic visits after patients were given the opportunity to mention the occurrence of any. In the placebo controlled trials 100-204, 100-305, 100-309, 0501 and 4-0501, patients had adverse events recorded at weekly intervals during clinic visits. In the case of the 6 month long term study, 100-307, these clinic visits were at monthly intervals. The number and frequency of adverse events may have been under reported.

In the *All Studies* patient population, patients that received more than one dose, i.e. PK cross-over studies, are included at each dose received. However, adverse events were counted only in the treatment group which the patient was assigned prior to or at the same time of the event.

In the *All Studies* patient population, the percentage of patients experiencing any adverse event was comparable in the All Tri-nasal group (78.4%; 931/1187 patients) and the placebo group (74.2%; 256/345), page 17, SU 3/7/96.

In all the tables that follow, the incidence of adverse events refer to the number of patients that reported the event and not to the number of occurrences. The incidence of occurrences of adverse events was not reported in the ISS report.

Adverse events in the *All Studies* population including Protocol 100-309, from ISS Table 2, SU 3/7/96

	All-Tri-nasal	Tri-nasal 50 μg	Tri-nasal 100 μg	Tri-nasal 200 μg	Tri-nasal ≥400μg*	Placebo
Total Number of Patients	1187	142	55	250	804	345
Any Adverse Event N(%)	931 (78.4%)	99 (69.7%)	33 (60.0%)	199 (79.6%)	619 (77.0%)	256 (74.2%)

* There were 794 patients who received 400 μg, 5 patients who received 800 μg , and 5 patients that received 1600 μg.

The percentage of patients reporting adverse events in the *All Studies* population was lower in the 50 and 100 μg groups than for the higher doses of Trinasal. However the incidence of adverse events in the placebo group was higher than the one reported for these two groups.

The placebo group for this and all the adverse event tables that follow are patients that received the drug's vehicle.

The most frequently reported individual adverse events in the All Studies population with a higher incidence in the Tri-nasal patients than in placebo patients, including patients from Study 100-309 (from ISS Table 2, SU 3/7/96) were:

	All Trinasal	Placebo
headache	47.4%	41.2%
application site reaction	22.5%	21.4%
pharyngitis	19.4%	8.1%
back pain	5.7%	3.5%
epistaxis	5.6%	3.2%
dysmenorrhea	5.1%	4.9%
taste perversion	4.8%	2.9%

The sponsor was requested in teleconference dated 6/4/96 to provide us

with narrative information on selected cases of adverse events of Tri-nasal treated patients that were included in the ISS Table 2 from the SU 3/7/96. This information was provided by the sponsor in Section 2 of the correspondence N (AM) dated 7/1/96. A summary of these cases can be found in Appendix 1.

Most of the patients took part in Study 100-307, the 6 month long term study. The majority of the adverse events appear to be intercurrent illnesses unrelated to study medication. The sponsor does not mention in any of these summaries the use of rescue medication. However, the role of the study drug cannot be completely ruled out for the following adverse events: slow reactions-CNS depression (0019), angioedema and urticaria (0214), amblyopia-blurry vision (0607), contact dermatitis (0128), altered consciousness-syncope (0208) lipoma (0223) hematuria (0516).

Adverse events by demographic subgroup

Excludes results of study 100-309

Gender

The overall incidence of adverse events was higher in females than in males in both the All Tri-nasal group and the placebo group. The overall incidence of adverse events for males was 70.5% (321/455) in the All Tri-nasal group and 65.0% (76/117) in the placebo group (Table 9.7.1 in vol 4.10). For females the overall incidence of adverse events was 83.4% for the Tri-nasal group (453/543) and 78.8% (104/132) in the placebo group (Table 9.7.2 in Vol 4.10).

The tables for incidence of adverse events by gender restricted to the placebo controlled studies were not included in the integrated summary of safety of the original submission. This information was provided in the correspondence N (AM) dated 7/1/96 and is included in this review in the section of Post Randomization Adverse Events.

The incidence of reviewer's selected adverse events by individual preferred term and gender is presented in the next table for the All Tri-nasal treated group versus placebo from Tables 9.7.1 and 9.7.2 from vol 4.10 in the All Studies population.

Selected incidences of adverse events for males and females by preferred term in the ALL Studies population, from Tables 9.7.1 and 9.7.2 in vol 4.10.

	All Trinasal		Placebo	
	Females	Males	Females	Males
headache	52.7%	36.7%	48.5%	26.5%

pharyngitis	23.2%	18.9%	9.8%	7.7%
application site reaction	22.5%	21.8%	21.2%	18.8%
Taste perversion	4.6% (25/543)	1.8% (8/455)	0.0%	0.9% (1/117)
rhinitis	8.5%	5.7%	6.8%	12.0%
epistaxis	6.6%	6.2%	4.5%	2.6%
back pain	6.6%	4.0%	5.3%	2.6%
pain	8.1%	5.5%	7.6%	4.3%
Dysmenorrhea	8.5%		6.1%	

The incidence of the more commonly reported adverse events is higher in female patients, in the All Studies population. For headache, application site reaction, and epistaxis, the difference in the incidence from these adverse events in Trinasal groups versus placebo is greater for males than for females. Taste perversion is reported more in female patients than in male patients. The incidence of rhinitis in male placebo patients is greater than in male patients treated with Tri-nasal.
The following table was provided as an update by the sponsor in telephone facsimile dated 6/17/96. It includes the results of study 100-309, for the All studies population:

	All Trinasal		Placebo	
	Females	Males	Females	Males
Taste perversion	6% (38/637)	3.5% (19/550)	3.8% (7/186)	1.9% (3/159)

Taste perversion was reported more frequently in the females patients than in the male patients for all placebo controlled studies, including 100-309. Update provided by the sponsor in telephone facsimile dated 6/17/96:

	All Trinasal		Placebo	
	Females	Males	Females	Males
Taste perversion	1.6% (6/375)	0.3% (1/318)	0%	1.3% (2/159)

The sponsor clarified why the 7 female placebo patients listed as reporting taste perversion in the ALL Studies population table, are not listed in the above, placebo-controlled studies table, in the telephone facsimile dated 7/18/96. The All Studies population table is correct but the table for the placebo controlled trials is not. There was an error in programming and some records were not included in the subset selected. It affected this table and the cough, rhinitis table by age group submitted in the 6/17/96 telephone facsimile. This problem was solved and the program re-run. The sponsor states that no other programs were affected by this error. The corrected table for all placebo controlled SAR trials follows:

	All Trinasal		Placebo	
	Females	Males	Females	Males
Taste perversion	4.8% (18/356)	3.8% (12/297)	3.8% (7/176)	1.9% (3/146)

Age

The overall incidence of adverse events in the All Studies population for the All Tri-nasal group was 77.4% (731/945 patients in the ≤55 year age group and 81.1% (43/53 patients) in the >55 year age group. The incidence of adverse events in the placebo groups were about 72% for both groups (Tables 9.8.1 and 9.8.2 in vol 4.10).

The incidence of adverse events in the respiratory system was higher in the ≥55 year age group. This higher incidence was due in turn to an increase in the reported cough and rhinitis. The incidence of increased cough was 13.5% (All Tri-nasal) vs 0% (placebo) for the ≥ 55 year age group and 3.6% (All Tri-nasal) vs 2.5% (placebo) in the < 55 year age group. Rhinitis was recorded in 11.3% (All Tri-nasal) vs 9.1% (placebo) in the ≥ 55 year age group and 7 % (All Trinasal) vs 9.2% (placebo) in the < 55 year age group (Tables 9.8.1 and 9.8.2 in vol 4.10).

The sponsor provided an update, including the results from study 100-309 (telephone facsimile dated 6/17/96) of the incidence of rhinitis and increased cough in the ≥55 year age group for the placebo controlled SAR studies population. As explained above a corrected table was provided for the SAR- placebo controlled trials, in the telephone facsimile dated 7/18/96. The corrected results are as follows: the incidence of increased cough was 12.9% (4/31, All Tri-nasal) vs 0% (placebo) for the > 55 year age group and 1.6% (10/622, All Tri-nasal) vs 1.9% (placebo) in the ≤55 year age group. Rhinitis was recorded in 3.2% (20/622,All Tri-nasal) vs 6.1% (19/310,placebo) in the ≤ 55 year age group

and 6.5% (2/31, All Trinasal) vs 0% (placebo) in the > 55 year age group.

Race

The overall incidence of adverse events in the All Studies population- Caucasian, for the All Tri-nasal group was 79.4% versus 75.7% in the placebo treated group (Table 9.9.1 in vol 4.10). For the Black population with only a total of 42 patients having received treatment with Tri-nasal vs 10 placebo treated patients, the incidence of recorded adverse events was 76.2% (All Tri-nasal) verses 50% (placebo), (Table 9.92 in vol 4.10). The number of patients from races other than Caucasians was too small to make adequate comparisons for individual adverse events between race groups.

Adverse events by severity

Excludes results from study 100-309

The majority of patients experienced mild to moderate adverse events. A list of selected common adverse events by severity follows in the next table from Tables 9.10.1, 9.10.2 and 9.10.3 in vol 4.10.

Adverse events by preferred term and severity in the All Studies population, from Tables 9.10.1, 9.10.2 and 9.10.3 in vol 4.10.

	All TAA	Placebo	TAA (total daily dose)			
			50 μg	100 μg	200 μ	≥400 μg
Headache						
mild	12%	12%	16%	22%	11%	11%
mod	22%	17%	25%	11%	26%	20%
sev	5%	5%	4%	0%	6%	5%
Pharyngitis						
mild	7%	4%	5%	4%	8%	7%
mod.	9%	4%	6.%	2%	10%	9%
sev.	3%	0.4%	0.7%	0%	3%	3%
Application site reaction						
mild	13%	10%	4%	0%	8%	16%
mod.	8%	10%	4%	0%	4%	9%
sev.	1%	0.4%	1%	0%	2%	0.1%

An increase in the percent of patients reporting application site reactions of mild severity is seen at the higher doses of Tri-nasal.

Adverse events by duration of exposure

Excluding data from study 100-309 (2 week study)

In patients treated with Tri-nasal for ≤1 day, headache was reported in 30% (11/37) of patients; the majority 10/11 in the ≥400 μg treatment group. Rhinitis was reported in 19% (7/37) of patients (all of them in the ≥ 400 μg treatment group), Table 9.11.1 in vol 4.10. There were no patient treated with placebo for ≤ 1 day.

For the 2-14 day, 15-28 day, and 29-42 day treatment duration, adverse event rates were relatively constant, with no large differences between the All Tri-nasal and placebo groups, page 034, vol. 4.10.

There were very few placebo and Tri-nasal 200 μg patients that were exposed to the drug for > 42 days. All adverse events reported by patients in study 100-307 that received 400 μg dose initially are reported under the 400 μg dose, whether the adverse event occurred when the patient was receiving 100 μg dose at the time. The majority of patients were listed as having received Tri-nasal ≥400 μg, Table 9.11.5 in vol 4.10.

Adverse events by preferred terms for patients with > 42 days of exposure, from Table 9.11.5 in vol 4.10.

	All TAA	Placebo	TAA 200 μg	TAA ≥400 μg
Total # of patients	352	17	24	328
headache	59%	35%	63%	59%
pharyngitis	40%	18%	79%	37%
application site reaction	27%	24%	38%	26%
epistaxis	13%	0%	13%	13%
rhinitis	10%	29%	46%	8%
pain	10%	6%	13%	10%
flu syndrome	6%	0%	30%	4%
cough increased	7%	0%	8%	6%
dysmenorrhea	7%	0%	17%	7%
bronchitis	3%	0%	13%	3%

dyspepsia	5%	0%	0%	6%
gastroenteritis	3%	0%	0%	4%
nausea	3%	0%	0%	3%

The incidence of adverse events for duration of exposure is not compared to other active nasal treatments because there were no patients treated with other nasal stercid formulations for > 42 days in the NDA studies. There were only 5 treated patients that are reported as having received an active control treatment for > 42 days in the NDA, Table 9.11.10 in vol. 4.10, these patients were treated with 10 mg of Prednisone.

Adverse events by duration of exposure and age groups

12-16 yrs

Adverse events by duration of exposure. The only patients 12-16 years of age who experienced adverse events were those who took ≥400 µg of Trinasal per day (sponsor's telephone facsimile dated 6/17/96).

	Duration of Exposure		
	≤ 1 Day	> 14 to 28 Days	> 28 to 42 days
Total Number of Patients	1	1	19
application site reaction	1(100%)	0	15(78.9%)
taste perversion	0	0	2 (10.5%)

> 55 yrs

The updated report (sponsor's telephone facsimile dated 6/17/96) does not include a table for patients over 55 years of age that had received Tri-nasal for > 42 days, in the All studies population.

The total number of patients reporting adverse events that received Trinasal for: >1-14 days=2, >14-28 days=12 and >28-42 days =21.

For the >28-42 days of exposure, the adverse events reported by >2 Trinasal patients were headache and pharyngitis. Headache had an incidence of 42.5%, (9/21), for All Tri-nasal and 33.3% (2/6) for placebo patients. Pharyngitis was reported by 19% (4/21) Trinasal patients and 0% placebo treated patients.

Adverse events for Tri-nasal dosing regimens

The incidence of patients reporting adverse events during once/day versus twice/ day doses was compared, Table 9.13 in vol 4.10. This table excludes patients from study 100-309 that were treated with once a day dosing for two weeks.

Of the more common adverse events reported, only the incidence of application site reaction was higher on the 200 μg bid dosing. It was 58.5% for the 200 μg twice/day versus 13.5% in the 200μg and 18.3% for the 400μg qd given once daily.

Adverse events possibly related to study drug

Including the results from study 100-309 in the *Placebo Controlled SAR population*, Table 5, in SU 3/7/96:

In the All Tri-nasal group 38.1% of patients experienced an adverse event which was possibly related to study drug versus 39.8% in the placebo treated group. The incidence of reported adverse events was higher in the Tri-nasal 200 μg treatment group versus that in placebo. The incidence of patients reporting adverse events was 24.6% (Tri-nasal 50 μg), 22.2% (Tri-nasal 100 μg), 46.0% (Tri-nasal 200 μg), and 41.0% (Tri-nasal 400 μg).

Individual adverse events that were rated as possibly related to drug (All Tri-nasal) were burning (10.4%), stinging (6.1%), and headache (15.5%). In the placebo group these were considered to be related to study drug in 12.7% (burning), 11.5% (stinging) and 15.2% (headache).

POST RANDOMIZATION ADVERSE EVENTS

In teleconference with the sponsor dated 6/10/96, we requested the adverse events that had been recorded post-randomization (eliminating AE that occurred during baseline only) in all placebo controlled studies. In Section 4 of the correspondence N (AM) dated 7/1/96, the sponsor provided us with this information. In this section the pages are not numbered and the tables do not have a specific identifier. All placebo treated patients received the drug's vehicle. The data from studies 100-309, 100-305, 100-204, 4-0501, 0501, 1-0501 and 3-0501 was included in these tables.

Adverse events in All Placebo controlled studies from the Table titled: Adverse Events by Costart and Preferred terms in All SAR and PAR placebo-controlled studies.

	All-Tri-nasal	Tri-nasal 50 μg	Tri-nasal 100 μg	Tri-nasal 200 μg	Tri-nasal ≥400μg*	Placebo

Total Number of Patients	683	142	27	204	310	345
Any Adverse Event N(%)	333 (48.8%)	92 (64.8%)	19 (70.4%)	82 (40.2%)	140 (45.2%)	169 (49.0%)

The percentage of patients reporting adverse events in the All-Tri-nasal and placebo treated group was about the same. The percentage of patients reporting adverse events in the Tri-nasal low dose groups was higher than in the placebo group.

In the All Placebo-controlled studies population the **incidence of adverse events from the most to least frequent at a ≥2% incidence in the All-Trinasal group:**

	All TAA	Placebo	TAA (total daily dose)			
			50 μg	100 μg	200 μg	≥400 μg
headache	28.7%	23.8%	40.1%	51.9%	22.5%	25.5%
application site reaction	10.2%	13.3%	9.9%	0%	6.9%	13.5%
pharyngitis	8.5%	5.8%	9.9%	11.1%	9.3%	7.1%
pain	3.7%	3.2%	5.6%	11.1%	2.9%	2.6%
rhinitis	3.5%	5.8%	3.5%	0%	2.9%	4.2%
back pain	3.1%	2.0%	3.5%	3.7%	3.4%	2.6%
dysmenorrhea	2.3%	1.7%	3.5%	3.7%	2.0%	1.9%
epistaxis	2.3%	2.6%	4.9%	0%	0%	2.9%
asthma	2.0%	1.2%	2.8%	3.7%	1.0%	2.3%
cough increased	2.0%	1.4%	2.1%	3.7%	2.0%	1.9%

For the most part the incidence of patients reporting adverse events was higher in the Tri-nasal low dose groups than in the higher doses.

The incidence of reported pharyngitis was higher in each of the Tri-nasal treated groups than in the placebo group.

Adverse events by demographic subgroups

Age

Adverse events in Patients between 17 and 55 yrs of age, All Placebo-controlled studies:

	All-Tri-nasal	Tri-nasal 50 μg	Tri-nasal 100 μg	Tri-nasal 200 μg	Tri-nasal ≥400μg*	Placebo
Total Number of Patients	651	135	26	193	297	332
Any Adverse Event N(%)	310 (47.6%)	86 (63.7%)	19 (73.1%)	74 (38.3%)	131 (44.1%)	163 (49.1%)

Since the patients between 17 and <55 years of age group makes up most of the population that participated in the placebo controlled trials the reported incidence of the more common adverse events is very similar to that presented in the previous table for all patients in placebo-controlled studies.

Adverse events in Patients >55 yrs of age, in All Placebo-controlled studies:

	All-Tri-nasal	Tri-nasal 50 μg	Tri-nasal 100 μg	Tri-nasal 200 μg	Tri-nasal ≥400μg*	Placebo
Total Number of Patients	32	7	1	11	13	13
Any Adverse Event N(%)	23 (71.9%)	6 (85.7%)	0 (0%)	8 (72.7%)	9 (72.7%)	6 (46.2%)

There were very few patients >55 yrs of age. **The most commonly reported adverse events in Patients >55 years** of age, in All-Placebo controlled studies were:

	All TAA	Placebo	TAA (total daily dose)			
			50 μg	100 μg	200 μg	≥400 μg
headache	12 (37.5%)	2 (15.4%)	2 (28.6%)	0%	4 (36.4%)	6 (46.2%)

pharyngitis	4 (12.5%)	0%	0%	0%	1(9.1%)	3 (23.1%)
cough increased	3 (9.4%)	0%	2 (28.6%)	0%	0%	1(7.7%)
rhinitis	3 (9.4%)	0%	1(14.3%)	0%	2(18.2%)	0%

The incidence of headache and pharyngitis was reported more in the high dose Tri-nasal groups than in low dose or placebo treated patients.

Adverse events in Patients < 17 years of age in All Placebo-Controlled studies

No patients between 12 and 16 years of age were enrolled in the placebo controlled studies (100-309, 100-305, 100-204, 4-0501, 3-0501, 1-0501, and 0501) and therefore there are no listings in the tables for this age group. Thirty eight patients less than 17 years of age were enrolled in studies 38-050 and 0485.

Gender

Adverse events in Male Patients in All Placebo-Controlled Studies

	All-Tri-nasal	Tri-nasal 50 μg	Tri-nasal 100 μg	Tri-nasal 200 μg	Tri-nasal ≥400 μg*	Placebo
Total Number of Patients	311	62	13	90	146	159
Any Adverse Event N(%)	126 (40.5%)	35 (56.5%)	8 (61.5%)	28 (31.1%)	55 (37.7%)	6 9(43.4%)

The **adverse events reported at a higher incidence in the Male population** in All Placebo-Controlled Studies were:

	All TAA	Placebo	TAA (total daily dose)			
			50 μg	100 μg	200 μg	≥400 μg
headache	70 (22.5%)	26(16.4%)	21 (33.9%)	7 (53.8%)	15 (16.7%)	27 (18.5%)
application site reaction	31 (10.0%)	20(12.6%)	9(14.5%)	0%	5(5.6%)	17 (11.6%)
pharyngitis	23 (7.4%)	7 (4.4%)	6(9.7%)	2 (15.4%)	7 (7.8%)	8 (5.5%)

Adverse events reported by the Female Patients in All Placebo-Controlled Studies

	All-Tri-nasal	Tri-nasal 50 μg	Tri-nasal 100 μg	Tri-nasal 200 μg	Tri-nasal ≥400μg*	Placebo
Total Number of Patients	372	80	14	114	164	186
Any Adverse Event N(%)	207 (55.6%)	57 (71.3%)	11 (78.6%)	54 (47.4%)	85 (51.8%)	100(53.8%)

The incidence of all adverse event for each treatment group including placebo was higher in the female than in the male population.

The **adverse events reported at a higher incidence in the female population** in All Placebo-Controlled Studies were:

	All TAA	Placebo	TAA (total daily dose)			
			50 μg	100 μg	200 μg	≥400 μg
headache	126(33.9%)	56(30.1%)	36 (45.0%)	7 (50.0%)	31 (27.2%)	52 (31.7%)
application site reaction	39 (10.5%)	26(14.0%)	5(6.3%)	0%	9(7.9%)	25 (15.2%)
pharyngitis	35 (9.4%)	13 (7.0%)	8(10.0%)	1 (7.1%)	12 (10.5%)	14 (8.5%)

The incidence of the three more common adverse events was higher in the female population than in the male population for both the All Tri-nasal and placebo treated patients.

Race

Adverse events in Caucasian patients in All Placebo-Controlled Studies:

	All-Tri-nasal	Tri-nasal 50 μg	Tri-nasal 100 μg	Tri-nasal 200 μg	Tri-nasal ≥400μg*	Placebo
Total Number of Patients	568	104	23	181	260	278
Any Adverse Event N(%)	280 (49.3%)	66 (63.5%)	17 (73.9%)	73(40.3%)	124 (47.7%)	144(51.8%)