

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-120

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL

(Addendum)

JUL 22 1996

Date: _____

NDA#: 20-120
Applicant: Muro Pharmaceutical, Inc.
Name of Drug: Tri-Nasal Spray (triamcinolone acetonide)
Indication: Treatment of seasonal allergic rhinitis
Documents Reviewed: Study #100-309: Volumes 6.1-6.13, 10.1-10.2;
Study #100-305: Volumes 4.30-4.45;
Study #100-204: Volumes 4.16-4.29;
Study #0501: Volume 4.46; 2/20/96
Statistical Reviewer: Ted (Jiyang) Guo, DOB II/OEB, HFD-715
Medical Input: Ana Marie Saavedra, ODE II, HFD-570

**APPEARS THIS WAY
ON ORIGINAL**

This report was prepared to respond to questions raised by the reviewing medical officer, Dr. Ana Marie Saavedra on July 15, 1996, in her review of NDA 20-120. The questions were typed as the original before the answers. The questions were answered in the sequence of the questions.

Study No. 100-309

Question No. 1: Table 5A1, vol 6.1--Patient Diary--SSI
Why for the ITT population do the week 1 and 2 analyses include less than the ITT population for each group? i.e., Trinasal goes 94-93-90.

Answer: Based on the sponsor's data, this reviewer found that the following seventeen (17) patients did not have complete observations over the course of the study, or their observations were not fully reported. This reviewer also found that the sponsor's analyses were based on these non-missing data, which represented part of the entire ITT population. The following table lists these patients with their missing-observation status. The number of the missing data is consistent with the number of missing patients shown on Table 5A1, vol 6.1 of the NDA. For example, in the Tri-Nasal 200 µg group, one patient (ID #1204) was missing from the week-one observations. Therefore, the total in week one reduced to 93 from 94 at baseline. Four patients (ID #724, #1012, #1204, and #1205) were missing from the week-two observations. Therefore, the total in week two became 90, which was four less than the 94 at baseline. These cases are highlighted below. An asterisk indicates that the observation did not appear in the submitted data.

**APPEARS THIS WAY
ON ORIGINAL**

Study 10-309:

| | Patient id | SSI baseline | SSI week 1 | SSI week 2 |
|----------|------------|-----------------|---------------|---------------|
| Placebo | 321 | 7.571 | 3.500 | * |
| | 507 | 7.714 | 8.143 | * |
| | 701 | 6.286 | * | * |
| | 1001 | 6.286 | 9.000 | * |
| | 1216 | 9.571 | 5.667 | * |
| | 1224 | 5.714 | * | 2.429 |
| 200_ug | 724 | 7.429 | 8.429 | * |
| | 1012 | 6.429 | 9.000 | * |
| | 1204 | 4.429 | * | * |
| | 1205 | 3.667 | 2.857 | * |
| 400_ug | 508 | 6.000 | 7.000 | * |
| | 615 | 6.143 | 6.833 | * |
| | 928 | 6.143 | * | * |
| | 1009 | 6.571 | 6.000 | * |
| Nasacort | 231 | 6.286 | * | * |
| | 1113 | 6.286 | 7.000 | * |
| | 1325 | 6.429 | 4.200 | * |

Note that the number of the original patients was 377. As an experiment, this reviewer used the 361 nonmissing patients in week 2 and reanalyzed the SSI. In this analysis, the number of patients remained the same for the baseline, week 1 and week 2. The following are the comparative results.

| | | P-value |
|------------------------|--------|---------|
| Use 377 patients' data | week 0 | 0.822 |
| | week 1 | 0.002 |
| | week 2 | <0.001 |
| Use 361 patients' data | week 0 | 0.826 |
| | week 1 | 0.001 |
| | week 2 | 0.0001 |

The results for the two patient populations are similar. Based on this crude analysis, we may not expect a significant impact on the efficacy results due to these missing observations.

**APPEARS THIS WAY
ON ORIGINAL**

Question No. 2: Table 5G1, vol 6.1-Rhinorrhea. Treatment by site interaction on week 2. What dose Biometrics think about it?

Answer: For the symptom of rhinorrhea, the treatment-site interaction for week 2 was statistically significant ($p=0.0897$). The protocol-specified limit for the test of interaction was $\alpha=0.10$. It was recognized that the treatment-by-site interaction was statistically significant. Following the protocol, the sponsor did by-site analyses of treatment effect. At two of the 13 study centers, Bronsky (#3) and Lumry (#7), Tri-Nasal at dose level 200 μg and 400 μg daily and Nasacort at 440 μg daily demonstrated statistical superiority to the placebo. The sponsor reported these results on page 0063, vol 6.1.

Note that when the treatment-center interaction exists, one cannot describe the magnitude of the baseline adjusted mean difference between the drugs or dose levels without pointing out that it differs depending on which center is considered. In other words, when the treatment-site interaction is found to be significant, we may think that the difference between drugs varies significantly from one center to another. The sponsor's approach was correct. However, the sponsor did not suppress the p values shown on Table 5G1 (page 0131, vol 6.1), which were not of interest to us.

Question No. 3: Table 5E1, 5G1 vol 6.1-Itchy nose/throat/palate. Why does the overall P value for week 1 is not statistically significant when the P values for the comparisons of the individual active treatments versus placebo are statistically significant?

Answer: A usual order for examining the treatment effect is to test the overall treatment effect first. Then, when this effect is significant, pairwise comparisons are carried out for pairs of interest. The purpose for pairwise comparisons is to find out which pair(s) significantly contribute(s) to the overall significance. When the overall treatment effect is found to be not significant, the results from the pairwise comparisons may not be of interest to us. The phenomenon observed in this case may be explained by confounding factors within the patients. It would take more time to conduct an additional research.

Question No. 4: Table 5H1 vol 6.1-SSI for treatment Day 1 and 2. Why does this analyses have more patients on Day 1 and 2 for the 3 active treatment arms than at baseline?

Answer: This reviewer reviewed the sponsor's computer program, entitled "TABLE5H1.SAS." The number of patients for the baseline, day 1 and day 2 were calculated by merging several data files and by subsetting based on the values of variable called "DAY" which was calculated from the difference between variables DOD and RDATE. (The definitions of these calendar-date variables are not clear to the reviewer.) The data collection and recording process might have affected the numbers reported on Table 5H1. The following are the patients that did not have complete data from baseline to day 2 of the treatment period.

**APPEARS THIS WAY
ON ORIGINAL**

| group | patient id | center | baseline SSI | week 1 SSI | week 2 SSI |
|----------|------------|--------|--------------|------------|------------|
| Placebo | 701 | 7 | 4 | * | * |
| | 1224 | 12 | 6 | * | * |
| | 1425 | 14 | * | 6 | 6 |
| 200_ug | 217 | 2 | 5 | * | 7 |
| | 817 | 8 | * | 6 | 4 |
| | 1204 | 12 | 5 | * | * |
| | 1223 | 12 | * | 7 | 7 |
| | 1410 | 14 | * | 9 | 4 |
| | 1415 | 14 | * | 5 | 5 |
| | 1426 | 14 | * | 3 | 3 |
| 400_ug | 427 | 4 | 5 | 2 | * |
| | 1202 | 12 | * | 3 | 1 |
| | 1414 | 14 | * | 6 | 5 |
| | 1429 | 14 | * | 7 | 4 |
| Nasacort | 202 | 2 | * | 9 | 5 |
| | 231 | 2 | 4 | * | * |
| | 606 | 6 | * | 8 | 7 |
| | 1113 | 11 | 6 | 7 | * |
| | 1412 | 14 | * | 8 | 8 |
| | 1413 | 14 | * | 8 | 1 |
| | 1417 | 14 | * | 6 | 4 |

The asterisk represents missing observations. These patient records may explain why there are more patients in the day-one and day-two records than in the baseline records for the three treatment arms. For example, for the 200 μ g group, there are three more patients missing at the baseline than those missing on day one. Therefore, the difference in number of patients between baseline and day one is three (=93-90). It would take more time to carry out additional research to assess the effect of those missing data on the efficacy analysis.

Question No. 5: Table 6G1 vol 6.1-Physician SSI scores. Treatment by site interaction on week 2. What does biometrics think about it?

Answer: Please see the response to question No. 2.

Study No. 100-204

Question No. 6: Table 5A1 and Table 5G1 for patient's SSI scores, vol 17. Treatment by site interaction at baseline and at week 2. what does biometrics think about it?

Answer: Please see the response to question No. 2.

Question No. 7: Table 5G1, vol 4.17 for patient's individual symptoms. Why baseline was not used as a covariate for: sneezing-week 1; rhinorrhea-week 4; and nasal congestion-week 2? In these weeks there was also a treatment by site interaction. What does biometrics think about it?

Answer: If the treatment-baseline interaction is significant, then it is appropriate to fit an ANOVA model with treatment, center and treatment-center interaction as factors. This method was specified in the protocol. In this case, the measurements of the treatment effect are not comparable to the baseline-adjusted measurements.

For the second part of this question, please see the response to question No. 2.

**APPEARS THIS WAY
ON ORIGINAL**

Study 0501

Questions No. 8: Table 5A1-vol 4.31 patient's SSI. Why does the intent to treat population for week 1 has listed N=65, when at baseline N=64 for the 400 µg group?

Answer: Table 5A1, vol 4.31 actually belongs to study 100-305. The patient who did not have complete observations are listed as follows. The asterisk indicates missing observations.

| Study 100-305 | | | | | | | |
|---------------|------------|--------|--------------|------------|------------|------------|------------|
| GROUP | patient id | center | baseline SSI | week 1 SSI | week 2 SSI | week 3 SSI | week 4 SSI |
| Placebo | 133 | 1 | 4.4 | 3.5 | * | * | * |
| | 211 | 2 | 5.0 | 4.6 | 4.0 | * | * |
| | 234 | 2 | 6.7 | 6.7 | 9.4 | * | * |
| | 240 | 2 | 5.3 | 5.5 | 3.4 | * | * |
| | 307 | 3 | 8.8 | 7.7 | * | * | * |
| 50_ug | 116 | 1 | 5.6 | 4.6 | 2.0 | * | * |
| | 210 | 2 | 5.3 | * | * | * | * |
| | 216 | 2 | 7.1 | 5.3 | * | * | * |
| | 220 | 2 | 8.7 | * | * | * | * |
| | 236 | 2 | 5.0 | 1.5 | 1.0 | 0.1 | * |
| | 239 | 2 | 8.0 | * | * | * | * |
| | 242 | 2 | 7.1 | 6.3 | 0.0 | 3.9 | * |
| | 421 | 4 | 6.7 | 6.7 | 6.7 | * | * |
| 200_ug | 115 | 1 | 6.2 | 4.4 | 5.0 | * | * |
| | 150 | 1 | 7.8 | 4.9 | 4.0 | 3.0 | * |
| | 215 | 2 | 5.8 | 3.5 | * | * | * |
| | 231 | 2 | 4.2 | 1.0 | 0.4 | * | * |
| | 408 | 4 | 8.0 | 8.0 | * | * | * |
| | 502 | 5 | 8.0 | 5.9 | * | * | * |
| 400_ug | 219 | 2 | * | 3.3 | 1.1 | 2.0 | 0.3 |
| | 233 | 2 | 7.0 | 7.0 | * | * | * |
| | 310 | 3 | * | 4.1 | 4.7 | 3.6 | 2.1 |
| | 509 | 5 | 5.1 | 5.6 | * | 0.9 | * |
| | 601 | 6 | 5.0 | * | * | * | * |

For the patients in the 400 µg group, patients #219 and #310, who had week-one data, did not have baseline data. Patient #601, who had baseline data, did not have the week-one observation. This explains why the total in week one became 65, while at baseline the total was 64. The reasons for these missing observation are unknown to this reviewer. As mentioned before, it would require

more information about individual-patient information and take additional research to fully assess the effect of the missing values.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Question No. 9: Sample size calculation on page 023, vol 4.15. Please clarify: In the study report the sponsor cites having done two power calculations, one having greater than 80% power and another 60%. The 60% one was a retrospective power calculation for the AUC of the serum cortisol-by time plot at the final evaluation. Don't we usually look for 80% power? Could you please discuss.

Answer: In planning a study, usually 80% power is needed. Note that the estimation of power requires: the mean difference that one wishes to detect, the sample size, and the sample standard deviation. The sample size was planned based on 80% power for the first analysis. (This reviewer cannot verify this power calculation, because the standard deviation was not given 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 Area Under the Curve (AUC) of the serum cortisol-by-time plot at the final evaluation between Tri-Nasal 1600 µg and Prednisone was to be done, given the sample size of 5 in each group. One would not satisfy a planned study with a 60% power. If the second analysis is used in planning a study, the desired sample size would be at least 8 to guarantee an 80% power.

/S/ 7/22/96

, Ted (Jiyang) Guo, Ph.D.
Mathematical Statistician

Concur: Steve Wilson, Ph.D. /S/ 7/22/96

cc:

Archival NDA 20-120
HFD-570/Division file
HFD-570/GStrange
HFD-570/JJenkins,
HFD-570/MHimmel
HFD-570/ASaavedra
HFD-715/Division file, Chron
HFD-715/ENevius
HFD-715/SWilson
HFD-715/TGuo
TG/July 19, 1996/July 22, 1996
rev/c:\indas\nda20120_doc\addendum.wpd

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

DEC 20 1999

NDA Number: 20-120
Applicant: Muro Pharmaceutical, Inc.
Name of Drug: Tri-Nasal Spray (Triamcinolone acetonide)
Statistical Reviewer: Barbara Elashoff, M.S. (HFD-715)
Chemistry Reviewer: Chong-Ho Kim, Ph.D. (HFD-570)
Documents Reviewed: 11-01-99 (no volume number)

Summary of Review

- The sponsor proposes an — month expiration date based on 9 months of data.
- This review focuses on the parameters: Drug Product and Total Impurities.
- The data support a 16-month expiration date.

I. Introduction

Muro Pharmaceuticals has submitted 9-month stability data for Tri-Nasal Spray. The sponsor has proposed an — month expiration period. The reviewing chemist has requested Division of Biometrics to perform a statistical review and evaluation of the sponsor's stability data for each of the parameters listed below.

Table 1: Specifications

| Parameter | Specifications |
|------------------|----------------|
| Drug Product | No More Than — |
| Total Impurities | No More Than — |

II. Reviewer's Analyses

The statistical procedures described in the FDA Guidelines (February 1987) were applied to the stability data provided by the sponsor. The estimated expiration dates were calculated from the specifications limits and the two-sided 95% confidence intervals of the regression lines. The estimated expiration dating periods are listed in Table 2.

Table 2: Results of Analyses

| Test | Intercepts | Slopes | Estimated Expiration Date (months) | | |
|------------------|------------|----------|------------------------------------|-------------|-------------|
| | | | Batch 80712 | Batch 80812 | Batch 80912 |
| Drug Product | Separate | Separate | — | — | — |
| Total Impurities | Separate | Separate | — | — | — |

**STATISTICAL REVIEW AND EVALUATION
CLINICAL**

(Addendum No. 2)

Date: 08/22/96

| | |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NDA#: | 20-120 |
| Applicant: | Muro Pharmaceutical, Inc. |
| Name of Drug: | Tri-Nasal Spray (triamcinolone acetonide) |
| Indication: | Treatment of seasonal allergic rhinitis |
| Documents Reviewed: | Study #1-0501: Volumes 4.15 Response to FDA statistical questions for Tri-Nasal NDA, facsimile 6/24/96 Response to FDA statistical questions and inquiry of data listing #10 resubmission for Tri-Nasal NDA, facsimile 8/2/96 |
| Statistical Reviewer: | Ted (Jiyang) Guo, DOB II/OEB, HFD-715 |
| Medical Input: | Ana Marie Saavedra-Delgado, ODE II, HFD-570 |

**APPEARS THIS WAY
ON ORIGINAL**

Table of Contents

| | |
|---------------------------------------------------------------------------------|----|
| Summary | 1 |
| Objective | 2 |
| Introduction | 2 |
| Sponsor's Analyses of AUC and Peak Cortisol level and Reviewer's Comments | 4 |
| Analysis of Change from Baseline | 7 |
| Analysis of Treatment Effect | 7 |
| Reviewer's Comments on Analysis of AUC | 8 |
| Reviewer's Comments on Analysis of Peak Cortisol Level | 8 |
| Reviewer's Analyses Based on Unadjusted AUC | 9 |
| Reviewer's Analysis of AUC Change from Baseline | 9 |
| Reviewer's Analysis of Peak-Cortisol Change from Baseline | 10 |
| Reviewer's Additional Analyses Based on Adjusted AUC: (AUC*) | 10 |
| Conclusion | 13 |
| Appendix 1: SAS output (Analysis based on AUC*) | 16 |
| Appendix 2: SAS output (Analysis based on AUC) | 27 |

**APPEARS THIS WAY
ON ORIGINAL**

Summary

The analyses based on the changes (at day 43) from baseline (day 1) in AUC and peak cortisol level showed:

Unadjusted AUC

- The differences in **AUC** changes from baseline between prednisone and other drug/dose levels (i.e., Tri-Nasal at 400, 800 and 1600 µg and the placebo) were statistically significant.
- The differences in AUC changes from baseline among Tri-Nasal 400, 800 and 1600 and the placebo were not statistically significant.
- Numerically, the AUC decreased at day 43 as compared to those at baseline, for all treatment groups.
- The difference in AUC change between Tri-Nasal 1600 and prednisone was significant.
- The differences in **peak cortisol level** changes from baseline between prednisone and other drug/dose levels were statistically significant, with one exception—The difference between prednisone and Tri-Nasal 1600 was not significant.
- The differences in peak cortisol level changes from baseline among Tri-Nasal 400, 800 and 1600 and the placebo were not statistically significant.
- The difference in peak cortisol change between Tri-Nasal 1600 and prednisone was NOT significant.

Adjusted AUC

- The differences in AUC* among the drug/dose levels were not significant.
- The differences in peak cortisol levels* among the drug/dose levels were not significant.

This reviewer concluded the following: Analyses using the sponsor-defined formula showed that the use of prednisone significantly decreased AUC and peak cortisol level at day 43 from day 1, while no significant decrease in these parameters occurred with the use of Tri-Nasal (400, 800, and 1600 µg) and the placebo. Analyses using the starting-time adjusted formula suggested by the reviewing medical officer resulted in a modified conclusion. That is, the differences among the drug/dose groups were not statistically significant.

**APPEARS THIS WAY
ON ORIGINAL**

Objective

This report is to respond to a statistical inquiry from the reviewing medical officer, Dr. Ana Marie Saavedra-Delgado on July 22, 1996, in the review of study 1-0501, NDA 20-120. This statistical inquiry is focused on (1) the area under curve (AUC) of the cortisol level, and (2) the peak of the cortisol level, following the cosyntropin stimulation.

This reviewer was requested to analyze the above two outcome measures (AUC and peak cortisol level) based on the change in AUC and peak cortisol level from the baseline. The results were to be compared to those based on the original outcome measures reported by the sponsor in the NDA. Furthermore, in consultation with Dr. Saavedra-Delgado, this reviewer used both the sponsor-defined formula for the AUC calculation and a different formula suggested by the reviewing medical officer for comparison purposes.

In addition to the original NDA for study 1-0501, the following two additional documents related to this study were evaluated: (1) The sponsor's response of July 24, 1996 to the query by the above medical officer during a telephone conference on July 22, 1996, regarding the methodological background of AUC; and (2) The sponsor's response of August 2, 1996 to the inquiry by this reviewer during a telephone conference on August 1, 1996, with respect to the electronic data submission of data listing no. 10 for study 1-0501.

Introduction

The purpose of study 1-0501 was to evaluate the effect of Tri-Nasal on adrenocortical responsiveness among the participating patients with allergic rhinitis. This study was a single-center, randomized, double-blind, placebo controlled study. It was designed to evaluate the effect of Tri-Nasal (400, 800 and 1600 μg daily doses) on the change of cortisol level following a cosyntropin stimulation. Prednisone (10 mg daily) was used as the positive control. In this NDA, the rise and fall in cortisol concentration level following the cosyntropin stimulation during an eight-hour period on day 1 (baseline) and the same outcome on day 43 (the final evaluation) were recorded. The two endpoints of interest were: (1) AUC which was the area under the curve of cosyntropin-stimulated cortisol concentration level for a time span of 0-8 hours, and (2) the peak cosyntropin-stimulated cortisol concentration level during the same time span. A sketch of change in cortisol level is shown in Figure 1. Note that, the AUC was defined, by the sponsor, as the area between the cortisol concentration curve and the time axis (i.e., the total area of A and B); and the peak cortisol level was the distance from x to z, assuming that the curve

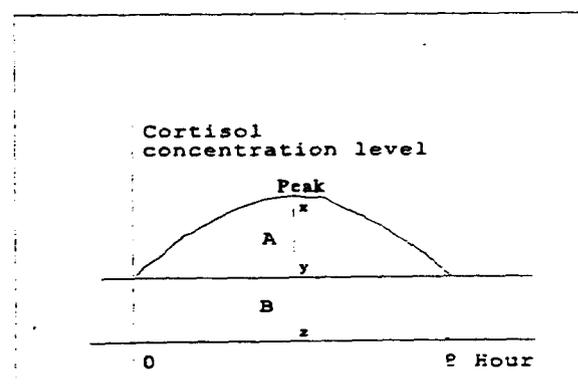


Figure 1. Cortisol concentration level

reached its peak (x). A different formula for the AUC calculation, suggested by Dr. Saavedra-Delgado, also was considered in this review. The modified AUC was the area (A) alone. In conjunction with this AUC, the peak cortisol level was the distance from x to y. The rationale for such a modification was to reduce the influence on AUC of the starting values, so that the treatment effect on the rise and fall of the cortisol curve would be better represented.

To differentiate the two formulae for the AUC, AUC* denotes the area (A) alone (Figure 1). The AUC* is called by this reviewer the adjusted (for hour=0) AUC in the following text. Likewise, an asterisk is used to signify an adjusted peak cortisol level (distance between x and y).

Twenty eight patients between the ages of 19-44 with a history of seasonal allergic rhinitis participated in this study. The numbers of patients assigned to the treatment groups and the number of patients measured on day 43 are listed on Table 1 below. Note that three patients were lost-to-follow-up at day 43.

Table 1. Number of Patients

| Day | Placebo | Prednisone | Tri-Nasal 400 | Tri-Nasal 800 | Tri-Nasal 1600 | Total |
|-----|---------|------------|---------------|---------------|----------------|-------|
| 1 | 8 | 5 | 5 | 5 | 5 | 28 |
| 43 | 6 | 5 | 5 | 5 | 4 | 25 |

In study 1-0501 of the NDA, the sponsor performed the following analyses on the raw outcome measures, the AUC and the peak cortisol concentration levels, for day 1 and day 43 (These analyses were based on unadjusted AUC and peak cortisol levels.):

- 1 Test the **overall treatment effect on AUC and peak cortisol**, for day 1 and day 43 separately;
- 2 Test the **differences between day 1 and day 43 for AUC and peak cortisol** within a selected treatment group;
- 3 **Pairwise comparisons** for differences in AUC and peak cortisol between the pairs of treatments. In addition,
 - 3.1 In the response to the FDA's inquiry of July 22, 1996, the sponsor presented: **Pairwise comparisons** using the change from baseline in AUC as the outcome measure;
 - 3.2 In the response to the FDA's inquiry on August 1, 1996, the sponsor reported: **Pairwise comparisons** using the change from baseline in peak cortisol as the outcome measure.

The following Table 2 summarizes the pairwise comparisons done by the sponsor and those analyzed by this reviewer.

Table 2. Summary of Analyses Done by the Sponsor and this Reviewer

| | Outcome Measure | Pairwise comparisons Based on | |
|-----------------------|----------------------|------------------------------------------|-------------------------------|
| | | Raw measures | Changes from baseline |
| Unadjusted | AUC | Original NDA and the response of 7/22/96 | Sponsor's response on 7/22/96 |
| | Peak Cortisol Level | Original NDA and the response of 8/2/96 | Sponsor's response on 8/2/96 |
| Adjusted (for hour=0) | AUC* | | This reviewer's analysis |
| | Peak Cortisol Level* | | This reviewer's analysis |

Sponsor's Analyses of AUC and Peak Cortisol level and Reviewer's Comments

The sponsor's statistical analyses are summarized in the following tables and figures. The numbers were quoted from study 1-0501, vol 4.15 of the NDA. Tables 3 and 4 describes the means for the AUC and peak cortisol levels for the drug/dose levels. The mean AUC values dropped at day 43 as compared to those at day 1, for all the groups. The mean peak cortisol levels increased at day 43 among the placebo group and the Tri-Nasal 400 µg group, while decreasing in the other groups. Prednisone appeared to have a significant drop from day 1.

Table 3. Mean (unadjusted) AUC for cortisol concentration levels

| Mean | Placebo | Prednisone | Tri-Nasal 400 | Tri-Nasal 800 | Tri-Nasal 1600 |
|--------|---------|------------|---------------|---------------|----------------|
| day 1 | 341.2 | 298.9 | 310.1 | 347.8 | 311.3 |
| day 43 | 332.9 | 189.2 | 289.7 | 332.4 | 278.6 |
| change | -8.3 | -109.7 | -20.4 | -15.4 | -32.7 |

Table 4. Mean (unadjusted) peak cortisol levels

| Mean | Placebo | Prednisone | Tri-Nasal 400 | Tri-Nasal 800 | Tri-Nasal 1600 |
|--------|---------|------------|---------------|---------------|----------------|
| day 1 | 55.4 | 49.7 | 48.8 | 58.1 | 50.3 |
| day 43 | 57.1 | 34.7 | 49.1 | 57.6 | 45.8 |
| change | 1.4 | -15 | 0.3 | -0.5 | -4.5 |

The following Figures 2 and 3 depict the cortisol levels that determine the AUC for day 1 and day 43. The Y-axis represents the mean cortisol levels.

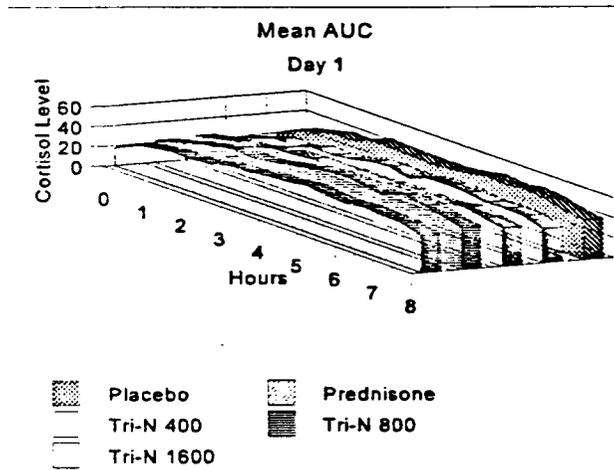


Figure 2. Unadjusted means at day 1

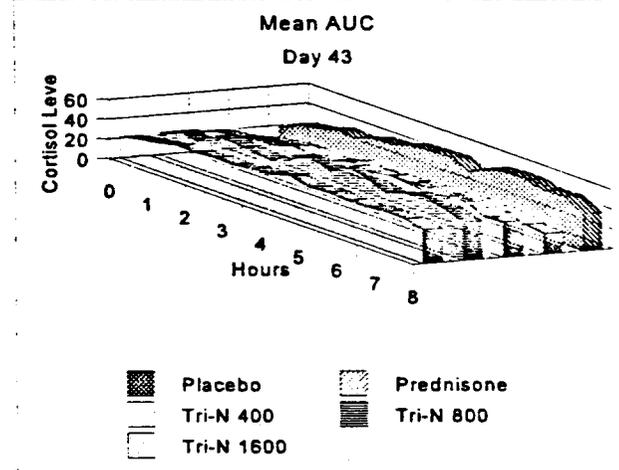


Figure 3. Unadjusted means at day 43

The following Figures 4 and 5 depict the adjusted AUC* at day 1 and day 43. In this review, the details based on AUC* are reported in a later section entitled "Reviewer's Analyses."

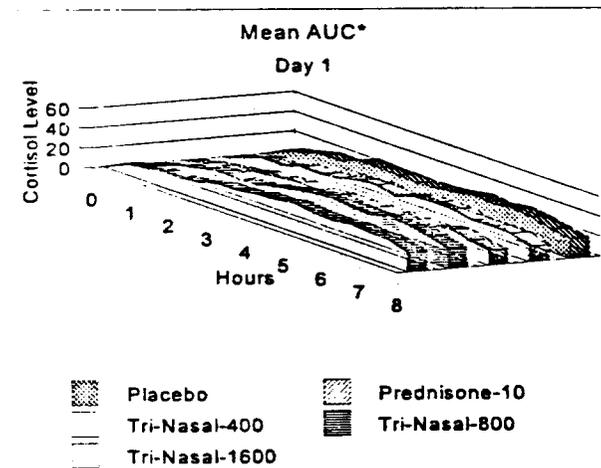


Figure 4. Adjusted means at day 1

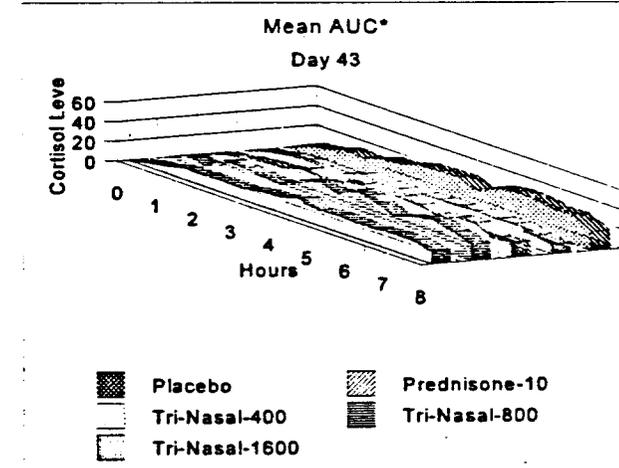
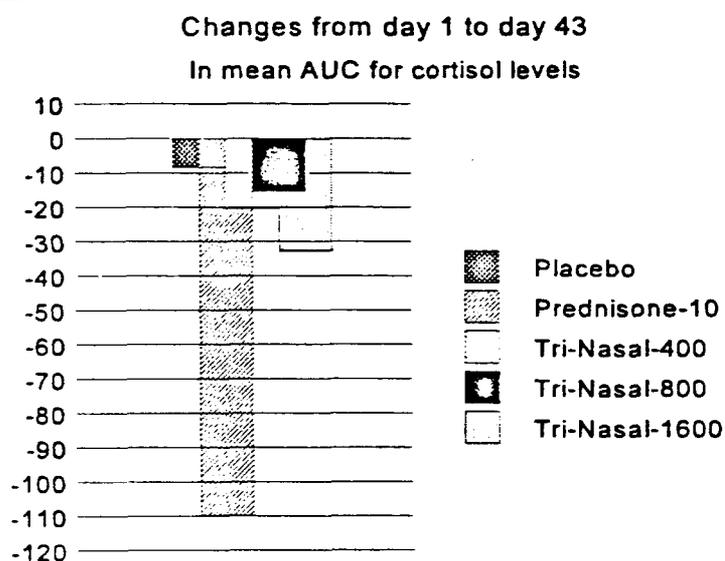


Figure 5. Adjusted means at day 43

APPEARS THIS WAY
ON ORIGINAL

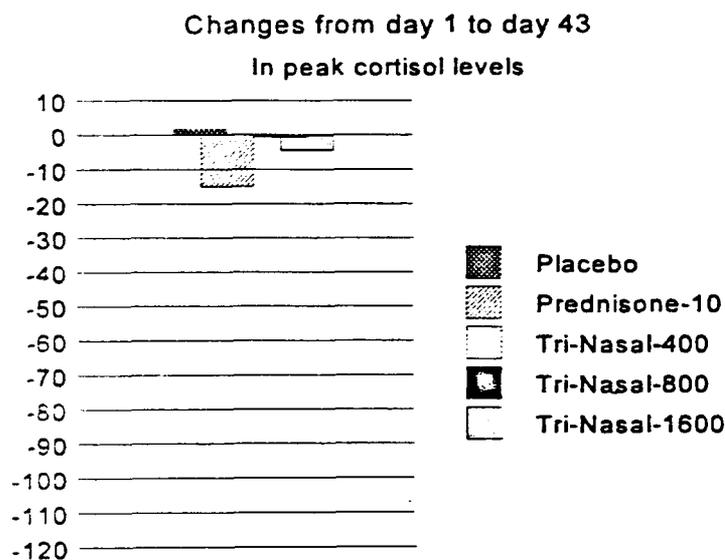
The more informative figures are displayed as Figures 6 and 7 depicting the changes from baseline for the drugs/dose levels.



AUC_Cortisol

Figure 6. Changes in mean AUC:
day 43 and day 1 compared

Figure 6 on the left shows the changes in AUC from day 1 to day 43 by treatment groups. Prednisone caused the greatest change (drop) among the drugs/doses. Tri-Nasal 1600 caused greater changes than the placebo and other two Tri-Nasal doses (400 and 800), but less changes than prednisone.



Peak_Cortisol

Figure 7. Change in peak cortisol levels:
day 43 and day 1 compared.

Figure 7 on the left shows the changes in peak cortisol levels from day 1 to day 43, by treatment groups. Prednisone caused the greatest change (drop) among the drugs/doses. Tri-Nasal 1600 caused greater changes than the placebo and the other two Tri-Nasal doses (400 and 800). Tri-Nasal 400 and 800 caused small changes in peak cortisol levels. Unlike Tri-Nasal 800, 1600 and prednisone, Tri-Nasal 400 and the placebo peak cortisol levels increased from day 1.

Analysis of Change from Baseline

The following Tables 5 and 6 summarize the sponsor's statistical results. The sponsor applied paired-t tests to compare the changes from baseline for each treatment. Prednisone reduced both AUC and peak cortisol level significantly at day 43 from day 1. The three Tri-Nasal dose levels did not have a significant effect in changing the above outcome variables. These effects can also be seen from the magnitude of the changes shown on the above Figures 6 and 7.

Table 5. Changes from Baseline for AUC and Peak Cortisol Levels

| Outcome | P-values: Changes from Baseline (day 1) | | | | |
|---------------|-----------------------------------------|--------------|---------------|---------------|----------------|
| | Placebo | Prednisone | Tri-Nasal 400 | Tri-Nasal 800 | Tri-Nasal 1600 |
| AUC | >0.05 | 0.014 | >0.05 | >0.05 | >0.05 |
| Peak Cortisol | >0.05 | 0.045 | >0.05 | >0.05 | >0.05 |

Source: Table 5B and Table 6B, Vol 4.15

Analysis of Treatment Effect

Table 6 below shows that, for both AUC and peak cortisol level, at day 1, the differences among the drug/dose groups were not significantly different.

For AUC at day 43, the differences between prednisone and the other drug/doses were significant. The differences among the Tri-Nasal doses and the placebo were not significant.

For peak cortisol at day 43, the difference between Tri-Nasal 1600 and Tri-Nasal 800 and the difference between Tri-Nasal 1600 and the placebo were both significant. However, the difference between Tri-Nasal 1600 and Tri-Nasal 400 was not significant-- This does not appear to be consistent with the comparison between Tri-Nasal 1600 and the placebo and the comparison between Tri-Nasal 1600 and Tri-Nasal 800. This issue is address below.

Table 6. Pairwise Comparisons for AUC and Peak Cortisol Levels

| Outcome | Overall Effect | Pairwise Comparison (placebo, prednisone, Tri-Nasal in 400,800, and 1600 µg) | Day |
|---------|----------------|------------------------------------------------------------------------------|-----|
| AUC | p=0.247 | pairwise differences not significant | 1 |
| | p=0.005 | p<0.05 for prednisone vs others | 43 |

(Table 6 continues on next page)

Table 6. (Continued)

| Outcome | Overall Effect | Pairwise Comparison (placebo, prednisone, Tri-Nasal in 400,800, and 1600 µg) | Day |
|---------------|----------------|-------------------------------------------------------------------------------------------------------------------------|-----|
| Peak Cortisol | p=0.052 | pairwise differences not significant | 1 |
| | p=0.001 | p<0.05 for prednisone vs others p=0.031 for placebo vs Tri-Nasal 1600 p=0.041 for Tri-Nasal 800 vs Tri-Nasal 1600 | 43 |

Source: Table 5C and Table 6C, Vol 4.15

Reviewer's Comments on Analysis of AUC

In Table 5C, vol 4.15, the sponsor reported the results for pairwise comparisons for AUC among the drug/doses. The same results also consistently appeared as a response of July 24, 1996 to the FDA's query on July 22, 1996. In those reports, the baseline measure was used as a covariate.

Reviewer's Comments on Analysis of Peak Cortisol Level

For peak cortisol level, in the response of August 2, 1996 to the FDA's query on August 1, 1996, the sponsor presented the pairwise comparisons for peak cortisol level at day 43. The results were somewhat different from those on Table 6C, vol 4.15, NDA. The following Table 7 shows the differences.

Table 7. Report of 8/2/96 and Table 6C, vol 4.15 (Analysis of peak cortisol)

| Source | 8/2/96 Report | Table 6C, Vol 4.15 |
|---------------------------------|---------------|--------------------|
| Placebo vs Prednisone | 0.0005 | <0.001 |
| Placebo vs Tri-Nasal 400 | 0.1864 | 0.116 |
| Placebo vs Tri-Nasal 800 | 0.9811 | 0.919 |
| Placebo vs Tri-Nasal 1600 | 0.0503 | 0.031 |
| Prednisone vs Tri-Nasal 400 | 0.0113 | 0.010 |
| Prednisone vs Tri-Nasal 800 | 0.0023 | <0.001 |
| Prednisone vs Tri-Nasal 1600 | 0.0463 | 0.040 |
| Tri-Nasal 400 vs Tri-Nasal 800 | 0.2749 | 0.130 |
| Tri-Nasal 400 vs Tri-Nasal 1600 | 0.5087 | 0.526 |
| Tri-Nasal 800 vs Tri-Nasal 1600 | 0.0980 | 0.041 |

It appears that the sponsor did not include baseline as the covariate for Table 6C, vol 4.15, however, the baseline was included in the 8/2/96 report. The latter seems to be

more appropriate.

Reviewer's Analyses Based on Unadjusted AUC

Reviewer's Analysis of AUC Change from Baseline

In the responses of 7/24/96 and 8/2/96 to the FDA's queries, the sponsor provided analyses based on the change from baseline instead of using raw AUC and peak cortisol level as outcome measures. When these new outcome measures were used, the sponsor argued that the pairwise comparisons lead to identical results. While analyzing change from baseline, the sponsor still included baseline as the covariate. Note that when the change from baseline is used as the outcome measure, it is not necessary to keep the baseline measure as a covariate in the statistical model.

The reviewer's analyzed the change in AUC from baseline. Note that AUC was calculated based on the total of area A and B shown on Figure 1. The resultant p-values are compared to the sponsor's in the following Table 8.

Table 8. Analysis of AUC Based on Change from Baseline

| Source | Reviewer's Analysis of AUC chg | Sponsor's 7/24/96 Report |
|---------------------------------|--------------------------------|--------------------------|
| Prednisone vs Placebo | 0.0012 | 0.0003 |
| Prednisone vs Tri-Nasal 400 | 0.0082 | 0.0038 |
| Prednisone vs Tri-Nasal 800 | 0.0164 | 0.0034 |
| Prednisone vs Tri-Nasal 1600 | 0.0200 | 0.0096 |
| Placebo vs Tri-Nasal 400 | 0.4895 | 0.2815 |
| Placebo vs Tri-Nasal 800 | 0.4264 | 0.6467 |
| Placebo vs Tri-Nasal 1600 | 0.2731 | 0.1415 |
| Tri-Nasal 400 vs Tri-Nasal 800 | 0.8855 | 0.6041 |
| Tri-Nasal 400 vs Tri-Nasal 1600 | 0.6899 | 0.6848 |
| Tri-Nasal 800 vs Tri-Nasal 1600 | 0.8160 | 0.3824 |

This table shows that despite the inappropriateness of the inclusion of the baseline by the sponsor when change from baseline was used as the outcome measure, the reviewer's analysis does not alter the conclusion for significance. The differences in AUC change from baseline were significant between prednisone and the other drug/dose levels. There were no significant differences among the Tri-Nasal dose levels and the placebo group.

Reviewer's Analysis of Peak-Cortisol Change from Baseline

The reviewer also analyzed the peak cortisol level changes from baseline. The following Table 9 summarizes and compares the results to the sponsor's 8/2/96 report.

Table 9. Analysis of Peak Cortisol Levels Based on Change from Baseline

| Source | Reviewer's Analysis of Peak Cortisol Level chg | Sponsor's 8/2/96 Report |
|---------------------------------|------------------------------------------------|-------------------------|
| Prednisone vs Placebo | 0.0050 | 0.0005 |
| Prednisone vs Tri-Nasal 400 | 0.0183 | 0.0113 |
| Prednisone vs Tri-Nasal 800 | 0.0359 | 0.0023 |
| Prednisone vs Tri-Nasal 1600 | 0.0910 | 0.0463 |
| Placebo vs Tri-Nasal 400 | 0.6434 | 0.1864 |
| Placebo vs Tri-Nasal 800 | 0.5419 | 0.9811 |
| Placebo vs Tri-Nasal 1600 | 0.2087 | 0.0503 |
| Tri-Nasal 400 vs Tri-Nasal 800 | 0.8646 | 0.2749 |
| Tri-Nasal 400 vs Tri-Nasal 1600 | 0.4367 | 0.5087 |
| Tri-Nasal 800 vs Tri-Nasal 1600 | 0.5714 | 0.0980 |

The reviewer's analysis, in most cases, is consistent with the sponsor's, despite the inclusion of the baseline (into the statistical model) by the sponsor.

According to this reviewer's analysis, the differences in peak cortisol level were significant between prednisone and the other drug/dose levels, except that the difference between prednisone and Tri-Nasal 1600 was not statistically significant ($p=0.091$). With the incorrect inclusion of baseline, the sponsor's test for this pair of drugs showed a significant difference ($p=0.0463$).

There were no significant differences among the Tri-Nasal dose groups and the placebo group.

Reviewer's Additional Analyses Based on Adjusted AUC: (AUC*)

Analyses Based on Adjusted AUC* and Peak Cortisol Level*

The following Tables 10 and 11 show the means of AUC* and the means of Peak Cortisol levels* for the drug/dose levels. For comparison purposes, Table 3 and 4 that show means of unadjusted AUC and unadjusted peak cortisol levels are

redisplayed.

Table 10. Adjusted mean AUC* for cortisol concentration levels

| Mean | Placebo | Prednisone | Tri-Nasal 400 | Tri-Nasal 800 | Tri-Nasal 1600 |
|-------------|---------|------------|---------------|---------------|----------------|
| day 1 | 181.13 | 148.36 | 119.72 | 170.64 | 168.44 |
| day 43 | 186.86 | 101.67 | 125.59 | 153.20 | 108.05 |
| day 43-day1 | 5.74 | -46.69 | 5.86 | -17.44 | -60.39 |

Table 3. Mean (unadjusted) AUC for cortisol concentration levels

| Mean | Placebo | Prednisone | Tri-Nasal 400 | Tri-Nasal 800 | Tri-Nasal 1600 |
|--------|---------|------------|---------------|---------------|----------------|
| day 1 | 341.2 | 298.9 | 310.1 | 347.8 | 311.3 |
| day 43 | 332.9 | 189.2 | 289.7 | 332.4 | 278.6 |
| change | -8.3 | -109.7 | -20.4 | -15.4 | -32.7 |

Table 11. Adjusted mean peak cortisol levels

| Mean | Placebo | Prednisone | Tri-Nasal 400 | Tri-Nasal 800 | Tri-Nasal 1600 |
|-------------|---------|------------|---------------|---------------|----------------|
| day 1 | 35.36 | 30.88 | 25.04 | 35.94 | 32.42 |
| day 43 | 38.82 | 23.72 | 28.56 | 35.20 | 24.48 |
| day 43-day1 | 3.45 | -7.16 | 3.52 | -0.74 | -7.94 |

Table 4. Mean (unadjusted) peak cortisol levels

| Mean | Placebo | Prednisone | Tri-Nasal 400 | Tri-Nasal 800 | Tri-Nasal 1600 |
|--------|---------|------------|---------------|---------------|----------------|
| day 1 | 55.4 | 49.7 | 48.8 | 58.1 | 50.3 |
| day 43 | 57.1 | 34.7 | 49.1 | 57.6 | 45.8 |
| change | 1.4 | -15 | 0.3 | -0.5 | -4.5 |

According to the comparison between Tables 10 and 3, for prednisone, the magnitude of change from baseline becomes smaller using the adjusted AUC than using the unadjusted AUC. Based on the comparison between Tables 11 and 4, for prednisone, The magnitude of change from baseline also becomes smaller using the adjusted peak cortisol than using the unadjusted peak cortisol level.

The more informative figures are displayed as Figures 8 and 9 that depict the changes from baseline for the drug/dose levels.

**APPEARS THIS WAY
ON ORIGINAL**

Figure 8 on the left shows the changes in AUC* from day 1 to day 43 by treatment groups. Both Tri-Nasal 1600 and Prednisone caused greater change than the other drugs/dose levels. The AUC* for the placebo and Tri-Nasal 400 went up at day 43 as compared to day 1. The AUC* for the other doses dropped at day 43 from day 1.

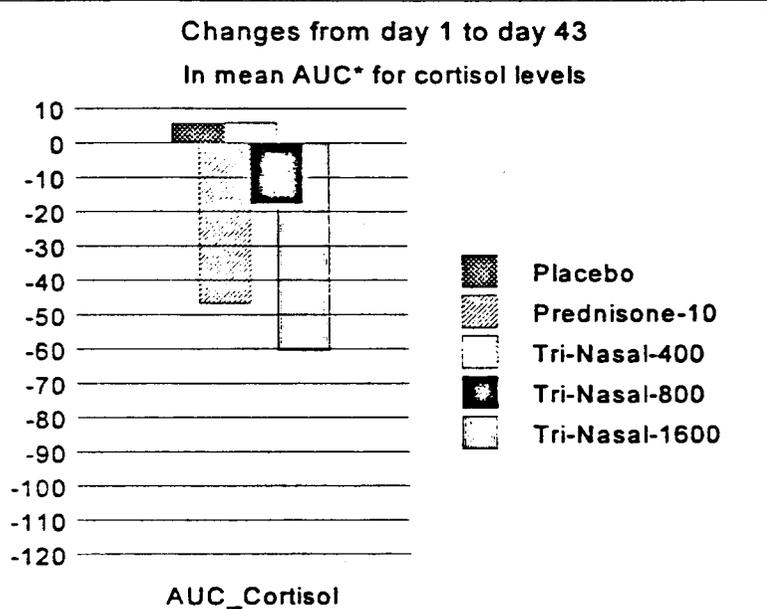


Figure 8. Changes in mean AUC*: day 43 and day 1 compared

Figure 9 on the left shows the changes in peak cortisol levels from day 1 to day 43 by treatment groups. All the drug/dose levels showed little changes.

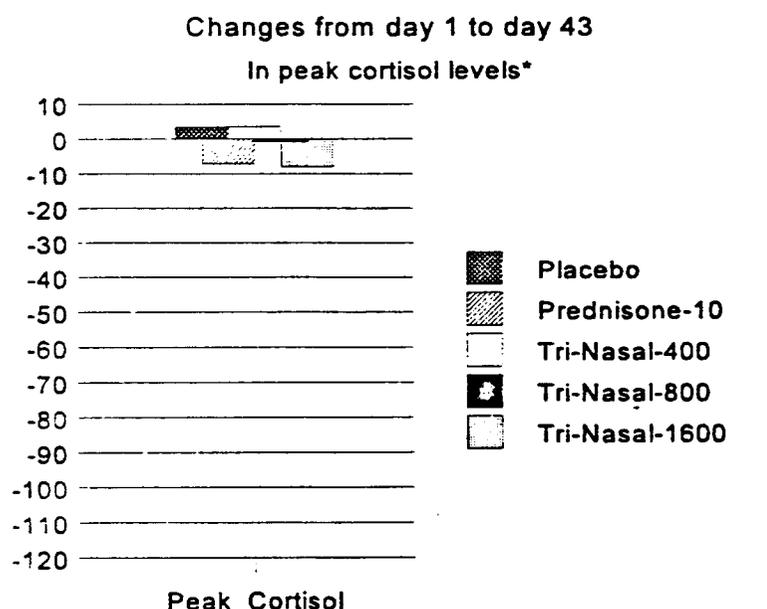


Figure 9. Change in peak cortisol levels: day 43 and day 1 compared

Figures 8 and 9 have shown much less changes from baseline than the changes shown on Figures 6 and 7, page 5.

This reviewer analyzed the changes from baseline in AUC* and peak cortisol levels* as outcome measures using ANOVA. The following Table 12 is a summary of these analyses. All the tests showed that the differences among the treatment groups were not significant.

Table 12. Analysis of AUC* and Peak Cortisol Levels* Based on Change from Baseline

| Source | Reviewer's Analysis of AUC* | Reviewer's Analysis of Peak Cortisol Level* |
|---------------------------------|-----------------------------|---------------------------------------------|
| Prednisone vs Placebo | 0.2074 | 0.1866 |
| Prednisone vs Tri-Nasal 400 | 0.2625 | 0.2313 |
| Prednisone vs Tri-Nasal 800 | 0.5156 | 0.4167 |
| Prednisone vs Tri-Nasal 1600 | 0.7669 | 0.9291 |
| Placebo vs Tri-Nasal 400 | 0.9225 | 0.9385 |
| Placebo vs Tri-Nasal 800 | 0.5991 | 0.6783 |
| Placebo vs Tri-Nasal 1600 | 0.1216 | 0.1594 |
| Tri-Nasal 400 vs Tri-Nasal 800 | 0.6753 | 0.7414 |
| Tri-Nasal 400 vs Tri-Nasal 1600 | 0.1616 | 0.2002 |
| Tri-Nasal 800 vs Tri-Nasal 1600 | 0.3558 | 0.3714 |

Conclusion

The reviewer's analyses on the changes (at day 43) from baseline (day 1) in AUC and peak cortisol level, other than the raw measures for AUC and peak cortisol level confirmed most (with only one exception) of the sponsor's analyses:

Unadjusted AUC

- The differences in AUC changes from baseline between prednisone and other drug/dose levels (i.e., Tri-Nasal at 400, 800 and 1600 µg and the placebo) were statistically significant.
- The differences in AUC changes from baseline among Tri-Nasal 400, 800 and 1600 and the placebo were not statistically significant.
- Numerically, the AUC decreased at day 43 as compared to those at baseline, for all treatment groups.
- Prednisone had the largest, and Tri-Nasal 1600 the second largest drop in AUC at day 43 among the groups. The difference in AUC drop between the two was significant.

Unadjusted Peak Cortisol Level

- The differences in peak cortisol level changes from baseline between

prednisone and other drug/dose levels were statistically significant, with one exception--The difference between prednisone and Tri-Nasal 1600 was not significant ($p=0.0910$).

- The differences in peak cortisol level changes from baseline among Tri-Nasal 400, 800 and 1600 and the placebo were not statistically significant.
- The peak cortisol levels increased at day 43 from day 1 for the placebo group. The Tri-Nasal 400 and 800 groups showed little changes. Prednisone had the largest, and Tri-Nasal 1600 the second largest drop in peak cortisol levels among the treatment groups. Unlike the analysis of AUC, the difference between prednisone and Tri-Nasal 1600 was not significantly different. Note that the sponsor's test for this pair showed a significant difference ($p<0.05$). This instance is the only discrepancy between this reviewer's analyses and the sponsor's analyses.

Adjusted AUC

- The differences in AUC* among the drug/dose levels were not significant.

Adjusted Peak Cortisol Level

- The differences in peak cortisol levels* among the drug/dose levels were not significant.

In summary, analyses using the sponsor-defined formula showed that the use of prednisone significantly decreased AUC and peak cortisol level at day 43 from day 1, while no significant decrease in these parameters occurred with the use of Tri-Nasal (400, 800, and 1600 μg) and the placebo. Analyses using the starting-time adjusted formula suggested by the reviewing medical officer resulted in a modified conclusion. That is, the differences among the drug/dose groups were not statistically significant.

/S/

Ted (Jiyang) Guo, Ph.D.
Mathematical Statistician

**APPEARS THIS WAY
ON ORIGINAL**

Concur: Steve Wilson, Ph.D.
Team Leader

/S/
10/22/96

cc:

Archival NDA 20-120

HFD-570/Division file

HFD-570/GStrange

HFD-570/JJenkins,

HFD-570/MHimmel

HFD-570/ASaavedra

HFD-715/Division file, Chron

HFD-715/SWilson

HFD-715/TGuo

TG/August 8, 1996/October 22, 1996/c:\indas\nda20120_doc\addendu2.wpd

**APPEARS THIS WAY
ON ORIGINAL**

Appendix 1: SAS output (Analysis based on AUC*)

**APPEARS THIS WAY
ON ORIGINAL**

A P P E N D I X

NDA 20-120 Study 1-0501, Analyses of AUC and Peak Cortisol Levels

Cortisol levels observed at time=0 were adjusted

Data Listing (A period '.' indicates a missing observation)

| Treatment | Patient | AUC Day 1 | AUC Day 43 | AUC Change from Day 1 | Peak Cortisol Day 1 | Peak Cortisol Day 43 | Peak Cortisol Change from Day 1 |
|----------------|---------|-----------|------------|-----------------------|---------------------|----------------------|---------------------------------|
| Placebo | 2 | | | | | | |
| | 4 | | | | | | |
| | 9 | | | | | | |
| | 13 | | | | | | |
| | 18 | | | | | | |
| | 21 | | | | | | |
| | 25 | | | | | | |
| | 27 | | | | | | |
| Prednisone-10 | 1 | | | | | | |
| | 3 | | | | | | |
| | 5 | | | | | | |
| | 6 | | | | | | |
| | 7 | | | | | | |
| Tri-Nasal-400 | 8 | | | | | | |
| | 10 | | | | | | |
| | 11 | | | | | | |
| | 12 | | | | | | |
| | 14 | | | | | | |
| Tri-Nasal-800 | 15 | | | | | | |
| | 16 | | | | | | |
| | 17 | | | | | | |
| | 19 | | | | | | |
| | 20 | | | | | | |
| Tri-Nasal-1600 | 22 | | | | | | |
| | 23 | | | | | | |
| | 24 | | | | | | |
| | 26 | | | | | | |
| | 28 | | | | | | |

APPEARS THIS WAY ON ORIGINAL

Cortisol levels observed at time=0 were adjusted

Mean AUC and Peak Cortisol Levels by Treatment Group

| TREAT | Mean AUC Day 1 | Mean AUC Day 43 | Peak Cortisol Level Day 1 | Peak Cortisol Level Day 43 |
|----------------|-------------------|--------------------|------------------------------------|-------------------------------------|
| Placebo | 191.13 | 186.86 | 35.36 | 38.62 |
| Prednisone-10 | 145.36 | 101.67 | 30.88 | 23.72 |
| Tri-Nasal-400 | 119.72 | 125.59 | 25.04 | 28.56 |
| Tri-Nasal-800 | 170.64 | 153.20 | 35.94 | 35.20 |
| Tri-Nasal-1600 | 166.44 | 108.05 | 32.42 | 24.48 |

**APPEARS THIS WAY
ON ORIGINAL**

Cortisol levels observed at time=0 were adjusted

Analysis based on raw AUC

General Linear Models Procedure
Class Level Information

| Class | Levels | Values |
|-------|--------|-----------|
| TREAT | 5 | 1 2 3 4 5 |

Number of observations in data set = 26

NOTE: Due to missing values, only 25 observations can be used in this analysis.

**APPEARS THIS WAY
ON ORIGINAL**

Cortisol levels observed at time=0 were adjusted

Analysis based on raw AUC

General Linear Models Procedure

Dependent Variable: AUC43

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|-----------------|----|----------------|---------------|---------|--------|
| Model | 5 | 27763.63975830 | 5552.76795166 | 1.78 | 0.1652 |
| Error | 19 | 59270.64524170 | 3119.50764430 | | |
| Corrected Total | 24 | 67034.46500000 | | | |

| | R-Square | C.V. | Root MSE | AUC43 Mean |
|--|----------|----------|-------------|--------------|
| | 0.316998 | 40.94162 | 55.85255271 | 136.42000000 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|--------|----|----------------|---------------|---------|--------|
| SEXT | 4 | 24434.52002234 | 6108.62000559 | 1.96 | 0.1421 |
| SEX | 1 | 721.60619580 | 721.60619580 | 0.23 | 0.6360 |

| Source | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------------|----|----------------|----------------|---------|--------|
| Sex vs placebo | 1 | 17653.97257556 | 17653.97257556 | 5.66 | 0.0260 |
| Sex vs Trt-Nar 400 | 1 | 1778.05268669 | 1778.05268669 | 0.57 | 0.4825 |
| Sex vs Trt-Nar 800 | 1 | 5327.25260928 | 5327.25260928 | 1.71 | 0.2069 |
| Sex vs Trt-Nar 1600 | 1 | 41.57557645 | 41.57557645 | 0.01 | 0.9093 |
| Sex vs Trt-Na 400 | 1 | 7096.20741831 | 7096.20741831 | 2.27 | 0.1479 |
| Sex vs Trt-Na 800 | 1 | 2552.97459590 | 2552.97459590 | 0.82 | 0.3770 |
| Sex vs Trt-Na 1600 | 1 | 16486.02101029 | 16486.02101029 | 5.29 | 0.0330 |
| Time vs Trt-Nar | 1 | 1002.05201361 | 1002.05201361 | 0.32 | 0.5778 |
| Time vs Trt-Na | 1 | 1200.55153460 | 1200.55153460 | 0.38 | 0.5424 |
| Time vs Trt-Na | 1 | 4542.51496973 | 4542.51496973 | 1.46 | 0.2424 |

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

Cortisol levels observed at time=0 were adjusted

Analysis based on AUC change from baseline

General Linear Models Procedure
Class Level Information

| Class | Levels | Values |
|-------|--------|-----------|
| TREAT | 5 | 1 2 3 4 5 |

Number of observations in data set = 28

NOTE: Due to missing values, only 25 observations can be used in this analysis.

**APPEARS THIS WAY
ON ORIGINAL**

Cortisol levels observed at time=0 were adjusted

Analysis based on AUC change from baseline

General Linear Models Procedure

Dependent Variable: DIFAUC

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|-----------------|----------|-----------------|---------------|--------------|--------|
| Model | 4 | 20636.00419167 | 5159.00104792 | 0.99 | 0.4340 |
| Error | 20 | 103665.06120833 | 5194.25406042 | | |
| Corrected Total | 24 | 124521.08540000 | | | |
| | R-Square | C.V. | Root MSE | DIFAUC Mean | |
| | 0.165723 | -357.6201 | 72.07117357 | -20.15300000 | |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|-----------------------------|----|----------------|----------------|---------|--------|
| Model | 4 | 20636.00419167 | 5159.00104792 | 0.99 | 0.4340 |
| Contrast | DF | Contrast SS | Mean Square | F Value | Pr > F |
| Red vs Placebo | 1 | 6816.40148485 | 6816.40148485 | 1.70 | 0.2074 |
| Red vs Tri-Ner 400 | 1 | 6905.07006250 | 6905.07006250 | 1.33 | 0.2608 |
| Red vs Tri-Ner 600 | 1 | 2275.91112500 | 2275.91112500 | 0.44 | 0.5158 |
| Red vs Tri-Ner 1600 | 1 | 469.22500000 | 469.22500000 | 0.09 | 0.7669 |
| Red vs Tri-Ner 400 | 1 | 50.46637121 | 50.46637121 | 0.01 | 0.9208 |
| Red vs Tri-Ner 600 | 1 | 1482.55104167 | 1482.55104167 | 0.29 | 0.5991 |
| Red vs Tri-Ner 1600 | 1 | 13577.02693939 | 13577.02693939 | 2.61 | 0.1116 |
| Tri-Ner 400 vs Tri-Ner 600 | 1 | 938.67834722 | 938.67834722 | 0.18 | 0.6756 |
| Tri-Ner 400 vs Tri-Ner 1600 | 1 | 10974.31256250 | 10974.31256250 | 2.11 | 0.1616 |
| Tri-Ner 600 vs Tri-Ner 1600 | 1 | 4641.59668056 | 4641.59668056 | 0.89 | 0.3998 |

BEST POSSIBLE COPY

**APPEARS THIS WAY
 ON ORIGINAL**

Cortisol levels observed at time=0 were adjusted

Analysis based on raw peak cortisol level

General Linear Models Procedure
Class Level Information

| Class | Levels | Values |
|-------|--------|-----------|
| TREAT | 5 | 1 2 3 4 5 |

Number of observations in data set = 25

NOTE: Due to missing values, only 25 observations can be used in this analysis.

**APPEARS THIS WAY
ON ORIGINAL**

Source: Sponsor-submitted data listing #10

Cortisol levels observed at time=0 were adjusted

Analysis based on raw peak cortisol level

General Linear Models Procedure

Dependent Variable: PEAR43

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|-----------------|----|----------------|--------------|---------|-------------|
| Model | 4 | 932.22366667 | 233.05591667 | 2.57 | 0.0699 |
| Error | 20 | 1816.53633333 | 90.82681667 | | |
| Corrected Total | 24 | 2748.76000000 | | | |
| R-Square | | C.V. | Root MSE | | PEAR43 Mean |
| 0.339143 | | 31.45317 | 9.53031042 | | 30.30000000 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|--------|----|--------------|--------------|---------|--------|
| PEAR | 4 | 932.22366667 | 233.05591667 | 2.57 | 0.0699 |

| Source | DF | Contrast SS | Mean Square | F Value | Pr > F |
|----------------------|----|--------------|--------------|---------|--------|
| PEAR vs Placebo | 1 | 621.57093939 | 621.57093939 | 6.84 | 0.0168 |
| PEAR vs T11-Nas 400 | 1 | 58.56400000 | 58.56400000 | 0.64 | 0.4313 |
| PEAR vs T11-Nas 800 | 1 | 292.86755556 | 292.86755556 | 3.22 | 0.0817 |
| PEAR vs T11-Nas 1600 | 1 | 1.44400000 | 1.44400000 | 0.02 | 0.8809 |
| PEAR vs T11-Na 400 | 1 | 256.90693939 | 256.90693939 | 3.16 | 0.0917 |
| PEAR vs T11-Na 800 | 1 | 31.39266667 | 31.39266667 | 0.35 | 0.5681 |
| PEAR vs T11-Na 1600 | 1 | 560.56366667 | 560.56366667 | 6.17 | 0.0200 |
| SI-Nas vs T11-Nas | 1 | 97.97688889 | 97.97688889 | 1.08 | 0.3114 |
| SI-Nas vs T11-Na | 1 | 41.61600000 | 41.61600000 | 0.46 | 0.5060 |
| SI-Na vs T11-Na | 1 | 255.37422222 | 255.37422222 | 2.81 | 0.1101 |

BEST POSSIBLE COPY

APPEARS THIS WAY
 ON ORIGINAL

Cortisol levels observed at time=0 were adjusted

Analysis based on peak cortisol change from baseline

General Linear Models Procedure
Class Level Information

| Class | Levels | Values |
|-------|--------|-----------|
| TREAT | 5 | 1 2 3 4 5 |

Number of observations in data set = 28

NOTE: Due to missing values, only 25 observations can be used in this analysis.

**APPEARS THIS WAY
ON ORIGINAL**

Cortisol levels observed at time=0 were adjusted
 Analysis based on peak cortisol change from baseline

General Linear Models Procedure

Dependent Variable: DIFPEAK

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|-----------------|----------|----------------|--------------|--------------|--------|
| Model | 4 | 699.78626667 | 174.94656667 | 0.94 | 0.4637 |
| Error | 20 | 3741.73533333 | 187.06676667 | | |
| Corrected Total | 24 | 4441.52160000 | | | |
| | R-Square | C.V. | Root MSE | DIFPEAK Mean | |
| | 0.157556 | -1099.515 | 13.67796647 | -1.24400000 | |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|--------------------|----|--------------|--------------|---------|--------|
| Model | 4 | 699.78626667 | 174.94656667 | 0.94 | 0.4637 |
| Contrast | DF | Contrast SS | Mean Square | F Value | Pr > F |
| ED VS PLACERO | 1 | 349.89103030 | 349.89103030 | 1.87 | 0.1866 |
| ED VS Tol-Med 400 | 1 | 285.15600000 | 285.15600000 | 1.52 | 0.2313 |
| ED VS Tol-Med 800 | 1 | 128.69355556 | 128.69355556 | 0.69 | 0.4167 |
| ED VS Tol-Med 1600 | 1 | 1.52100000 | 1.52100000 | 0.01 | 0.9291 |
| ED VS Tol-Med 400 | 1 | 1.14048485 | 1.14048485 | 0.01 | 0.9385 |
| ED VS Tol-Med 800 | 1 | 33.15266667 | 33.15266667 | 0.18 | 0.6783 |
| ED VS Tol-Med 1600 | 1 | 399.74012121 | 399.74012121 | 2.14 | 0.1594 |
| ED VS Tol-Med 400 | 1 | 20.94422222 | 20.94422222 | 0.11 | 0.7414 |
| ED VS Tol-Med 800 | 1 | 325.32900000 | 325.32900000 | 1.75 | 0.2002 |
| ED VS Tol-Med 1600 | 1 | 156.42688889 | 156.42688889 | 0.84 | 0.3714 |

BEST POSSIBLE COPY

APPEARS THIS WAY
 ON ORIGINAL

Appendix 2: SAS output (Analysis based on AUC)

APPEARS THIS WAY
ON ORIGINAL

Cortisol levels observed at time=0 were not adjusted

Data Listing (A period '.' indicates a missing observation)

| Treatment | Patient | AUC Day 1 | AUC Day 43 | AUC Change from Day 1 | Peak Cortisol Day 1 | Peak Cortisol Day 43 | Peak Cortisol Change from Day 1 |
|----------------|---------|--------------|---------------|--------------------------|---------------------------|----------------------------|------------------------------------------|
| Placebo | 2 | ┌ | | | | | |
| | 4 | | | | | | |
| | 9 | | | | | | |
| | 13 | | | | | | |
| | 18 | | | | | | |
| | 21 | | | | | | |
| | 25 | | | | | | |
| | 27 | | | | | | |
| Prednisone-10 | 1 | | | | | | |
| | 3 | | | | | | |
| | 5 | | | | | | |
| | 6 | | | | | | |
| | 7 | | | | | | |
| Tri-Nasal-400 | 8 | | | | | | |
| | 10 | | | | | | |
| | 11 | | | | | | |
| | 14 | | | | | | |
| Tri-Nasal-600 | 15 | | | | | | |
| | 16 | | | | | | |
| | 17 | | | | | | |
| | 19 | | | | | | |
| | 20 | | | | | | |
| Tri-Nasal-2600 | 22 | | | | | | |
| | 23 | | | | | | |
| | 24 | | | | | | |
| | 26 | | | | | | |
| | 28 | | | | | | |
| | | | | | | | |

APPEARS THIS WAY
 ON ORIGINAL

A P P E D I X
NDA 20-120 Study 1-0501, Analyses of AUC and Peak Cortisol Levels

Cortisol levels observed at time=0 were not adjusted

Mean AUC and Peak Cortisol Levels by Treatment Group

| TREAT | Mean AUC Day 1 | Mean AUC Day 43 | Peak Cortisol Level Day 1 | Peak Cortisol Level Day 43 |
|----------------|-------------------|--------------------|------------------------------------|-------------------------------------|
| Placebo | 341.23 | 332.86 | 55.35 | 57.07 |
| Prednisone-10 | 299.92 | 189.19 | 49.70 | 34.66 |
| Tri-Nasal-400 | 310.12 | 289.75 | 48.84 | 49.05 |
| Tri-Nasal-800 | 347.76 | 332.40 | 56.08 | 57.60 |
| Tri-Nasal-1600 | 311.32 | 276.61 | 50.25 | 45.80 |

**APPEARS THIS WAY
ON ORIGINAL**

Cortisol levels observed at time=0 were not adjusted

Analysis based on raw AUC

General Linear Models Procedure
Class Level Information

| Class | Levels | Values |
|-------|--------|-----------|
| TREAT | 5 | 1 2 3 4 5 |

Number of observations in data set = 28

NOTE: Due to missing values, only 25 observations can be used in this analysis.

**APPEARS THIS WAY
ON ORIGINAL**

Cortisol levels observed at time=0 were not adjusted

Analysis based on raw AUC

General Linear Models Procedure

Dependent Variable: AUC43

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|-----------------|----------|-----------------|----------------|--------------|--------|
| Model | 5 | 79475.47412617 | 15695.09482523 | 7.78 | 0.0004 |
| Error | 19 | 38812.21087383 | 2042.74794073 | | |
| Corrected Total | 24 | 118287.68500000 | | | |
| | R-Square | C.V. | Root MSE | AUC43 Mean | |
| | 0.671883 | 15.86192 | 45.19676914 | 264.56000000 | |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|------------------------|----|----------------|----------------|---------|--------|
| TREAT | 4 | 43772.63457692 | 10943.15864423 | 5.36 | 0.0046 |
| CONC | 1 | 10533.41456367 | 10533.41456367 | 5.16 | 0.0350 |
| Contrast | DF | Contrast SS | Mean Square | F Value | Pr > F |
| placeb vs placebo | 1 | 39492.88654420 | 39492.88654420 | 19.33 | 0.0003 |
| placeb vs Trt-Nas 400 | 1 | 22134.20120169 | 22134.20120169 | 10.84 | 0.0038 |
| placeb vs Trt-Nas 800 | 1 | 22830.62981663 | 22830.62981663 | 11.18 | 0.0034 |
| placeb vs Trt-Nas 1600 | 1 | 16925.55333622 | 16925.55333622 | 8.29 | 0.0096 |
| placeb vs Trt-Na 400 | 1 | 2510.12698923 | 2510.12698923 | 1.23 | 0.2815 |
| placeb vs Trt-Na 800 | 1 | 442.96321376 | 442.96321376 | 0.22 | 0.6467 |
| placeb vs Trt-Na 1600 | 1 | 4606.61775571 | 4606.61775571 | 2.35 | 0.1415 |
| Trt-N400 vs Trt-N800 | 1 | 567.96022908 | 567.96022908 | 0.28 | 0.6041 |
| Trt-N400 vs Trt-N1600 | 1 | 347.09337927 | 347.09337927 | 0.17 | 0.6848 |
| Trt-N800 vs Trt-N1600 | 1 | 1633.73301361 | 1633.73301361 | 0.80 | 0.3824 |

BEST POSSIBLE COPY

APPEARS THIS WAY
 ON ORIGINAL

Cortisol levels observed at time=0 were not adjusted

Analysis based on AUC change from baseline

General Linear Models Procedure
Class Level Information

| Class | Levels | Values |
|-------|--------|-----------|
| TREAT | 5 | 1 2 3 4 5 |

Number of observations in data set = 26

NOTE: Due to missing values, only 25 observations can be used in this analysis.

**APPEARS THIS WAY
ON ORIGINAL**

Source: Sponsor-submitted data listing #10

Cortisol levels observed at time=0 were not adjusted

Analysis based on AUC change from baseline

General Linear Models Procedure

dependent Variable: DIFAUC

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|-----------------|----|----------------|---------------|---------|--------|
| Model | 4 | 36772.67619167 | 9193.16904792 | 3.96 | 0.0189 |
| Error | 20 | 46429.46520633 | 2321.47326042 | | |
| Corrected Total | 24 | 83202.14140000 | | | |

| R-Square | C.V. | Root MSE | DIFAUC Mean |
|----------|-----------|-------------|--------------|
| 0.441968 | -131.8709 | 48.18166934 | -36.53700000 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|--------|----|----------------|---------------|---------|--------|
| REAT | 4 | 36772.67619167 | 9193.16904792 | 3.96 | 0.0189 |

| contrast | DF | Contrast SS | Mean Square | F Value | Pr > F |
|-------------------------|----|----------------|----------------|---------|--------|
| rep vs placebo | 1 | 32938.02912121 | 32938.02912121 | 14.19 | 0.0012 |
| rep vs Trt-Nas 400 | 1 | 19960.79006250 | 19960.79006250 | 8.60 | 0.0085 |
| rep vs Trt-Nas 600 | 1 | 15920.78401389 | 15920.78401389 | 6.86 | 0.0184 |
| rep vs Trt-Nas 1600 | 1 | 14630.20100000 | 14630.20100000 | 6.39 | 0.0200 |
| leped vs Trt-Na 400 | 1 | 1150.80018939 | 1150.80018939 | 0.50 | 0.4895 |
| leped vs Trt-Na 600 | 1 | 1530.65504167 | 1530.65504167 | 1.66 | 0.4264 |
| leped vs Trt-Na 1600 | 1 | 2947.84148485 | 2947.84148485 | 1.27 | 0.2781 |
| rs-Na400 vs Trt-Na600 | 1 | 49.35034722 | 49.35034722 | 0.02 | 0.8855 |
| rs-Na600 vs Trt-Na1600 | 1 | 380.38056250 | 380.38056250 | 0.16 | 0.6899 |
| rs-Na1600 vs Trt-Na1600 | 1 | 129.11668056 | 129.11668056 | 0.06 | 0.8166 |

BEST POSSIBLE COPY

APPEARS THIS WAY
 ON ORIGINAL

Cortisol levels observed at time=0 were not adjusted

Analysis based on raw peak cortisol level

General Linear Models Procedure
Class Level Information

| Class | Levels | Values |
|-------|--------|-----------|
| TREAT | 5 | 1 2 3 4 5 |

Number of observations in data set = 26

NOTE: Due to missing values, only 25 observations can be used in this analysis.

**APPEARS THIS WAY
ON ORIGINAL**

Cortisol levels observed at time=0 were not adjusted

Analysis based on raw peak cortisol level

General Linear Models Procedure

Dependent Variable: PEAK43

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|-----------------|----------|----------------|--------------|---------|-------------|
| Model | 4 | 1764.86666667 | 441.21666667 | 6.83 | 0.0010 |
| Error | 20 | 1291.15333333 | 64.55766667 | | |
| Corrected Total | 24 | 3056.02000000 | | | |
| | R-Square | C.V. | Root MSE | | PEAK43 Mean |
| | 0.577305 | 16.45797 | 8.03477857 | | 48.52000000 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|-------------------------|----|---------------|---------------|---------|--------|
| PEAK | 4 | 1764.86666667 | 441.21666667 | 6.83 | 0.0010 |
| Contrast | DF | Contrast SS | Mean Square | F Value | Pr > F |
| Ref vs 1-18000 | 1 | 1369.25103030 | 1369.25103030 | 21.21 | 0.0002 |
| Ref vs 1-18000 400 | 1 | 519.84100000 | 519.84100000 | 8.05 | 0.0102 |
| Ref vs 1-18000 800 | 1 | 1169.43022222 | 1169.43022222 | 18.11 | 0.0004 |
| Ref vs 1-18000 1200 | 1 | 310.24900000 | 310.24900000 | 4.81 | 0.0404 |
| 1-18000 vs 1-18000 400 | 1 | 173.96412121 | 173.96412121 | 2.69 | 0.1165 |
| 1-18000 vs 1-18000 800 | 1 | 0.68266667 | 0.68266667 | 0.01 | 0.9191 |
| 1-18000 vs 1-18000 1200 | 1 | 346.19393939 | 346.19393939 | 5.36 | 0.0313 |
| 1-18000 vs 1-18000 1600 | 1 | 161.31200000 | 161.31200000 | 2.50 | 0.1226 |
| 1-18000 vs 1-18000 2000 | 1 | 26.89600000 | 26.89600000 | 0.42 | 0.5260 |
| 1-18000 vs 1-18000 2400 | 1 | 309.42222222 | 309.42222222 | 4.79 | 0.0409 |

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

Cortisol levels observed at time=0 were not adjusted

Analysis based on peak cortisol change from baseline

General Linear Models Procedure
Class Level Information

| Class | Levels | Values |
|-------|--------|-----------|
| TREAT | 5 | 1 2 3 4 5 |

Number of observations in data set = 28

NOTE: Due to missing values, only 25 observations can be used in this analysis.

**APPEARS THIS WAY
ON ORIGINAL**

Cortisol levels observed at time=0 were not adjusted

Analysis based on peak cortisol change from baseline

General Linear Models Procedure

dependent Variable: DIFFPEAK

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|-----------------|----------|----------------|--------------|---------|---------------|
| Model | 4 | 1014.64906667 | 253.66201667 | 2.87 | 0.0499 |
| Error | 20 | 1768.71033333 | 88.43551667 | | |
| Corrected Total | 24 | 2783.35940000 | | | |
| | R-Square | C.V. | Root MSE | | DIFFPEAK Mean |
| | 0.364841 | -285.6627 | 9.40401599 | | -3.29300000 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|----------------------------|----|---------------|--------------|---------|--------|
| REAT | 4 | 1014.64906667 | 253.66201667 | 2.87 | 0.0499 |
| contrast | DF | Contrast SS | Mean Square | F Value | Pr > F |
| red vs placebo | 1 | 879.38693939 | 879.38693939 | 9.94 | 0.0050 |
| red vs Tri-Nas 400 | 1 | 583.69600000 | 583.69600000 | 6.60 | 0.0183 |
| red vs Tri-Nas 800 | 1 | 447.45500000 | 447.45500000 | 5.06 | 0.0353 |
| red vs Tri-Nas 1600 | 1 | 275.76400000 | 275.76400000 | 3.15 | 0.0820 |
| place vs Tri-Nas 400 | 1 | 19.53966667 | 19.53966667 | 0.22 | 0.6334 |
| place vs Tri-Nas 800 | 1 | 34.05066667 | 34.05066667 | 0.39 | 0.5419 |
| place vs Tri-Nas 1600 | 1 | 149.21093939 | 149.21093939 | 1.69 | 0.2067 |
| red vs red vs Tri-Nas 400 | 1 | 2.64022222 | 2.64022222 | 0.03 | 0.8646 |
| red vs red vs Tri-Nas 800 | 1 | 55.69600000 | 55.69600000 | 0.63 | 0.4307 |
| red vs red vs Tri-Nas 1600 | 1 | 29.26200000 | 29.26200000 | 0.33 | 0.5714 |

BEST POSSIBLE COPY

APPEARS THIS WAY
 ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION
CLINICAL

SEP - 4 1996

Date: _____

NDA#: 20-120
Applicant: Muro Pharmaceutical, Inc.
Name of Drug: Tri-Nasal Spray (triamcinolone acetonide)
Indication: Treatment of seasonal allergic rhinitis
Documents Reviewed: Study #100-309: Volumes 6.1-6.13, 10.1-10.2;
Study #100-305: Volumes 4.30-4.45;
Study #100-204: Volumes 4.16-4.29;
Study #0501: Volume 4.46; 2/20/96
Response to FDA Statistical Questions for the Tri-Nasal
NDA, facsimile 5/29/96
Statistical Reviewer: Ted (Jiyang) Guo, DOB II/OEB, HFD-715
Medical Input: Ana Marie Saavedra, ODE II, HFD-570

APPEARS THIS WAY
ON ORIGINAL

Table of Contents

| | |
|-------------------------------------------------|----|
| Summary | 1 |
| Introduction | 2 |
| Sponsor's Results and Reviewer's Comments | 4 |
| Reviewer's Additional Analyses | 15 |
| Discussion | 16 |
| Conclusion | 17 |
| Appendix 1 (Study No. 100-309) | 18 |
| Objectives of the trial | 18 |
| Study design | 18 |
| Sponsor's results and reviewer's comments | 20 |
| Sponsor's conclusions | 24 |
| Reviewer's analyses | 24 |
| Appendix 2 (Study No. 100-204) | 29 |
| Objectives of the trial | 29 |
| Study design | 29 |
| Sponsor's results and reviewer's comments | 31 |
| Sponsor's conclusions | 34 |
| Reviewer's analyses | 34 |
| Appendix 3 (Study No. 100-305) | 39 |
| Objectives of the trial | 39 |
| Study design | 39 |
| Sponsor's results and reviewer's comments | 41 |
| Sponsor's conclusions | 45 |
| Reviewer's analyses | 45 |
| Appendix 4 (Study No. 0501) | 51 |
| Objectives of the trial | 51 |
| Study design | 51 |
| Sponsor's conclusions | 55 |
| Reviewer's analyses | 55 |

Summary

The sponsor conducted nine studies from 1988 through 1993 to support the claim that Tri-Nasal (triamcinolone acetonide) nasal spray solution is safe and effective in treating seasonal allergic rhinitis.

This review evaluates four of the studies (100-309, 100-204, 100-305, and 0501) on the efficacy of the drug, based on the intent-to-treat (ITT) patients. Nasacort and Kenalog served as positive controls in study 100-309 and 100-204, respectively. The most important results from these four studies are stated as follows.

- Study 100-309, a two-week (1995) study, showed that Tri-Nasal at 200 µg once daily, 400 µg once daily and Nasacort at 440 µg once daily were more effective than the placebo for the treatment of seasonal allergic rhinitis.
- Study 100-204, a four-week (1994) study, demonstrated that Tri-Nasal at 400 µg once daily was more effective than Tri-Nasal at 50 µg once daily and intramuscularly administered Kenalog at 4 mg once weekly.
- Study 100-305, a four-week (1993) study, designed to compare three dose levels of Tri-Nasal, found that Tri-Nasal at 50 and 200 µg once daily were statistically superior to the placebo. However, the highest dosed group (400 µg once daily) did not show a statistical superiority to the placebo. This finding was not consistent with those from studies 100-309, 100-204, and 0501.
- Study 0501, a four-week study and also the earliest investigation (1988) among these four studies, concluded that Tri-Nasal at 200 µg twice daily or 400 µg daily was more effective than the placebo in relieving the following symptoms: sneezing, nasal congestion, itching nose/throat/palate and red/watery eyes. Also, the patients treated with Tri-Nasal took significantly less concomitant antihistamines.

This review confirmed that, overall, Tri-Nasal at 200 and 400 µg daily dose was superior to the placebo in relieving the symptoms of seasonal allergic rhinitis, based on the observations on the ITT patients.

Introduction

Triamcinolone acetonide (TAA) nasal spray solution (Tri-Nasal) was developed to treat seasonal allergic rhinitis (SAR). The drug is delivered as a nasal spray. Tri-Nasal at 200 µg once daily and 400 µg once daily are the proposed market doses. Nine efficacy studies were conducted: 100-204, 100-305, 4-0501, 0501, 3-0501, 3-0501OL, 100-307, 38-050 and 0485. In consultation with the reviewing medical officer, Dr. Ana Marie Saavedra Delgado, ODEI, CDER, and based on the importance of the studies, this statistical reviewer examined the following four studies on the efficacy aspect on the intent-to-treat (ITT) patients: 100-309, 100-204, 100-305, and 0501. These four studies are briefly described in the following Table 1.

Table 1. Number of Patients

| Protocol | Number of Patients | | | | | Number of Centers | Duration of Treatment (in weeks) |
|----------|--------------------|-----------------------|------------------------|------------------------|----------------------------|-------------------|----------------------------------|
| | Placebo | Tri-Nasal 50 µg/daily | Tri-Nasal 200 µg/daily | Tri-Nasal 400 µg/daily | a. Nasacort. b. Kenalog | | |
| 100-309 | 96 | NA | 94 | 95 | 92 (a) | 13 | 2 |
| 100-204 | 73 | 74 | NA | 75 | 74(b) | 5 | 4 |
| 100-305 | 66 | 68 | 69 | 64 | NA | 6 | 4 |
| 0501 | 59 | NA | NA | 59 | NA | 5 | 4 |

The number of centers included in study 100-309 was about twice that in the other studies; the study period was half that of the other studies. All of these studies included patients, 18-65 years of age, of both sexes. The breakdown of the number of patients by center can be found in every appendix at the end of this review.

The time lines of these studies are described in the following Table 2. Study 100-309 was the latest study of the four, while study 0501 was conducted eight years ago in 1988.

Table 2. Time lines of the Studies

| Protocol | Time line | |
|----------|----------------|----------------|
| | Beginning | Ending |
| 100-309 | May, 1995 | July, 1995 |
| 100-204 | December, 1993 | February, 1994 |
| 100-305 | April, 1993 | July, 1993 |
| 0501 | April, 1988 | June, 1988 |

The studies were double-blind, randomized, parallel, placebo-controlled, multicenter studies. Tri-Nasal was delivered as a nasal spray. As indicated in the sponsor's protocol, the treatments in study 100-309 were double-blind except that