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The majority of patients treated with Tri-nasal were Caucasian (566/683=83.1%). The overall incidence of adverse events in this population as well as the incidence of the more commonly reported adverse events is very similar to that seen in the All Patient Placebo-Controlled study population.

The **adverse events reported by more patients in the Caucasian population** in All Placebo-Controlled Studies were:

	All TAA	Placebo	TAA (total daily dose)			
			50 μg	100 μg	200 μg	≥400 μg
headache	164(28.9%)	66(23.7%)	41 (39.4%)	13(56.5%)	41 (22.7%)	69 (26.5%)
application site reaction	61 (10.7%)	42(15.1%)	9(8.7%)	0%	12(6.6%)	40 (15.4%)
pharyngitis	46 (8.1%)	16 (5.8%)	9(8.7%)	2 (8.7%)	18 (9.9%)	17 (6.5%)

The percent of patients that received Tri-nasal in all placebo controlled studies of races other than Caucasian was small. Hispanics (47/683=6.9%), black (29, 29/683=4.2%), and Asian (33, 33/683=4.8%). The incidence of any reported adverse events for these groups follows.

The **incidence of Any Adverse Event by race in All Placebo-controlled studies**:

Caucasian		Black		Hispanic		Asian	
All TAA	Placebo	All TAA	Placebo	All TAA	Placebo	All TAA	Placebo
49.3% (280/568)	51.8% (144/278)	37.9% (11/29)	26.3% (5/19)	53.2% (25/47)	46.7% (14/30)	45.5% (15/33)	35.7% (5/14)

Of the patients treated with Tri-nasal, Black patients had the lowest incidence of reported adverse events and Hispanic patients the highest.

Adverse events that occurred only during the baseline period in the long term study 100-307

The sponsor was asked to provide us with a listing of the adverse events that were reported only during the baseline period to get an adequate picture of the adverse event data reported while patients were on study drug. This information was submitted in Section 4 of the correspondence N (AM) dated 7/1/96. This listing was reviewed and it was confirmed that the adverse events of interest reported for study 100-307 in the original submission 10/31/95 (which included those reported pre and post study drug) had not been reported during the baseline period.

Deaths, Drop-outs due to adverse events, and other serious adverse events

There were no deaths in any Tri-nasal clinical trials, page 019, SU 3/7/96.

From a total of 58/1768 patients, 51/1187 (4.3%) Tri-nasal treated patients, 6/345 (1.7%) placebo treated patients, and 1/276 active control patients were discontinued due to adverse events/intercurrent illnesses. Forty of these were in the Tri-nasal 400 μg dose group, SU 3/7/96, page 019.

The following list of Tri-nasal treated patients in the original NDA database submitted 10/31/95, excluding patients from the study 100-309, were discontinued (50/1062) due to adverse events/intercurrent illnesses, page 039 in vol 4.10:

12 within the first 2 weeks
9 within >2 to 4 weeks
7 within > 4 to 6 weeks
3 within > 6 to 8 weeks
6 within > 8 to 12 weeks
4 within > 12 to 16
9 after > 16 weeks

Of the patients included in the original submission (10/31/95), excluding patients treated in the study 100-309, there were a total of 1062 patients treated with Tri-nasal in this database, Table 8 in vol 4.10. The reviewer could not find a table of exposure to treatments in the NDA or in the safety update with corresponding exposure intervals as is shown in the above list. Using the sum of all patients that were exposed to Tri-nasal 400 μg during the first 6 weeks, the percentage of patients discontinuing the study within 6 weeks was 4% (28/710). Using the sum of patients that were exposed to Tri-nasal 400 μg for over 6 weeks, the percentage of patients that discontinued the study was 6.3% (22/352). It should be noted that the data from patients in clinical trials that received Tri-nasal 400 μg for more than six weeks comes from study 100-307 in which dose titration was permitted. The dose of Tri-nasal that the patients were randomized to initially, regardless of whether the patients used it only for one month out of six, is what is listed, even though the patient may have been using 100 μg of Tri-nasal at the time that an adverse event was recorded.

Five patients had serious adverse events, page 019, SU 3/7/96. These were: lipoma of the back (patient 0223 of study 100-307), hospitalization for abdominal pain (patients 0415, 0631 of study 100-307), post-operative bleeding secondary to an elective laparoscopy (patient 1211 of study 100-307), and an allergic reaction to food (patient 0618 of study 100-309). All of these were considered to be of unknown cause or not related to study drug.

The narratives for patients with serious adverse events and adverse events leading to discontinuation of the patient from the clinical trial were reviewed, NDA vol 4.10 and vol 6.1 [N(AZ)-2/15/96] as well as the case reports for the five patients with serious adverse events and the patients that discontinued the studies due to adverse events, NDA volumes 4.150-4.155. After the review of the CRFs of patients reporting serious adverse events, there does not appear to be a direct relationship between the study drug and the adverse event. For patient #223, even though the patient's lipoma was not noted on physical exam at study initiation, the patient was also taking acetaminophen on a daily basis for headache. Even though two patients had abdominal pain that may have precipitated the laparoscopies, patient #415 had been using Grisactin for ringworm and patient #1211 had severe bleeding during elective laparoscopy. Patient 0631 had severe abdominal pain and was hospitalized but the patient had an UTI starting a couple of days after study drug initiation and later on during treatment it is recorded that the patient received Demerol for kidney stones. The anaphylactic reaction in patient 0618, was apparently related by history to something that the patient had eaten. After recuperating from this episode this patient received the study drug without an adverse event.

A short summary of the cases of patients that discontinued the study due to adverse events that were not included in the MO review of the study reports for 0501, 1-0501, 100-204 and 100-305 is included in Appendix 2.

Of the 34 patients from study 100-307 that discontinued the study due to adverse events, see Appendix 1 (vol 4.151-4.155), 2 of these were due to a laboratory adverse event. One patient had elevated liver enzymes and the other had a high glucose value at screening. These labs were repeated and as they were still abnormal, the patients were discontinued from the study.

Of the 34 patients from study 100-307 that discontinued the study due to adverse events, see Appendix 1 (vol 4.151-4.155), 27 were women and 7 were men. Ten patients had adverse events that the investigator considered that they could have been related to study drug (page 59, Vol 4.52): moderate epistaxis (#213), moderate headaches (#516), severe nasal burning and cracking (#615), moderate pain and numbness in nose and forehead (#905), severe eye tearing, itching and swelling (#910), severe headaches (#914), moderate sore spot in nostril (#924), moderate gagging upon study drug administration (#1227), severe sneezing upon study drug administration (#1329), and a moderate sinus infection (#1401).

There were seventeen patients that discontinued the study because they had received antibiotic treatment. Sinusitis:patients #127, #426, 803, 1112, 1120, 1123, 1304, and 1401; Bronchitis: patients #513, 803, 833, and 1321; URI: patients #124, 430, 816, 817, 1102 and 1304; bacterial eye infection: patient #412.

Clinical Laboratory

The integrated safety summary, vol 4.10, does not integrate the clinical lab results from study 100-309 with the results for the other studies. The sponsor was requested (teleconference dated 6/4/96) to integrate the data from study 100-309, for platelet and lymphocyte number (mean change from baseline) and mean change from baseline and % of patients shifting categories for CPK and serum cholesterol. Abnormal values for these clinical parameters had been reported in the NDA's ISS. The repose to this request was provided in telephone facsimile dated 6/25/96.

As mentioned previously, discrepancies were found in the listings provided in the NDA's ISS (provided to the sponsor by a contract research organization) and the database generated by the sponsor in trying to integrate the results of the labs from study 100-309 to the rest of the database. The mistake was identified as the inclusion of results of interim lab values as screening values in 20 patients.

The reviewer agrees with the sponsor that hematology and clinical lab results reported in the telephone facsimile dated 6/25/96 do not differ in a significant way from those reported in the NDA's Integrated Summary of Safety. The values reported in the original NDA are the ones reported in this review.

The sponsor was requested to further clarify the statement used in their 6/25/96 telephone facsimile regarding what would they consider a significant change in the lab results that would determine if FDA will be informed, and what was the total number of patients from each study whose records had errors in the assignment of laboratory values. The requested information was provided in the sponsor's telephone facsimile dated 7/18/96. Clinical significance was defined as a change that would move the mean values significantly toward the equivalent of a high or low flag value. The list of all corrected values were presented in a table next to those that had been submitted in the ISS of the original NDA. The reviewer agrees with the sponsor that reported mean corrected lab values in this telephone facsimile do not differ in a significant way from those reported in the NDA's Integrated Summary of Safety. The sponsor also provided a listing of all patients whose records were affected. Study 0501 (Site 19): 7 pts., Study 3-0501: 1 pt., Study 100-305: 9 patients, Study 100-204: 2 pts. for hematology and 4 for chemistry, for a total of 23 patients.

In general, the integrated safety summary for clinical labs uses two types of tables to present a summary of the results. One type includes the results from all patients treated with placebo, as well as the results from all patients treated with Trinasal including the data at the individual dose levels. In the other, the results of Trinasal treated patients (200 and 400 μg) are shown next to those from patients treated with the active controls. No statistical comparisons were made within or between treatment groups, only descriptive statistics are included.

In the review narrative that follows, the statements referring to significant differences within or between treatment groups are descriptive and are not based on statistical analyses.

The review of the clinical labs results for study 100-305, was included in the safety review of the study report. In this study, there were a number of abnormal CPK results for patients on the active drugs and placebo. Eight patients treated with Trinasal had normal/elevated CPK results at baseline and elevated levels at the end of the study. We asked the sponsor to provide us with an explanation on a teleconference dated May 2, 1996. In the sponsor's response dated May 7, 1996 a short summary of the requested cases was provided with a statement indicating what, if any, was the likely cause of the clinical lab abnormalities. The sponsor's response was reviewed and for the most part the abnormal results were attributed to exercise. The ISS results for this particular laboratory parameter, do not suggest that this is an abnormality that would be drug related.

Hematology

Mean change

There was a mean decrease in platelet counts of approximately 2% from baseline to final evaluation. This was not seen in the placebo or Prednisone treatment groups, page 095 and Table 11.1-page 324, vol 4.10. In the shift analysis table for this parameter, there were 21 Trinasal treated patients that had a shift to low values at final evaluation, see table below.

There was a 1.7% within group decrease in mean (%) lymphocytes in the ≥400 μg treatment group. The clinical significance of this finding is unknown, since no absolute numbers are reported and Prednisone treated patients had an increase (0.40%)in percent lymphocytes by the end of treatment. There was an increase in mean % lymphocytes in the placebo treated group (0.88%), as well as in the 50 (0.22%) and 200 μg (1.0%) treatment groups, Table 11.1, vol 4.10. From looking at the shift table analysis for this parameter, shown in the next section, sixteen patients treated with Trinasal (1.7%) had a shift from normal to low values at final evaluation versus 3(1.3%) in the placebo treated group.

The reviewer compared this listing of patients with abnormal lymphocyte values from Table 15.1, vol 4.10 with the listing of patients that participated in study 100-307, and with the listing of patients that discontinued the study due to the adverse events. Three (#1110, #1220 and #1304) of the six patients, with normal lymphocyte values at screening and low values at final exam included in the listing (Table 15.1 in vol 4.10), reported sinus infections, Study 100-307, Data Listing 12, vol 4.111. Two of these patients (#1220 and #1304), discontinued the study because they required antibictics to treat the sinus infection after 5 months of treatment with study drug, vol 4.10.

Laboratory shifts

There were no shifts in any hematological parameter that occurred at a frequency of > 10% and only 1 that occurred at a frequency >5%. Shifts in eosinophils from normal at baseline to above normal at final evaluation occurred in 6% (14/232) of the patients in the placebo group, page 096 vol 4.10.

The following table shows the results in category shift for lymphocytes and platelets. These hematology parameters had changes in mean values from baseline to final evaluation.

Hematology-Shift analysis from Table 14.1 in vol 4.10

	All Trinasal-Final Evaluation			Placebo-Final Evaluation		
	Below	Normal	Above	Below	Normal	Above
Baseline Evaluation						
Lymphocytes N (%)						
Below	6 (0.6%)	11 (1.2%)	1(0.1%)	5(2.1%)	2(0.8%)	0
Normal	16 (1.7%)	847 (89.7%)	29 (3.1%)	3 (1.3%)	214 (89.5%)	8 (3.3%)
Above	0	15 (1.6%)	19 (2.0%)	0	5 (2.1%)	2 (0.8%)
Platelets N(%)						
Below	1 (0.1%)	0	0	0	0	0
Normal	21 (2.4%)	802 (92.5%)	13 (1.5%)	0	233 (97.1%)	2 (0.8%)
Above	0	18 (2.1%)	12 (1.4%)	0	2 (0.8%)	3 (1.3%)

Serum Chemistry

Mean change

Serum CPK values increased 21% from baseline levels at final evaluation in the 200 μg treated group (a 23.87 U/L increase from 115.42 at baseline), page 351, Table 12.1, vol 4.10. This was not a consistent change among the other Tri-nasal treated groups. The changes from baseline for the 400, and 50 μg groups were 0.42 and -7.65 U/L (<1% and 6% decrease) respectively. The values in the placebo group decreased 15% (17.95 U/L from a baseline of 122.25 U/L). No associated abnormal clinical findings were reported in selected patients treated with Trinasal (50, 200 and 400 μg) from study 100-305 that had "normal to above normal shifts", N (BM) dated May 7, 1996.

There was an increase in the mean triglyceride value at final

evaluation compared to that at baseline within the Prednisone treated group. The mean value at baseline was 113.80 mg/dL and it increased at final evaluation by 65.0 mg/dL (57% above baseline), page 371, Table 12.2, vol 4.10. The serum phosphorous level increased 18% above baseline (0.62 mg/dL from 3.42 mg/dL), p363, Table 12.1, vol 4.10.

Shifts in category

No shifts in any serum chemistry parameters occurred at a frequency of >10%. Shifts from normal to abnormal which occurred at a frequency of >5% were detected for serum CPK, serum cholesterol and serum triglycerides. Serum cholesterol shifted from normal to high for 5.6% of patients in the ALL Trinasal group, compared with 2.9% of the patients in the placebo group. A shift from normal at baseline to high at final evaluation was seen more frequently in the placebo group versus the TAA treated group for serum CPK (5.2% vs 4.6%) and serum triglyceride (9.5% vs 6.9%), page 096, and Table 14.2 in vol 4.10.

	All Trinasal-Final Evaluation			Placebo-Final Evaluation		
	Below	Normal	Above	Below	Normal	Above
Baseline Evaluation						
CPK N (%)						
Below	0	0	0	0	0	0
Normal	0	316 (80.6%)	18 (4.6%)	0	114 (85.1%)	7 (5.2%)
Above	0	28 (7.1%)	30 (7.7%)	0	9 (6.7%)	4 (3.0%)
Cholesterol N (%)						
Below	24 (2.5%)	10 (1.1%)	0	12 (5.0%)	1 (0.4%)	0
Normal	11 (1.2%)	638 (67.1%)	53 (5.6%)	4 (1.7%)	191 (79.6%)	7 (2.9%)
Above	0	57 (6.0%)	158 (16.6%)	0	8 (3.3%)	17(7.1%)

Analysis of individual laboratory abnormalities

Lymphocytes and eosinophils

Tables 15.1 and 15.2 list all lymphocyte and eosinophil results for patients that presented any values outside the normal ranges. The sponsor did not considered any of the individual values to be clinically significant, page 097, vol 4.10. These results as they refer to a shift from normal to below normal in percent

lymphocytes, in patients that participated in study 100-307, were discussed above under the Hematology, mean change section.

Other laboratory parameters

No serious laboratory abnormalities were reported. Two patients were withdrawn from study 100-307 due to laboratory abnormalities. These were patients 0519 (elevated GGT and SGPT after 2 wk Rx), and 1020 (elevated serum glucose level). The two patients were also included in the adverse event listing for patients discontinued due to adverse events and in both cases these patients had abnormal labs before study drug administration.

Urinalysis parameters

There were no significant changes in mean pH and specific gravity values from baseline to final visit. There were no "normal to abnormal" shifts in any urinalysis parameters that occurred at a frequency of >5%, page 097 in vol 4.10. For urine protein, there was a "normal to abnormal shift" of 2.4% in the All Trinasal group versus 0.8% in the placebo group. For microscopic WBC, the percent of patients with a "normal to abnormal shift" was 2.0% in the All Trinasal group and 1.4% in the placebo group, Table 14.3 in vol 4.10.

Other safety studies conducted by the Sponsor:

Study of HPA axis suppression

Study 1-0501

For the reader's convenience the reviewer's conclusion for study 1-0501 follow:

This study was a single-center, six week, randomized, double blind, placebo controlled study designed to evaluate the effect of 400, 800, and 1600 μg total daily doses (200, 400 and 800 μg bid) on the HPA axis in comparison to placebo and 10 mg/day of prednisone in adults with seasonal allergic rhinitis.

In this study, 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 0-8 hrs and peak). In the analysis to compare the effect at Day 43 vs Day 1, the ANCOVA used the individual patient's Day 1 values as a baseline covariate. The results for peak serum cortisol levels did not subtract the serum cortisol levels prior to stimulation.

Two patients (#23 and #24) treated with Trinasal 1600 μg (800 μg bid),

had lower than expected AUCs 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 and versus the Trinasal 800 treated group.

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 serum corisol post-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.

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.
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 and peak values) after 42 days of treatment. Two patients (#23 and #24) treated with Trinasal 1600 μg (800 μg bid), had lower than expected AUCs during the treatment period, suggesting that in some patients this dose could cause HPA-axis suppression.

Human Pharmacokinetic studies

The results of three human PK studies are included in this submission. Study 100-104 was a single dose, 4 way crossover that compared the PK of triamcinolone acetonide (TAA) after the administration of the intranasal solution of Tri-nasal 200 and 400 μg with the IM administration of Kenalog 4 and 8 mg in patients with PAR. Study 100-105 was a single dose study, 2 way crossover that compared the PK of TAA after using the intranasal solution of Tri-nasal 400 μg with the intranasal suspension of Nasacort 440 μg in patients with PAR. Study 100-106 was a single and multiple dose, 3 way crossover study that compared the PK of TAA after using the intranasal solution of Tri-nasal at doses of 100, 200 and 400 μg.

The following table show the mean PK parameters for TAA obtained after intranasal dosing with Tri-nasal or Nasacort - Study 100-105. From Table 2, page 087 in volume 4.1

	Tri-nasal 400 μg Mean (SD)	Nasacort 440 μg Mean (SD)
C max (ng/mL)	1.12 (0.38)	0.14 (0.13)
T max (h)	0.47 (0.26)	2.28 (0.68)
AUC 0-t (ng•h/mL)	3.31 (1.59)	0.63 (0.95)

The expected exposure to TAA from the intranasal administration of Tri-nasal is expected to be higher than the exposure to the intranasal

administration of Nasacort 440 μg.

Nasacort 440 μg is an approved intranasal suspension of TAA indicated for the nasal treatment of seasonal and perennial allergic rhinitis symptoms. The labeling for Nasacort 440 μg also references safety data from the approved drug Azmacort. Azmacort is indicated for the control of symptoms of bronchial asthma and the recommended doses in adults are 200 μg three to four times per day, not to exceed 1600 μg.
The following information was obtained from Dr. C. Kwong's MOR for Nasacort Nasal Inhaler Pediatric Supplement (N19798).

TAA Product	Study #	Age	Dose (μg/day)	Cmax (ng/ml)	AUC0-∞ (ng•hr/mL)	Relative systemic biovailability (among adults)
Nasacort CFC	Study 101	18-50	220	0.07	0.65 (projected)	1
			440	0.14	1.31	2
Azmacort CFC	Study 119	19-50	600	0.95	6.07	9.3
			800	1.36	9.49	14.6

Comparing the above PK data with the data from study 100-105 for TAA, the exposure to TAA from Tri-nasal at the 400 μg dose would be higher than that of Nasacort CFC but within the exposure to Azmacort CFC at the recommended doses.

Therefore, in terms of systemic adverse events due to systemic exposure to TAA we would expect to see a similar range and frequency of adverse effects with the use of this drug as would be expected with the use of Azmacort at recommended doses if asthma related adverse events were excluded.

Foreign Marketing Safety Data

According to the sponsor's statement, there are no nasal solution dosages of triamcinolone acetonide (TAA) available in the foreign market, no TAA nasal product has been withdrawn from the market related to safety or efficacy issues, and there are no foreign applications pending for Muro's Trinasal spray, vol 4.1, page 043.

APPEARS THIS WAY
ON ORIGINAL

Conclusions

This application is considered a 505(b)(2) submission. The sponsor has conducted a total of 14 clinical trials in the U.S. that enrolled 1,768 patients. Safety data was collected in these trials.

The formulation that was used in the clinical studies 100-309, 100-204, 100-305, 0501, 100-307 and 1-0501 was the same as the to be marketed formulation, 39-050-2. According to the sponsor's table in page 053 in volume 4.1, the to be marketed unit pump, [redacted] nasal actuator is not the same pump that was used in any of the clinical studies. The characteristics of the to- be marketed pump need to be supported by comparative data from the unit pumps used in the clinical studies.

Of the patients studied 1187 received Trinasal at various doses, most patients received Trinasal for >28 to 42 days. A total of 352 patients received Trinasal for > 42 days. The majority of them were enrolled in an open, 6 month, dose titration study. Of these, 77 patients received 400 µg of Tri-nasal for >42 days consecutively. 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%.

The majority of the patients that were exposed to Trinasal, were Caucasian, 1031 (87.1%). There were 4.8% Black, 4.6% Hispanic, 3.1% Asian and 0.4% others. There were 637 female patients (53.7%) and 550 male patients (46.3%) that received Tri-nasal (all doses). The mean age of patients that were treated with Trinasal was 34.15 ± 10.67. The general population studied under -represents races other than Caucasians, is adequate for gender and under represents the 12 to 18 and ≥ 55 y/o age groups.

The adverse events which occurred prior to receiving study medication were not separated from those which occurred while on study drug in the original integrated safety summary. The sponsor was asked to provide us with adverse event data post randomization in all placebo controlled studies. This information was submitted in the correspondence dated July 1, 1996. The data provided in this update was included in the previous section, Post Randomization Adverse Events. The review of this data does not raise further safety concerns.

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 population the overall incidence of adverse events was 78.4% for patients treated with Trinasal and 74.2% for placebo treated patients. In the placebo controlled studies for SAR the overall incidence of adverse events was 74.0% and 73.6% in placebo treated patients. The majority of patients experienced mild to moderate adverse events. The adverse events most commonly reported in the SAR placebo controlled studies were headache, pharyngitis and local reactions: burning and stinging. The percent of patients reporting these local adverse events was higher in patients treated with placebo than those receiving active treatment.

The incidence of post-randomization adverse events for all placebo controlled studies are 48.8% for All Trinasal and 49.0% for Placebo treated patients. The following table compares the incidence of the most frequent individual adverse events for the All Studies population including pre and post randomization adverse events and the corresponding incidence of post randomization adverse events in the All Placebo-Controlled Studies population.

	All Studies Pre and Post Randomization		All Placebo-Controlled Studies Post Randomization	
	All Trinasal	Placebo	All Trinasal	Placebo
headache	47.4%	41.2%	28.7%	23.8%
application site reaction	22.5%	21.4%	10.2%	13.3%
pharyngitis	19.4%	8.1%	8.5%	5.8%
back pain	5.7%	3.5%	3.1%	2.0%
epistaxis	5.6%	3.2%	2.3%	2.6%
dysmenorrhea	5.1%	4.9%	2.3%	2.6%
taste perversion	4.8%	2.9%	0.9%	0.3%

In teleconference dated 6/4/96, the sponsor was requested to provide us with narrative information on selected cases of adverse events that were included in the ISS Table 2 from the SU 3/7/96. This information was provided in the correspondence dated 7/1/96 and reviewed. Most of the cases were reported in Study 100-307, the 6 month long term study. The majority of them 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).

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 a 100 μg dose at the time. For All Trinasal treated patients for > 42 days, the following adverse events were reported by >5 % of patients: headache, pharyngitis, application site reaction, epistaxis, rhinitis, pain, flu syndrome, cough increased and dysmenorrhea.

The incidence of patients reporting adverse events during once/day versus twice/day doses, excluding the data from study 100-309, that used once/day dosing, of the more common adverse events reported, only the incidence of application site reaction was higher when 200 μg bid (58.5%) was compared to 400 μg qd (18.3%) and 200 μg qd (13.5%).

There were no deaths reported in these clinical trials. Five patients had serious adverse events, page 019 SU 3/7/96. 'These were lipoma of the back (patient 0223 of study 100-307), hospitalization for abdominal pain (patients 0415, 0631 of study 100-307), post-operative bleeding secondary to an elective laparoscopy (patient 1211 of study 100-307), and an allergic reaction to food (patient 0618 of study 100-309). All of these were considered to be of unknown cause or not related to study drug.

From a total of 58/1768 patients, 51/1187 (4.3%) Tri-nasal treated patients, 6/345 (1.7%) placebo treated patients, and 1/276 active control patients were discontinued due to adverse events/intercurrent illnesses. Forty of these were in the Tri-nasal 400 μg dose group.

Of the 34 patients from study 100-307 that discontinued the study due to adverse events, see Appendix 1 (vol 4.151-4.155), 27 were women and 7 were men. Ten patients had adverse events that the investigator considered that they could have been related to study drug: moderate epistaxis (#213), moderate headaches (#516), severe nasal burning and cracking (#615), moderate pain and numbness in nose and forehead (#905), severe eye tearing, itching and swelling (#910), severe headaches (#914), moderate sore spot in nostril (#924), moderate gagging upon study drug administration (#1227), severe sneezing upon study drug administration (#1329), and a moderate sinus infection (#1401).

There were seventeen patients that discontinued the study because they had received antibiotic treatment. Sinusitis:patients #127, #426, 803, 1112, 1120, 1123, 1304, and 1401; Bronchitis: patients #513, 803, 833, and 1321; URI: patients #124, 430, 816, 817, 1102 and 1304; bacterial eye infection: patient #412.

The integrated safety summary, vol 4.10, does not integrate the

clinical lab results from study 100-309 with the results for the other studies, as was mentioned earlier. The sponsor was requested (teleconference dated 6/4/96) to integrate the data from study 100-309, for clinical parameters with reported abnormal values in the NDA ISS (lymphocytes, platelet, CPK and cholesterol). This information was received via telephone facsimile on 6/25/96. The reviewer agrees with the sponsor that the revised report does not differ significantly from the one included in the NDA's ISS.

The sponsor found discrepancies in the listings provided in the NDA's ISS (provided to the sponsor by a contract research organization) and the database generated by the sponsor in trying to integrate the results of the labs from study 100-309 to the rest of the database.. The mistake was identified as the inclusion of results of interim lab values as screening values in 20 patients. The rest of the lab database would be checked and any other discrepancies would be informed to FDA.

The sponsor was requested to further clarify the statement used in their 6/25/96 telephone facsimile regarding what would they consider a significant change in the lab results that would determine if FDA will be informed, and what was the total number of patients from each study whose records had errors in the assignment of laboratory values. The requested information was provided in the sponsor's telephone facsimile dated 7/18/96. Clinical significance was defined as a change that would move the mean values significantly toward the equivalent of a high or low flag value. The list of all corrected values were presented in a table next to those that had been submitted in the ISS of the original NDA. The reviewer agrees with the sponsor that reported mean corrected lab values in this telephone facsimile do not differ in a significant way from those reported in the NDA's Integrated Summary of Safety. The sponsor also provided a listing of all patients whose records were affected. Study 0501 (Site 19): 7 pts., Study 3-0501: 1 pt., Study 100-305: 9 patients, Study 100-204: 2 pts. for hematology and 4 for chemistry, for a total of 23 patients. The specific laboratory values included in this review are those submitted in the original NDA.

There was a mean decrease in platelet counts of approximately 2% from baseline to final evaluation. This was not seen in the placebo or Prednisone treatment groups, page 095 and Table 11.1-page 324, vol 4.10. In the shift analysis table for this parameter, there were 21 Trinasal treated patients that had a shift to low values at final evaluation, see table below.

There was a 1.7% within group decrease in mean (%) lymphocytes in the ≥400 μg treatment group. The clinical significance of this finding is unknown, since no absolute numbers are reported and Prednisone treated patients had an increase (0.40%)in percent lymphocytes by the end of treatment. There was an increase in mean % lymphocytes in the placebo treated group (0.88%), as well as in the 50 (0.22%) and 200 μg (1.0%) treatment groups, Table 11.1, vol 4.10. From looking at the shift table analysis for this parameter, shown in the next section, sixteen patients treated with Trinasal (1.7%) had a shift from normal to low

values at final evaluation versus 3(1.3%) in the placebo treated group.

The reviewer compared this listing of patients with abnormal lymphocyte values from Table 15.1, vol 4.10 with the listing of patients that participated in study 100-307, and with the listing of patients that discontinued the study due to the adverse events. Three (#1110, #1220 and #1304) of the six patients, with normal lymphocyte values at screening and low values at final exam included in the listing (Table 15.1 in vol 4.10), reported sinus infections, Study 100-307, Data Listing 12, vol 4.111. Two of these patients (#1220 and #1304), discontinued the study because they required antibiotics to treat the sinus infection after 5 months of treatment with study drug, vol 4.10. Mean platelet values fell approximately 2% during the treatment period. This was not seen in the placebo or Prednisone treatment groups. In the shift analysis table for this parameter, there were 21 Trinasal treated patients that had a shift to low values at final evaluation.

Serum CPK values increased 21% from baseline levels at final evaluation in the 200 μg treated group (a 23.87 U/L increase from 115.42 at baseline). This was not a consistent change among the other Tri-nasal treated groups. The changes from baseline for the 400, and 50 μg groups were 0.42 and -7.65 U/L (<1% and 6% decrease) respectively. The values in the placebo group decreased 15% (17.95 U/L from a baseline of 122.25 U/L). No associated abnormal clinical findings were reported in selected patients treated with Trinasal (50, 200 and 400 μg)from study 100-305 that had "normal to above normal shifts".

The sponsor conducted a single-center, six week, randomized, double blind, placebo controlled study designed to evaluate the effect of 400, 800, and 1600 μg total daily doses (200, 400 and 800 μg bid) on the HPA axis in comparison to placebo and 10 mg/day of prednisone in adults with seasonal allergic rhinitis. 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 and peak values) after 42 days of treatment.

Based on the PK data provided in the NDA, the systemic exposure to TAA from Tri-nasal at the 400 μg dose would be higher than that of Nasacort CFC but within the exposure to Azmacort CFC at the recommended doses.

The conducted clinical program does not adequately support the safe use of Trinasal at doses up to 400 μg/day beyond ——————— The long term open studies did not measure TAA blood levels, clinical parameters of HPA-axis suppression, effects on bone metabolism or effects on intraocular pressure. In terms of systemic adverse events due to systemic exposure to TAA we would expect to see a similar range and frequency of adverse effects with the use of this drug as would be expected with the use of Azmacort at recommended doses if asthma related adverse events were excluded. The extensive safety data with the use of Azmacort with comparable levels of systemic exposure to TAA should be referenced to support the safety of ——————— use of Trinasal. Since the risk benefit ratio for a patient treated for asthma may be different from one treated for perennial allergic rhinitis, the

reviewer recommends that the labeling includes a statement where it is made clear to the physician that for the individual patient,

[ ]

The conducted clinical program does not adequately support the safety of the drug for patients with seasonal or perennial allergic rhinitis in the <18 yrs age group. The safety experience with the marketed drugs Nasacort and Azmacort in this population should be referenced to support the safe use of Trinasal at the recommended doses in the <18 year population.

As part of the secondary review, the following issue was raised and has not been resolved: whether the analyses used in the Study 1-0501 were the appropriate ones to evaluate Tri-nasal's effect on the HPA axis. The analyses submitted included the comparison of the patient's response to cosyntropin stimulation using AUC 0-8 hrs for serum cortisol and peak serum cortisol levels before and after 42 days of treatment without using the change from the patient's baseline on that day. The analyses that we are familiar with in the Division are those that look at changes at 2, 4, and 6 hrs post-stimulation from the same day baseline or changes from patient's baseline.

In a teleconference with the sponsor dated 7/22/96 we asked the sponsor to explain why they had selected the AUC analysis in preference to an analysis and we clarified that the patient's 0 hr timepoint for that day had been included in the AUC analyses. In the sponsor's telephone facsimile dated 7/24/96 it was clarified that the AUC 0-8 hrs included the area under the curve down to the origin. The sponsor also submitted the pertinent calculations to support their comment on the teleconference that an analysis of covariance with baseline as a covariate and change from baseline as the outcome measure is mathematically equivalent to the analysis with post-treatment as an outcome measure, in the sense that the same p-values for treatment comparisons will result from both analyses.

The Biometrics reviewer was asked review the sponsor's fax and to analyze the data of the serum cortisol AUC 0-8 post stimulation on Day 43 and on Day 1 using the patient's baseline for that day and to calculate and make treatment comparisons for the serum cortisol max change from baseline on Day 1 and Day 43.

The sponsor's telephone facsimile dated 7/25/96 also referenced the use of the AUCs as an endpoint in Flonase's summary basis for approval and in the literature. The review of the referenced material has not been completed at the time of this review.

Therefore, pending the resolution of the outstanding review issue mentioned above, the conducted clinical program for this NDA and the safety data from the approved and marketed drugs Nasacort and Azmacort can support the safety of a daily dose of Trinasal of up to 400 μg per day for the indications of seasonal and perennial allergic rhinitis in patients 12 years of age and older.

13. LABELING

An updated proposed labeling was submitted on the correspondence, N (EL), dated 4/29/96. At this time the reviewer will emphasize selected areas of the labeling for comments.

Reviewer's comments: the clinical study 100-204 does not support the claim for topical effect for Tri-nasal.

A topical effect for Tri-nasal 400 μg vs Kenalog 4 mg IM was not demonstrated in this 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.

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. Therefore, the efficacy of Tri-nasal could be

considered to be secondary to a higher systemic exposure rather than to a local topical effect.

Study 100-104, page 067, vol 4.1

	Trinasal 400	Kenalog 4 mg IM
C max	1.91 ng/ml	0.40 ng/ml
AUC $_{0\text{-}168}$	33.22 ng•h/ml	44.89 ng•h/ml
AUC $_{0\text{-}12}$	6.92 ng•h/ml	3.22 ng•h/ml
T $_{max}$	0.36 h	18.67 h

In this study the difference in onset of action for Trip-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.

Reviewer's comments: Two patients (#23 and #24) treated with Trinasal 1600 μg (800 μg bid), had lower than expected AUCs during the treatment period (Day 43) compared to baseline's Day 1 AUCs, suggesting that in some patients this dose could cause HPA-axis suppression.

CLINICAL TRIALS: The efficacy of **Trip-Nasal™ Spray** has been evaluated in 746 patients with seasonal or perennial allergic rhinitis who completed 8 controlled clinical trials.

Reviewer's comments: In the sponsor's correspondence dated 7/1/96, the sponsor lists all placebo controlled studies for SAR and PAR as:100-309, 100-305, 100-204, 4-0501, 0501, 1-0501 and 3-0501. These are a total of seven studies. The total number of Tri-nasal treated patients in these studies, as listed in the 7/1/96 submission is 683.

In total, 1187 patients have been treated with **Trip-Nasal™ Spray** in _____. Three adequate and well controlled multi-center trials involving 541 patients with seasonal allergic rhinitis who received doses of **Tri-Nasal™ Spray** ranging from 50 mcg to 400 mcg once daily were conducted. The results showed that patients who received _____

Reviewer's comments:

[ ]

2. The efficacy of the — mcg dose was supported by only one study 100-305 and therefore is not an indicated dose.

3. The labeling should specify what were the cardinal symptoms of seasonal allergic rhinitis that were supported by the pivotal clinical studies.

INDIVIDUALIZATION OF DOSAGE:
Dosing of Tri-Nasal™ Spray should be individualized since there are many variables that determine clinical response. These variables include the degree of patient allergy, degree of pollen exposure,

A starting dose of 200 mcg (2 sprays/nostril) once daily is recommended for most patients.

Reviewer's comments: In the analysis for study 100-309, of the patient's symptom severity index for Treatment Day 1 and 2 (Intent to Treat)- Table I1 in vol 6.1, no statistically significant differences were observed between Tri-nasal 200 μg and placebo for Day 1 or Day 2.

maximum relief of symptoms may take several days

After symptoms have been brought under control

Reviewer's comments: A was not studied in any of the placebo controlled studies. Study 100-307 was an open label study.

Adverse Reactions: In adequate, well-controlled and uncontrolled studies, 1187 patients have received **Tri-Nasal™ Spray.**

Reviewer's comments: it is suggested that the sponsor specifies that these studies were

The adverse reactions summarized below, are based upon placebo controlled clinical trials mcg per day of Tri-Nasal™

Reviewer's comments: the above paragraph should be modified to include the experience with all placebo controlled trials.

Reviewer's comments: The paragraph should specify that the placebo used in the studies was the drug's vehicle. The submitted table (≥2%) and listing of adverse events observed infrequently (<2%) needs to be revised to include the data from all placebo controlled studies. In addition, it is suggested that the % of patients reporting adverse events be listed by All Tri-nasal, Tri-nasal 400 μg and placebo.

The sponsor should specify what were all the individual adverse event terms that are grouped under application site reaction in all placebo-controlled studies. If for a specific individual adverse event term, the % of patients reporting an adverse event is higher in the Tri-nasal treated patients than in patients receiving placebo, this should be stated.

DOSAGE AND ADMINISTRATION

[redacted]

Reviewer's comments: There are no placebo controlled studies that support the efficacy of the suggested dosing regimen after the desired effect is obtained.

APPEARS THIS WAY
ON ORIGINAL

14. RECOMMENDED REGULATORY ACTION

Assuming that the chemistry issues are appropriately resolved and that the characteristics of the to-be marketed pump are supported by comparative data from the unit pumps used in the pivotal clinical studies, the efficacy of Tri-nasal for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in patients 12 years of age and older is supported for the following doses by the following studies: Tri-nasal 200 μg qd (Studies 100-309 and 100-305), Tri-nasal 400 μg qd (Studies 100-309 and 100-204) and Tri-nasal 200 μg bid (Study 0501). In general the results of these four studies do not support the efficacy of the Tri-nasal formulations for the relief of

Pending the resolution of the outstanding review issue regarding Study 1-0501 that studied Tri-nasal's effect on the HPA axis, the conducted clinical program for this NDA and the safety data from the approved and marketed drugs Nasacort and Azmacort can support the safety of a daily dose of Trinasal of up to 400 μg per day for the indications of seasonal and perennial allergic rhinitis in patients 12 years of age and older.

15. RECOMMENDATIONS TO THE SPONSOR:

An updated proposed labeling was submitted on the correspondence, N (EL), dated 4/29/96. At the time of this review the reviewer has genral comments on selected areas of the labeling that could be communicated to the sponsor after a regulatory action is taken.

PHARMACODYNAMICS:

Reviewer's comments: the clinical study 100-204 does not support the claim for topical effect for Tri-nasal. The previous paragragh and sentence should be deleted

A topical effect for Tri-nasal 400 μg vs Kenalog 4 mg IM was not demonstrated in this 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.

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. Therefore, the efficacy of Tri-nasal could be considered to be secondary to a higher systemic exposure rather than to a local topical effect.

Study 100-104, page 067, vol 4.1

	Trinasal 400	Kenalog 4 mg IM
C max	1.91 ng/ml	0.40 ng/ml
AUC_{0-168}	33.22 ng•h/ml	44.89 ng•h/ml
AUC_{0-12}	6.92 ng•h/ml	3.22 ng•h/ml
T_{max}	0.36 h	18.67 h

In this study the difference in onset of action for Trip-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.

Reviewer's comments: It is recommended that the above paragraph be modified to include that:

CLINICAL TRIALS: The efficacy of **Trip-Nasal™ Spray** has been evaluated in 746 patients with seasonal or perennial allergic rhinitis who completed 8 controlled clinical trials.

Reviewer's comments: In the correspondence dated 7/1/96, there are a total of seven placebo controlled studies. The total number of Tri-nasal treated patients in these studies, as listed in the 7/1/96 submission is 683. Please clarify and modify above paragraph accordingly.

In total, 1187 patients have been treated with **Trip-Nasal™ Spray** in . Three adequate and well controlled multi-center trials involving 541 patients with seasonal allergic rhinitis who received doses of **Tri-Nasal™ Spray** ranging from 50 mcg to 400 mcg once daily were conducted. The results showed that patients who received

Reviewer's comments:

[ ]

2. The efficacy of the mcg dose was supported by only one study 100-305 and therefore is not an indicated dose.

3. The labeling should specify what were the cardinal symptoms of seasonal allergic rhinitis that were supported by the pivotal clinical studies.

INDIVIDUALIZATION OF DOSAGE:
Dosing of Tri-Nasal™ Spray should be individualized since there are many variables that determine clinical response. These variables include the degree of patient allergy, degree of pollen exposure,

A starting dose of 200 mcg (2 sprays/nostril) once daily is recommended for most patients.

Reviewer's comments: The stated onset of action for 200 μg dose is not supported by the data in study 100-309. In the analysis for study 100-309, of the patient's symptom severity index for Treatment Day 1 and 2 (Intent to Treat)- Table I1 in vol 6.1, nc statistically significant differences were observed between Tri-nasal 200 μg and placebo for Day 1 or Day 2. The following

statement should be modified or deleted:

After symptoms have been brought under control

Reviewer's comments: A was not studied in any of the placebo controlled studies. Study 100-307 was an open label study. The following statement should be modified or deleted:

Adverse Reactions: In adequate, well-controlled and uncontrolled studies, 1187 patients have received **Tri-Nasal™ Spray**.

Reviewer's comments: it is suggested the labeling specifies that these studies were

The adverse reactions summarized below, are based upon placebo controlled clinical trials mcg per day of Tri-Nasal™

Reviewer's comments: the above paragraph should be modified to include the experience with all placebo controlled trials.

Reviewer's comments: Please specify that the placebo used in the studies was the drug's vehicle. The submitted table (≥2%) and listing of adverse events observed infrequently (<2%) needs to be revised to include the data from all placebo controlled studies. In addition, it is suggested that the % of patients reporting adverse events be listed by All Tri-nasal, Tri-nasal 400 μg and placebo.

Please state what were all the individual adverse event terms

that are grouped under application site reaction in all placebo-controlled studies. If for a specific individual adverse event term, the % of patients reporting an adverse event is higher in the Tri-nasal treated patients than in patients receiving placebo, this should be stated.

DOSAGE AND ADMINISTRATION

Reviewer's comments: There are no placebo controlled studies that support the efficacy of the suggested dosing regimen after the desired effect is obtained; these statement should be deleted.

cc: Orig NDA 20 120
Div File
HFD-570 Sanchez-Delgado
HFD 570 Barnes

APPEARS THIS WAY
ON ORIGINAL

Appendix 1 to the Integrated Safety Summary.

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. The narratives of the cases submitted were reviewed. A reviewer's summary of these cases follow.

Tri-nasal 200 μg

pyuria: Study 100-104 Pt.# 0006 and Study 3-0501, Pt.# 0102
Initial u/a 6-10 wbc/hpf repeat u/a lower count.

Tri-nasal 400 μg

herpes simplex: Study 100-309, Pt.# 0608 and Study 100-307, Pt.# 0236
fungal dermatitis: Study 100-307 Pt.# 0120-tinea versicolor-prior hx; Pts.# 0312 and 0415-ringworm; the onset for the ringworm described for Pts.# 0312 and 0415 was > 42 days after the study drug had been initiated, there was no previous hx and no other concomitant drug were listed. These patients were treated and recovered.

contact dermatitis: Study 100-307, Pts.# 0128, 0822 and 1001
The exposure in Pt. # 0822 was to poison ivy, and in Pt. #1001 the suspected exposure was to suntan lotion. In Pt. # 0128 the involved areas were the cheeks and around the eyes and the cause was unknown.

lipoma on back: Study 100-307, Pt.# 0223-
The mass was found to be a lipoma after surgical removal. It was originally noted 6 weeks after study initiation.

positive skin test for TB: Study 100-307, Pt.# 0319
This patient had the record in the CRF of a positive skin test after he was in the study, the reason for having a TB test done was not given. The patient was asymptomatic, and had a negative chest-X ray. The patient was started on INH. Although the screening hx was negative for hx of tuberculosis, it is unknown what was the status of the TB test prior to receiving the study drug.

periodontal abscess: Study 100-307, Pts.#1017 and 1232
Pt.# 1017 had neg hx. of periodontal disease at screening and had a root canal for an abscessed tooth in the fourth week of study drug treatment. Pt.# 1232 had the abscess diagnosed the first day on study drug.

hematuria: Study 100-307, Pts.# 0125 and 0516
Patient 0125 had reported in the diary, "hematuria CT scan". This was transcribed to the CRF without comments. The severity was described as mild, the finding as not drug related with no action taken and the outcome reported as recovered. There was no history for kidney disease at screening and the urinalyses both at screening and final evaluation were negative for blood. The patient was dropped from the study due to treatment failure, after 28 days of treatment with study drug.

Patient 0516 had microscopic hematuria with 3-5 RBCs and +1 occult blood at screening with negative history for kidney disease. The patient dropped from the study due to headache after two weeks on study drug. The final u/a was similar to the screening one and the patient was referred to the private physician to rule out kidney disease.

nephritis: Study 100-307, Pt.# 0110
Agree with the sponsor that this episode described as nephritis appears to have been a cystitis.

osteoporosis: Study 100-307, Pt.# 0804
41 y/o patient with neg screening hx was diagnosed to have osteoporosis of the neck by the private physician, 2 1/2 mo after study drug initiation based on an x ray.

CNS neoplasm: Study 100-307, Pt.# 0123
The CNS neoplasm was a neuroma of the left foot present prior to treatment.

Hypotension: Study 100-307, Pt.# 1211
This was one of the symptoms recorded by a patient that underwent laparotomy due to significant bleeding during a laparoscopy procedure. The patient had hx of endometriosis.

Syncope: Study 100-307, Pt#. 0208
The episode of syncope is not clear. The patient had hx of reactive hypoglycemia". The episode was reported as severe and described as "altered consciousness". Even though the patient was referred to his physician for an EEG, a follow EEG was not reported.

Gout: Study 100-307, Pts. #1528 and #208
Both patients had hx of gout prior to study initiation.

amblyopia: Study 100-307, Pt.# 0607
This term was used to describe "blurry vision" for 2 months after having been on study medication for 3 months. The episode was reported as mild, of unknown etiology and required no action. Patient recovered after two months. This episode was associated with a report of mucus in the eye at the time of onset. The sponsor interprets this episode as conjunctivitis.

angioedema: Study 100-307, Pt.# 0214
Angioedema of the lip and urticaria, for 2-3 weeks, about three months after study drug initiation. Since the patient had to be treated with prednisone she was dropped from the study.

photosensitivity: Study 100-305, Pt.# 0328 and Study 100-307, Pt.# 0915
According to the sponsor, these patients had sunburn and the episode was coded as photosensitivity.

pneumonia: Study 100-307, Pt.#1513
A patient had pneumonia, 4-5 months after study drug initiation. He was treated with antibiotics and recovered.

Tri-nasal 800 μg

CNS depression: Study 1-0501, Pt.# 0019
This was a 33 y/o female that took part in the HPA axis study. This was the term used to code slow reactions. This episode was associated with complaints of being tired, light headed and having headaches and dizziness on an intermittent basis.

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ON ORIGINAL

Appendix 2 to Integrated Safety Summary

Serious Adverse Events

There was one serious event reported for study 100-309, patient 0618. This case was included in the safety review of the 100-309 study report.

Protocol 100-307

#0223, T400, 40WF, D/c after 2 mo Rx. This patient started treatment on 4/1/93, the onset of adverse event -lipoma, was on 5/4/93. Tri-nasal dose had been titrated to 200 after 1 wk of treatment, and down to 100 after 2 wks of Rx. The screening physical exam does not describe any abnormality in the skin, at the time of the last visit on 6/2/93, the investigator recorded large 20 x10 cm mass subcutaneous, left subcapsular area, CRF-page 077, vol 4.152. The CRF also records the use of Chlorpheniramine as a rescue medication for 7 days during the first mo of Rx, acetaminophen 1000mg/day for headache on a daily basis, and a one time use of ibuprophen. After excision the ISS, vol 4.10, reports that the mass was a 10x7x2.5 cm lipoma.

#0415, T400, 32WF, 9 wks Rx with study drug, D/c due to severe abdominal pain on 5/26/93, patient was hospitalized. Initiated Rx on 3/16/93. Ringworm Dx 4/7/93, from 5/4/93 to 5/23/93 on Grisactin for ringworm. On 5/25/93 abd pain-used Toradol. Two weeks after withdrawal pt had a diagnostic laparoscopy. No evidence of endometriosis was found. The peritoneal biopsy showed no other diagnostic features other than hemorrhage. Pain resolved two wks after laparoscopy.

#031, T400, 41WF, 2 months of Rx with study drug, D/C due to hospitalization for severe abdominal pain. Rx started 4/19/93. Patient hospitalized on 6/11/93. Trinasal titrated down to 200 after 1 mo of Rx. Patient had a course of Septra for UTI (4/21/93 to 4/27/93, and received Demerol on 5/9/93 for pain from kidney stone. Patient had been on Desyrel for depression. The CRF does not record what was found during the hospitalization. The final visit and patient status was dated 6/17/93.

#1211, T 400, 34WF, D/c treatment because of laparotomy done after severe bleeding during for elective laparoscopy for endometriosis (in-hospital procedure). The patient had been on study drug for 4 mo. Treatment initiated on 3/18/93 and continued until 8/16/93. Hospitalization : 7/16/93 to 7/18/93. Patient had prior hx of endometriosis and had laparoscopy done before. Trinasal was titrated down to 200 after 1 wk, down to 100 after 2 weeks, back to 200 after 1 month and down to 100 after 2 months.

Drop-outs due to adverse events

The cases of patients that discontinued the study due to adverse events in studies 1-0501, 0501, 100-204, 100-305 and 100-309 were included as part of the safety review of the individual studies.

Protocol 0501

Patient 1675 (Trinasal 200 QD)- 41 y/o wf-**sinus infection**-Visit 5, originally thought it was monilia- it grew Staph in culture - pt was hypothyroid prior to study.

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Protocol 3-0501

#113, Placebo-25, WM- 2 weeks of treatment, bilateral septal excoriations-epistaxis moderate was noted after 3 days.

#118, Placebo-23-WF-severe migraine-change in oral contraceptive 2 wks prior to onset of AE.

Protocol 4-0501

#8, T100, 40BF, 1 wk of study drug, **sinusitis**- antibiotics for sinusitis were not allowed in protocol and patient was D/c.

#31,T200, 32WM, 1 wk Rx, sore throat due to URI.

Protocol 100-307

#104, T400, 26WF, **URI**, strept throat requiring antibiotics (Amoxicillin), D/c after 5 wks of Rx. Trinasal titrated down to 200 after 1 mo of Rx.

#107, T400, 30WF, 1 mo study Rx drug, **sinusitis** needing antibiotics.

#109, T400, 31WF, 3.5 weeks RX, contact dermatitis face- cheeks and eyes, cause unknown, required topical steroid. In phys. exam cold sores on upper lip and contact dermatitis in face.

#110, T400, 31 WF, 19 wks Rx, epistaxis moderate, preceded by excoriations [illegible], nasal-tinged mucus (>3 mo), epistaxis 1 wk.

#115, T400, 42WF, 7 week Rx, headache associated with hypertension. This patient also had diagnosis of anoxic eye ulcer-"from prolonged use of contacts" CFR page 034-vol 4.152. This patient titrated to 200 after 17 days and to 100 after 1 mo.

#117, T400, 23WF, 4 mo Rx, treatment initiated on 4/22/93 with study drug. The last bottle was dispensed on 5/21/93, page 127 CRF, vol 4.152. D/C due to asthma exacerbation that began 9 wks after RX was started. It required a burst of steroids; given on 6/15/93. On final exam, 8/23/93, recorded cold sore of upper lip and mild erythema of the conjunctiva, lungs were recorded as normal, CFR p.126, vol 4.152. Other problems listed in the narrative were from the patient's past medical hx:bursitis, infected ankle, chicken pox, bronchitis and asthma. Nearsightedness diagnosed in 1992, pt. used corrective glasses. At the time of the study the patient was using prn use of methocarbamol and difuorophenyl salicylic acid for bursitis, and prn albuterol for asthma.

#119, T400, 19WF, 19 wk Rx, D/C due to positive TB skin test (8/93), neg chest X ray, started on INH. Study drug initiated on 4/30/93. Pt was titrated down to 200 after aprox 2 mo Rx.

#412, T400, 49WF, 5 week Rx, no dose reduction recorded in CFR, D/C due to eye infection, swelling and tearing. Study drug initiated 3/22/93. According to CRF p247, vol 4.152, on 4/27/93-final evaluation, WBC count 11.4., neutrophils 9.2, segs 81, GGT 73-**bacterial eye infection**. Antibiotic Rx initiated on 4/27/93.

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#426, T400, 46WM, 17 wks of Rx, **sinusitis** (severe), req Rx with erytromycin. WBC 11.7x10³ and absolute neutrophils 8.7x10³. After 2 wks of Rx initiation, Trinasal reduced to 200 μg. Improvement of symptoms until 6 days before antibiotics started.

***Pt of Dr. ——— (CRF, vol 4.152-p.354-406) not of Dr. ——— as it is stated in page 069 vol 4.10

#430, T400, 46 y/o WF, **URI** after 5 mo of Rx. This respiratory infection began after 2 mo of Rx, for which patient was D/C (patient received an **antibiotic-amoxicillin**) from the study at 5 months. Tri-nasal lowered to 200 after 1 mo of Rx, and then to 100 after 2 mo of Rx, then to 200 after 4 mo Rx.

#510, T400, 44 WM, **bronchitis** after 1 mo of study drug, patient had to be discontinued because he needed antibiotics (amoxicillin and phenergan) started 11 days after starting study drug.

#516, T400, 23WF, after 2 weeks of Rx, D/C study due to headaches (mild throbbing 30 min after study administration-not every day). The Trinasal was reduced to 200 after 1 week of Rx. Patient chose to D/C. Mild asthma exacerbations were noted on three separate days, while on study drug, but were associated with allergen or irritant exposures.

#519, T400, 32WM, elevated GGT and SGPT after 2 wks of study drug.
screening: SGPT 51 U/L (N:0-48)
GGT 108 U/L (N: 0-64)
SGOT:NL
1 wk later: SGPT 68
GGT 117
2 wks after SGPT 52
GGT 102
Investigator: moderate severity enzyme elevation and unrelated to study drug; patient d/c.

#615, T400 31WF, D/C study, nasal burning and nasal cracking after 1 wk of week of Rx. Pt had total bilirubin =1.9, at screening (3/31/93), and 1.7 on D C (4/15/93).

#618, T400, 41WF, sx of fluid accumulation in inner ear with sx of facial pain, (?sinus infection) CAT scan found sinus fluid (date not given); adverse events record sinus infection for 1 day. D/c after 9 wks of Rx. Lower to 200 at 3 wks and then back up to 400 at 4.5 weeks.

#803, T400, 49WF, **bronchitis/sinusitis** after 5 mo of Rx with study drug. Lowered to 200 in 1 wk and to 100 after 1 mo of treatment. ——— for Rx.

#816, T400, 26WF, **URI requiring antibiotics**. D/c after 3 mo of treatment. Down to 200 after 17 days, down to 100 after 1 mo treatment. Received two courses of antibiotics (10 days) but patient was D/c as per sponsor instruction after the second course of antibiotics.

#817, T400, 39WF, **URI requiring antibiotics.**, D/C after 3.5 mo Rx with study drug. Lowered to 200 after 22 days and to 100 after 1 mo.

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#833, T400, 45WF, **bronchitis** requiring antibiotics (Augmentin), d/c after 3.5 mo of Rx with study drug. Lowered to 200 after 10 days of Rx, and to 100 after 3 mo of treatment.

#905, T400, 19WF, pain ("sharp pains in nose which radiate into forehead and create persistent numbing and stinging"-"worsening over time", vol 4.154, page 084 and 099) and numbness in nose and forehead after study administration. D/c after 1 mo of treatment. Cold sore in mouth, previous hx and hx of use of Zovirax.

#910, T400, 34WF, severe tearing, swelling and itching in both eyes after 1 week of Rx. Trinasal dose was not lowered.

#914, T400, 34HM, severe headaches; D/C after 2 weeks on study drug. Dose lowered to 200 after 1 wk of treatment.

#924, T400, 24WF, sore nasal spot and scab; D/C after 11 wks of Rx. Dose lowered to 200 after 1 wk, up to 400 after 2 wks of Rx, and down to 200 after 4 wks of Rx.

#1001, T400, 49WF, rash-contact dermatitis-sunscreen, face, upper torso, legs, arms and face. D/c after aprox 3 mo of starting Rx.

#1020, T400, 48WF, glucose levels elevated after 1 week on study drug. Screening values: glucose 210, cholesterol 278, after 1 wk: glucose 193 and cholesterol 275. One week after stopping Rx, glucose was 127 and cholesterol 198.

#1102, T400, 34WF, **URI requiring antibiotics**; D/c after 6 wks of starting Rx. Titrated down to 200 after 9 days of Rx. PMH of prn asthma, on final exam expiratory wheezing. Nasal burning (lasts 5 min after dose) also reported.

#1112. T400, 28WF, **sinusitis** requiring antibiotics; D/c after 6 wks of Rx with study drug. Titrated down to 200 after 1 month and back to 400 after 2 mo. Pt was D/c after 2.5 mo of starting Rx.

1123, T400, 18WF, **sinusitis** requiring antibiotics, D/c after 4 mo of treatment with study drug. Titrated down to 200 after 10 wks.

#1220, T400, 34WM, **sinusitis** requiring antibiotics, D/c after 5 mo of treatment with study drug. Titrated down to 200 after 1 week and down to 100 after 2 weeks. WBC 12.1, neutrophils 8.59 eosino abs. 0.74 thou/mcl.

#1227, T400, 49WM, intolerable gagging, D/C after 2 wks of Rx. Titrated to 200 after 1 wk of Rx.

#1304, T400, 33 WM, acute **sinusitis and URI** (Augmentin), D/c after 5 mo of Rx with study drug. Pt. stayed at 400 through the study. Nasal burning initially but after 1 mo mostly an irritant.

#1321, T400, 41WF, acute **bronchitis** (purulent sputum and diffuse wheezing (Amoxicillin), D/C after 20 wks of Rx with study drug. Titrated down to 200 after 1 wk, down to 100 after 1 mo, back to 400 during wk 7 and down to 200 at wk 8. No prior hx of asthma.

#1329, T400, 21WF, severe sneezing after study drug, burns nose, D/c study

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after 6 wks of Rx with study drug. Titrated down to 200 after 1 wk and back to 400 after 1 mo.

F140I, T400, 28WF, **sinus infection** needing antibiotics, D/c after 19 days of Rx with study drug-allergies did not get better.

APPEARS THIS WAY
ON ORIGINAL

Appendix 3 - Biometrics Addendum Review by Dr. Ted Guo

APPEARS THIS WAY
ON ORIGINAL

Adverse Events by COSTART Preferred Terms
In All SAR and PAR Placebo-Controlled Studies
Protocols 100-309, 100-305, 100-204, 4-0501, 0501, 1-0501, and 3-0501
Tri-Nasal and Placebo Treatments
All Patients

COSTART Event	All Tri-Nasal	Placebo	Tri-Nasal (total daily dose)			
			50 mcg	100 mcg	200 mcg	>=400 mcg
Total Number of Patients	683	345	142	27	204	310
HEADACHE	196 (28.7)	82 (23.8)	57 (40.1)	14 (51.9)	46 (22.5)	79 (25.5)
APPLICATION SITE REACTION	70 (10.2)	46 (13.3)	14 (9.9)	0 (0.0)	14 (6.9)	42 (13.5)
PHARYNGITIS	58 (8.5)	20 (5.8)	14 (9.9)	3 (11.1)	19 (9.3)	22 (7.1)
PAIN	25 (3.7)	11 (3.2)	8 (5.6)	3 (11.1)	6 (2.9)	8 (2.6)
RHINITIS	24 (3.5)	20 (5.8)	5 (3.5)	0 (0.0)	6 (2.9)	13 (4.2)
BACK PAIN	21 (3.1)	7 (2.0)	5 (3.5)	1 (3.7)	7 (3.4)	8 (2.6)
DYSMENORRHEA	16 (2.3)	6 (1.7)	5 (3.5)	1 (3.7)	4 (2.0)	6 (1.9)
EPISTAXIS	16 (2.3)	9 (2.6)	7 (4.9)	0 (0.0)	0 (0.0)	9 (2.9)
ASTHMA	14 (2.0)	4 (1.2)	4 (2.8)	1 (3.7)	2 (1.0)	7 (2.3)
COUGH INCREASED	14 (2.0)	5 (1.4)	3 (2.1)	1 (3.7)	4 (2.0)	6 (1.9)
DYSPEPSIA	12 (1.8)	1 (0.3)	0 (0.0)	1 (3.7)	6 (2.9)	5 (1.6)
NAUSEA	10 (1.5)	2 (0.6)	2 (1.4)	0 (0.0)	2 (1.0)	6 (1.9)
ALLERGIC REACTION	9 (1.3)	4 (1.2)	2 (1.4)	0 (0.0)	2 (1.0)	5 (1.6)
CONJUNCTIVITIS	9 (1.3)	3 (0.9)	1 (0.7)	0 (0.0)	4 (2.0)	4 (1.3)
ACCIDENTAL INJURY	8 (1.2)	4 (1.2)	2 (1.4)	0 (0.0)	4 (2.0)	2 (0.6)
ASTHENIA	8 (1.2)	3 (0.9)	0 (0.0)	0 (0.0)	3 (1.5)	5 (1.6)
FLU SYNDROME	8 (1.2)	4 (1.2)	3 (2.1)	0 (0.0)	1 (0.5)	4 (1.3)

Adverse Events by COSTART Preferred Terms

In All SAR and PAR Placebo-Controlled Studies

Protocols 100-309, 100-305, 100-204, 4-0501, 0501, 1-0501, and 3-0501

Tri-Nasal and Placebo Treatments

All Patients

COSTART Event	All Tri-Nasal	Placebo	Tri-Nasal (total daily dose)			
			50 mcg	100 mcg	200 mcg	>=400 mcg
Total Number of Patients	683	345	142	27	204	310
MYALGIA	8 (1.2)	6 (1.7)	3 (2.1)	0 (0.0)	2 (1.0)	3 (1.0)
RASH	7 (1.0)	0 (0.0)	2 (1.4)	0 (0.0)	1 (0.5)	4 (1.3)
CHEST PAIN	6 (0.9)	2 (0.6)	2 (1.4)	0 (0.0)	2 (1.0)	2 (0.6)
GASTROENTERITIS	6 (0.9)	1 (0.3)	0 (0.0)	0 (0.0)	3 (1.5)	3 (1.0)
TASTE PERVERSION	6 (0.9)	1 (0.3)	0 (0.0)	0 (0.0)	3 (1.5)	3 (1.0)
DIARRHEA	5 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.0)	2 (0.6)
FEVER	5 (0.7)	3 (0.9)	1 (0.7)	0 (0.0)	0 (0.0)	4 (1.3)
NECK PAIN	5 (0.7)	3 (0.9)	1 (0.7)	2 (7.4)	2 (1.0)	0 (0.0)
URTICARIA	5 (0.7)	0 (0.0)	3 (2.1)	0 (0.0)	0 (0.0)	2 (0.6)
ABDOMINAL PAIN	4 (0.6)	1 (0.3)	1 (0.7)	0 (0.0)	2 (1.0)	1 (0.3)
EAR PAIN	4 (0.6)	2 (0.6)	2 (1.4)	0 (0.0)	1 (0.5)	1 (0.3)
INFECTION	4 (0.6)	1 (0.3)	0 (0.0)	1 (3.7)	2 (1.0)	1 (0.3)
PRURITUS	4 (0.6)	2 (0.6)	2 (1.4)	0 (0.0)	1 (0.5)	1 (0.3)
ANXIETY	3 (0.4)	0 (0.0)	1 (0.7)	1 (3.7)	0 (0.0)	1 (0.3)
BRONCHITIS	3 (0.4)	2 (0.6)	1 (0.7)	0 (0.0)	1 (0.5)	1 (0.3)
DIZZINESS	3 (0.4)	1 (0.3)	1 (0.7)	0 (0.0)	0 (0.0)	2 (0.6)
DYSPNEA	3 (0.4)	2 (0.6)	2 (1.4)	0 (0.0)	1 (0.5)	0 (0.0)

Adverse Events by COSTART Preferred Terms

In All SAR and PAR Placebo-Controlled Studies

Protocols 100-309, 100-305, 100-204, 4-0501, 0501, 1-0501, and 3-0501;

Tri-Nasal and Placebo Treatments

All Patients

COSTART Event	All Tri-Nasal	Placebo	Tri-Nasal (total daily dose)			
			50 mcg	100 mcg	200 mcg	>=400 mcg
Total Number of Patients	683	345	142	27	204	310
NERVOUSNESS	3 (0.4)	3 (0.9)	1 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)
SINUSITIS	3 (0.4)	11 (3.2)	0 (0.0)	1 (3.7)	1 (0.5)	1 (0.3)
URINARY TRACT INFECTION	3 (0.4)	2 (0.6)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)
VOICE ALTERATION	3 (0.4)	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)
VOMITING	3 (0.4)	3 (0.9)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.6)
ACNE	2 (0.3)	4 (1.2)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
CONSTIPATION	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
CYSTITIS	2 (0.3)	3 (0.9)	1 (0.7)	1 (3.7)	0 (0.0)	0 (0.0)
EAR DISORDER	2 (0.3)	4 (1.2)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
EYE PAIN	2 (0.3)	1 (0.3)	0 (0.0)	1 (3.7)	1 (0.5)	0 (0.0)
INSOMNIA	2 (0.3)	2 (0.6)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
LACRIMATION DISORDER	2 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
PHOTOSENSITIVITY REACTION	2 (0.3)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (0.3)
ARTHRALGIA	1 (0.1)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
ARTHRITIS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
CARCINOMA OF MOUTH	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
CERVIX DISORDER	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse Events by COSTART Preferred Terms

In All SAR and PAR Placebo-Controlled Studies

Protocols 100-309, 100-305, 100-204, 4-0501, 0501, 1-0501, and 3-0501

Tri-Nasal and Placebo Treatments

All Patients

COSTART Event	All Tri-Nasal	Placebo	Tri-Nasal (total daily dose)			
			50 mcg	100 mcg	200 mcg	>=400 mcg
Total Number of Patients	683	345	142	27	204	310
CHILLS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
CNS DEPRESSION	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
COLITIS	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
DEHYDRATION	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
DRY EYES	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
DRY MOUTH	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
DRY SKIN	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
ECCHYMOSIS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
EMOTIONAL LABILITY	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
ENDOMETRIAL DISORDER	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
EUPHORIA	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
EYE DISORDER	1 (0.1)	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
GASTRITIS	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
GASTROINTESTINAL HEMORRHAGE	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
HANGOVER EFFECT	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
HEMORRHAGE	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
HYPERTONIA	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)

Adverse Events by COSTART Preferred Terms
In All SAR and PAR Placebo-Controlled Studies
Protocols 100-309, 100-305, 100-204, 4-0501, 0501, 1-0501, and 3-0501:
Tri-Nasal and Placebo Treatments
All Patients

COSTART Event	All Tri-Nasal	Placebo	Tri-Nasal (total daily dose)			
			50 mcg	100 mcg	200 mcg	>=400 mcg
Total Number of Patients	683	345	142	27	204	310
HYPERVENTILATION	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
HYPESTHESIA	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
LAB TEST ABNORMAL	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
LARYNGITIS	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
LEUKODERMA	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
LUNG DISORDER	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
MALAISE	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
MIGRAINE	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
MOUTH ULCERATION	1 (0.1)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
MUCOUS MEMBRANE DISORDER	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
NASAL SEPTUM DISORDER	1 (0.1)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
PUPILLARY DISORDER	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
SOMNOLENCE	1 (0.1)	2 (0.6)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)
STOMACH ULCER	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
TACHYCARDIA	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
TINNITUS	1 (0.1)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
TONGUE DISCOLORATION	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Adverse Events by COSTART Preferred Terms

In All SAR and PAR Placebo-Controlled Studies

Protocols 100-309, 100-305, 100-204, 4-0501, 0501, 1-0501, and 3-0501

Tri-Nasal and Placebo Treatments

All Patients

COSTART Event	All Tri-Nasal	Placebo	Tri-Nasal (total daily dose)			
			50 mcg	100 mcg	200 mcg	>=400 mcg
Total Number of Patients	683	345	142	27	204	310
TOOTH DISORDER	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
UNEXPECTED BENEFIT	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
VAGINITIS	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
VASODILATATION	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
VESICULOBULLOUS RASH	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
WEIGHT GAIN	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
ABNORMAL VISION	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DEAFNESS	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ECZEMA	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
FACE EDEMA	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
FLATULENCE	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GASTROINTESTINAL DISORDER	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GENERALIZED EDEMA	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
INJECTION SITE PAIN	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
LEG CRAMPS	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MACULOPAPULAR RASH	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MOUTH NEOPLASIA	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse Events by COSTART Preferred Terms
In All SAR and PAR Placebo-Controlled Studies
Protocols 100-309, 100-305, 100-204, 4-0501, 0501, 1-0501, and 3-0501
Tri-Nasal and Placebo Treatments
All Patients

COSTART Event	All Tri-Nasal	Placebo	Tri-Nasal (total daily dose)			
			50 mcg	100 mcg	200 mcg	>=400 mcg
Total Number of Patients	683	345	142	27	204	310
NEURALGIA	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PARESTHESIA	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
RESPIRATORY DISORDER	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SWEATING	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

APPEARS THIS WAY
ON ORIGINAL