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Demographics

There were no statistically significant differences at baseline with respect to treatment groups for: sex, race, age, height, weight, and blood pressure, Appendix B, Table 3, vol 46. Only 3/118 patients were not Caucasian. There were 63 females and 55 males. The mean age of the study population was 33.9 years, and ages ranged from 18.0 to 56.3 years.

Comparison at baseline

At baseline there were no statistically significant differences between treatment groups in terms of years of hx of diagnosis of spring hay fever, Appendix B, Table 4, Vol 46. Two years was the minimum value listed in the range of mean duration in years of spring hay fever.

In addition, there were no significant differences between treatment groups with respect to previous use of steroids, medical history, physical examination and nasal examination at baseline, Appendix B, Table 5, volume 46.

Discontinuations

Two patients from the Fairfax study site, discontinued the study. TAA treated patient #1675, discontinued the study at Visit 6 due to a suspected monilial infection. Placebo treated patient #1075, discontinued the study at visit 7 due to pregnancy. The results from all patients were analyzed for both safety and efficacy through their last visit.

Efficacy

Reviewer's comments:

Study medication

Triamcinolone acetonide

Concentration 0.5 mg/ml in a 15 ml high density polypropylene bottle using a _____ pump _____ actuator, page 053, vol 4.1); each 100 μ l delivered by the pump contains 50 μ g of medication. Lot 81002CS, exp. 8/88. According to the Data listing of Patient Dosing in vol 93, the last dose of study medication was used on 6/30/88.

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According to page 054 vol 4.1, the formula for this lot is #39-05-2. It is the formula for which market approval is sought.

Placebo

Supplied in a bottle identical to the active drug container with the same pump. Volume of the spray 100 μ l. Lot 81002CSP, exp 8/88.

Symptomatic medication

Marketed Seldane 60 mg, Afrinol Repetabs, Afrin, and Opcon -A drops.

Evaluable Patients

Of the 118 patients evaluated for efficacy, 2 patients: TAA patient #1675, suspected monilia infection, (from week #3 onwards) and placebo patient #1438 (for week #4, due to travel) had data invalidated during the active treatment period. One patient had the second week of baseline invalidated due to travel (placebo #1351).

Statistical methods used

An ANOVA, with terms for center, treatment, week, and center-by-treatment and week-by-treatment was used to compare the mean changes over all patients at each week. When there was no statistically significant treatment-by-center interaction, the centers were pooled. The mean changes of the treatment groups were compared overall and for each week during active treatment using the t-tests of least squares means. If the patients in the two treatment groups were not equivalent at baseline, their baseline values were used as a covariate in the model.

Patient evaluation of symptom severity

Patient evaluation of symptom severity, from Table 20, vol 46 and Tables 9A-9E, Appendix B, vol 46.

	Baseline	Week 1	Week 2	Week 3	Week 4	Overall
Sneezing						
TAA	1.12	0.77*	0.60*	0.52*	0.46*	0.59*
Placebo	1.31	1.16	1.22	1.27	1.20	1.21
Nasal congest						
TAA	1.51*	1.10*	0.95*	0.82*	0.85*	0.93*
Placebo	1.87	1.69	1.56	1.63	1.58	1.62

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Nasal secret						
TAA	1.48	1.14*	0.95*	0.79*	0.79*	0.92*
Placebo	1.60	1.51	1.38	1.50	1.46	1.46
Itchy N/T/P						
TAA	1.11	0.77*	0.56*	0.40*	0.47*	0.55*
Placebo	1.26	1.16	1.02	1.05	0.97	1.05
Eye sympt						
TAA	1.10	0.83	0.78	0.65*	0.67	0.73
Placebo	1.08	0.96	0.96	0.96	0.84	0.94

The mean values in the table above are the mean averages for the week except for baseline that was calculated as the average of Week -2 and Week -1. The (*) depicts P values for the difference in scores from baseline; the actual values for these differences are not shown.

* $p \leq 0.05$ (between group p value, using least squares; mean change in intensity of symptom scores from baseline).

The symptom score of patients treated with TAA were significantly improved compared to those treated with placebo during the 4 active treatment weeks for the individual symptoms of sneezing, nasal secretions, and itchy nose/throat/palate. The symptom nasal congestion, was statistically significant different at baseline between the two treatment groups. The statistical analysis (least squares) done by the sponsor, took into consideration baseline differences. When this was done, the symptom scores from patients that received the TAA treatment had significantly lower scores than the placebo treated group for the overall study period. Appendix B, Table 9B.2, vol 46. There were no significant differences in the eye symptom scores for patients receiving active treatment and those that were not.

Investigator evaluation of symptom severity

The results from the symptom severity scores by the investigators parallel those by the patients, except for the assessment of symptoms during the first week of treatment. For the first week of active treatment, the investigator's symptom scores did not show a statistical difference between the symptom scores of those patients receiving active treatment and those receiving placebo. There were statistically significant differences at baseline for nasal congestion; the placebo group had a higher score. When the differences in baseline were accounted for, there were still significant differences favoring patients actively treated, for the overall treatment period (Appendix B, Table 10.B2, vol 46). There were no statistically significant differences in eye symptom scores for those patients treated with TAA and patients that received placebo.

Investigator evaluation of symptom severity, from Table 21 in vol 46 and Tables 10A-10E, Appendix B, vol 46.

	Baseline	Week 1	Week 2	Week 3	Week 4	Overall
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Sneezing TAA Placebo	1.42 1.51	0.98 1.27	0.83* 1.29	0.67* 1.47	0.56* 1.38	0.76* 1.35
Nasal congest TAA Placebo	1.76* 2.07	1.34 1.80	1.02* 1.57	0.83* 1.77	0.92* 1.67	1.03* 1.70
Nasal secret TAA Placebo	1.75 1.83	1.27 1.46	1.03* 1.47	0.81* 1.61	0.85* 1.53	0.99* 1.52
Itchy N/T/P TAA Placebo	1.40 1.50	0.88 1.03	0.66* 1.09	0.41* 1.19	0.58* 1.07	0.63* 1.14
Eye sympt TAA Placebo	1.41 1.32	0.98 1.03	0.95 1.14	0.84* 1.25	0.85 1.00	0.91 1.10

The mean values in the table above are the mean averages for the week except for baseline that was calculated as the average of Week -2 and Week -1. The (*) depicts P values for the difference in scores from baseline; the actual values for these differences are not shown.

* $p \leq 0.05$ (between group p value, using least squares; mean change in intensity of symptom scores from baseline).

Concomitant antihistamines

The study reports the mean number of Seldane tablets consumed per day, by week and by treatment group. The baseline number of Seldane tablets consumed was the average of the mean number of tablets consumed during Weeks -2 and -1.

Mean number of Seldane tablets taken per day, from Table 16, vol 46 and Table 6, Appendix B, vol 46.

	Baseline Tablets	Week 1 Tablets	Week 2 Tablets	Week 3 Tablets	Week 4 Tablets	Overall Tablets
TAA N=59	0.48	0.16	0.14*	0.21*	0.23*	0.19*
Placebo N=59	0.57	0.32	0.41	0.57	0.62	0.48

* $p \leq 0.05$ (between group p value)

Thirty-nine (39/118, 33%) patients did not take any of the dispensed symptomatic medication; 21 (21/59, 36%) were in the triamcinolone group and 18 (18/59, 30%) were in the placebo treated group, vol 46, page 60, section 5.7.3.

There were no statistical difference in the number mean number of Seldane tablets that patients took during baseline or during the first week of active treatment. Thereafter the TAA treated group took less Seldane than the placebo group.

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It is important to note that the report does not link or weights the use of concurrent antihistamines to symptom scores assessments from either the patients or the investigators. The symptom scores were recorded at 7 PM in the evenings. The protocol did not specify recording the symptoms prior to the use of concurrent rescue medication nor did it specify that a period of time had to elapse after taking the rescue antihistamine before filling out the symptom score assessment.

Other concomitant medication

The following patients took concomitant medication during the study, from Table 17, vol 46.

	TAA		Placebo		All Patients	
	N	%	N	%	N	%
Afrinol Repetabs	22	37	27	46	49	41
Afrin Nasal Spray	9	15	17	29	26	22
Isoton-A-Eye-Drops	23	39	28	47	51	43

The report does not analyze the use of the above other concomitant rescue medication between treatment groups. It does not link or weights the use of the above concurrent drugs to symptom scores assessments from either the patients or the investigators.

The results in the above table show that a smaller number of patients treated with TAA used these medications during the study than those treated with placebo. However except for the use of Afrin spray these differences may not be clinically significant. A table depicting the number of days that the medication was used by week according to treatment is not included in the report. The Data listing in volume 93, beginning in page 356, gives the individual record of concurrent medication use by treatment. The frequency of use of the individual medication is included. Looking at the data listing by treatment it appears that the frequency of use of Afrin and Afrinol in the third and fourth weeks of the study (weeks 6 and 7) is more prevalent in placebo treated patients than in patients receiving TAA.

Overall control of symptoms

Patient (global): statistical significant differences were found during the 4 weeks of active treatment and beginning at week 1 for mean improvement in symptom control, between treatment groups, favoring TAA. The weekly range of the mean was 2.88 to 3.43 for the TAA group and 2.04 to 2.28 in the placebo group, Appendix B, Table 7, vol 46. A score of 2= slight relief, and a score of 3= moderate relief.

Physician (global): statistical significant differences were found during the four weeks of active treatment beginning at week 1 for mean

improvement in symptom control, between treatment groups favoring TAA. The weekly range of the mean was 2.81 to 3.40 for the TAA group and 2.02 to 2.29 in the placebo group, Appendix B, Table 8, vol 46. A score of 2= slight relief, and a score of 3= moderate relief.

Nasal Examination

Physical changes were recorded by the investigators at the clinic visits. According to Tables 11A-C in Appendix B, vol 46, patients treated with TAA had an improvement of the nasal color (from pale blue to light red) at weeks 2, and 3, less nasal secretion on weeks 2 and 3 and reduction in the intensity of nasal swelling at week 3, when compared to the patients receiving placebo.

Safety

Reviewer's comments:

Extent of exposure

All one hundred and eighteen patients were evaluable for safety. Fifty-eight patients received TAA 200 µg twice daily by nasal spray for four weeks and fifty-eight patients received placebo twice daily by nasal spray for four weeks. Two patients were prematurely discontinued from the study: Patient #1675 received TAA for three weeks, he was suspected to have a monilia infection and was discontinued from the study on Visit #6. Placebo patient #1363 received placebo for three weeks and was discontinued from the study on Visit # 7 due to pregnancy.

Adverse events

Thirty-six (61%) TAA patients and 39 (66%) placebo-treated patients reported at least one adverse event during the study. All reported adverse events were classified to be of mild or moderate severity.

The most frequently reported adverse events were nasal stinging and nasal burning. There were no statistically significant differences between treatment groups, from Table 10, vol 46.

Nasal stinging

	Patients	(%)	occurrences
TAA	19/59	(32%)	42
placebo	28/59	(47%)	62

Nasal burning

	Patients	(%)	occurrences
TAA	13/59	(22%)	30

placebo 21/59 (36%) 46

Patient # 1675 was discontinued at Visit #6 due to a monilial infection. The laboratory culture of the nasal smear grew *Staphylococcus aureus*.

Clinical laboratory evaluations

Hematology

The mean eosinophil count decreased over the course of the study in the TAA group (mean change = -0.61%), but increased in the placebo group (mean change = 0.15%). This difference between groups was statistically significant, ($p=0.04$), Appendix B, Table 15A, vol 46. There were no statistically significant changes in total WBC counts or in the percent of segmented neutrophils, suggesting that the change observed in the eosinophils were not due to the presence of systemic exposure to corticosteroids.

Chemistry

There were two statistically significant mean changes in blood chemistry (triglycerides and carbon dioxide) between the treatment groups; a decrease in the triglycerides and carbon dioxide levels for the placebo group. These changes were small and within normal lab limits, Appendix B, Table 15B, vol 46. There were no statistically significant mean changes in urine pH, the only parameter analyzed for the urinalysis, Appendix B, Table 15B, vol 46.

Non-laboratory evaluation

Patient evaluation of nasal stinging and irritation

Patients used the previously described 0-3 scale to evaluate nasal stinging and or irritation. There were no statistically significant differences between treatments for the first three weeks. Only in week 4, there is, $p=0.01$, Appendix B, Table 12, vol 46. According to the scale for the evaluation of nasal irritation/nasal stinging, the experienced symptoms fall in the mild range.

Patient assessment of nasal stinging/irritation, Table 14, vol 46.

	Week 1	Week 2	Week 3	Week 4
TAA				
N	59	59	59	59
Mean	0.78	0.88	0.78	0.69

Placebo				
N	59	59	59	59
Mean	0.98	1.05	0.98	1.02

Monilial infections

Although a monilia infection was suspected by the investigator for patient #1675, the nasal smear revealed heavy growth of staph aureus.

Physical examination

The reported nasal examination changed from abnormal at baseline, to normal at the final visit for 22 TAA treated patients (37%) and 27 placebo treated patients (46%), Table 15, vol 46. There were no differences in the percent of patients whose nasal physical exam improved by the end of treatment regardless of the treatment given, active drug or placebo.

Clinically significant changes in nasal exam, from Table 15, vol 46.

Change Wk-2 to Wk+4	TAA N=59	Placebo N=59	All Patients N=118
Normal to abnor	6 (10%)	4 (7%)	10 (8.4%)
Abnor to norm	22 (37%)	27 (46%)	49 (41%)
No change	31 (52%)	28 (47%)	59 (50%)

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Summary and conclusions:**Reviewer's comments:**

In this study the following results support the efficacy of the 200 µg dose over placebo:

Patient daily diary symptom scores- results favor TAA over placebo for 4 weeks of active treatment for sneezing, nasal secretions, and itchy nose/throat/palate. For the individual symptom of nasal congestion there were significant differences at baseline. In the statistical analysis provided by the sponsor taking into consideration the baseline difference for the overall analysis favored TAA. Table 20, vol 46 and Tables 9A-9E, Appendix B, vol 46.

Investigator weekly symptom severity assessment- results favor TAA over placebo for weeks 2, 3 and 4 for sneezing, nasal congestion, nasal secretions and itchy nose/throat/palate using the by week analysis. When the overall treatment period is considered then the results favor TAA over placebo for all individual symptoms. Table 21 in vol 46 and Tables 10A-10E, Appendix B, vol 46.

Concomitant antihistamine used- There were no statistical difference in the mean number of Seldane tablets that patients took during baseline or during the first week of active treatment. Thereafter the TAA treated group took less Seldane than the placebo group, Table 16, vol 46 and Table 6, Appendix B, vol 46.

Patient global scores of symptom control- Appendix B, Table 7, vol 46.

Physician global scores of symptom control- Appendix B, Table 8, vol 46

Nasal evaluation exam for efficacy, by the investigators- patients treated with TAA had an improvement of the nasal color (from pale blue to light red) at weeks 2, and 3, less nasal secretion on weeks 2 and 3 and reduction in the intensity of nasal swelling at week 3, when compared to the patients receiving placebo. Tables 11A-C in Appendix B, vol 46.

Assessment of pollen counts during the study duration was not required. The study could enroll patients that were sensitive to grass and/or trees. The centers conducted the active treatment part of the study during mid May to end of June. It is not clear that patients may have had adequate pollen exposure to the allergen that they were sensitive to during the study duration. Since there are no records available, it would need to be assumed that the pollen exposure was adequate for the 5 centers during the study duration.

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The to be marketed unit pump, a ~~unit pump~~ with a ~~unit pump~~ nasal actuator is the same pump but with a different actuator than the one that was used in this study. The characteristics of the to be marketed pump need to be supported by comparative data from the unit pump used in this and other pivotal clinical studies.

All one hundred and eighteen patients were evaluable for safety. Fifty-eight patients received TAA 200 μ g twice daily by nasal spray for four weeks and fifty-eight patients received placebo twice daily by nasal spray for four weeks. Two patients were prematurely discontinued from the study: Patient #1675 received TAA for three weeks, he was suspected to have a monilial infection and was discontinued from the study on Visit #6. Placebo patient #1363 received placebo for three weeks and was discontinued from the study on Visit # 7 due to pregnancy.

Thirty-six (61%)TAA patients and 39 (66%) placebo-treated patients reported at least one adverse event during the study. All reported adverse events were classified to be of mild or moderate severity. The most frequently reported adverse events were nasal stinging and nasal burning. There were no statistically significant differences between treatment groups, Table 10, vol 46. There were no differences in the percent of patients whose nasal physical exam (safety assessment) improved by the end of treatment, regardless of the treatment received. There were no clinical significant changes in clinical laboratory parameters between treatment groups.

Therefore, this study supports the safety of 200 μ g bid in adult patients with seasonal allergic rhinitis taking Seldane, Afrin, Afrinol and Opticon-A as concurrent medications.

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10.d. Study 100-305

Title: A dose response study of nasal triamcinolone acetonide in patients with seasonal allergic rhinitis.

Objective: To compare the efficacy of Trinasal at dosages of 50 μ g, 200 μ g and 400 μ g q.d. versus placebo for 4 weeks in the treatment of seasonal allergic rhinitis due to grass pollen in adults ages 18-65 years.

To evaluate the safety profile of Trinasal at dosages of 50 μ g, 200 μ g and 400 μ g q.d. over 4 weeks in the treatment of seasonal allergic rhinitis due to grass pollen sensitivity in adults ages 18-65 years.

Protocol: Appendix A.1 in volume 4.31

Study design:

This is a double-blind, parallel, multicenter study that will compare the efficacy and safety of Trinasal at dosages of 50 μ g, 200 μ g and 400 μ g q.d. versus placebo for 4 weeks in the treatment of seasonal allergic rhinitis due to grass pollen in adults 18-65 years of age.

Approximately 300 patients in 6 sites are expected to participate in the study. Patients will be randomized to treatment within a 5 day window after a 4-21 day baseline period. Patients will evaluate treatment keeping a daily diary of symptom severity. Physicians will evaluate the effect of the treatment on symptoms at weekly clinic visits. Chlorpheniramine 4 mg will be allowed as a rescue medication during the treatment phase of the study.

Population:

Approximately 300 seasonal allergic rhinitis (SAR) patients, male and female, will be enrolled at 6 sites; 50/site.

Inclusion criteria

18-65 years of age, male or female

- Patients must meet criteria for the diagnosis of SAR to grass pollen: positive skin test to grass pollen, hx of SAR symptoms to grass pollen for a minimum of 2 years prior to study season.
- Patients are expected to have at least 2 hrs per day of outdoor exposure.
- If there is concomitant hx of perennial allergic rhinitis, these symptoms must be mild and would not be expected to contribute to a significant change in the patients symptoms during the study.
- Prior to randomization to treatment these patients must have a total score of 4/8, on a 0-4 scale, for the two symptoms of rhinorrhea and nasal congestion on at least 4 of the last 7 days

of baseline.

Exclusion criteria

- Disease or condition that may interfere with the evaluation of safety or efficacy (pregnancy, infection, active TB, compromised immunity, acute or chronic rhinosinusitis, nasal obstruction, asthma requiring steroids or Cromolyn, DM requiring drug therapy, hypertension >140/90, malignancy, clinically significant abnormal labs, etc.).
- Hx of significant adverse reactions to nasal steroids.
- Use of restricted concomitant medication, as presented in section 3.3 of the protocol.

Study Plan

Visit 1 (screening): obtain medical history, physical exam, nasal examination, allergy skin testing, clinical labs, and for females, a serum pregnancy test; patients will be given a diary to evaluate symptom severity.

Patients will record the overall symptom severity and duration (on average for the past 24 hrs) of each allergy symptom: nasal congestion, runny nose, sneezing, itchy nose/throat/palate and itchy red watery eyes, at approximately 7:00AM.

In addition, patients will record in the diary: concomitant medications and hours and type of outdoor air exposure.

The following scale will be used to score symptom severity:

- 0= not present
- 1= mild; present, but not annoying
- 2= moderate; present and annoying
- 3= severe; interferes with daily activities
- 4= very severe; unable to participate in daily activities

Baseline: for patients with >7 days baseline data, the last 7 days were used in the calculation. For patients with ≤7 days baseline data, all days were used; submission N (BM) dated 6/4/96.

According to this last submission, in 49% of patients the baseline was ≤ 7 days and for the rest of the patients, the baseline period consisted of 8-19 days.

Visit 2 (Day 1, start of treatment phase): determine eligibility for enrollment; physician's nasal exam and assessment of patient's symptoms; diary review; review of records of adverse events; dispense study drug (two bottles of Trinasal, 48 tablets of chlorpheniramine); instruct patient in correct use of spray bottles.

The physician assessment will rate the severity of the symptoms at each visit for the previous week. The symptoms to be rated in the physician assessment are: nasal congestion, rhinorrhea (runny nose/post nasal drip), sneezing, itchy nose/throat/palate and itchy red watery eyes. The symptom scoring method will be identical to the one used for the patient's diary.

The rating for the nasal examination for secretions and swelling will be done using the following scale:

Symptoms	0	1	2	3
Secretions	WNL	Slight	Moderate	Great
Swelling	WNL	Slight	Moderate	Great

Visit 3, 4, and 5, (Day 14± 1 day, Day 21 ± 1 day, and Day 28± 1 day, respectively): the diary and record of adverse events will be reviewed, the physician will do a symptom assessment and both patient and physician will do a global evaluation comparing the present treatment week to the baseline phase.

The following scale will be used for the global assessments:

- 6= symptoms are markedly worse
- 5= symptoms are moderately worse
- 4= symptoms are slightly worse
- 3= symptoms are the same
- 2= symptoms are slightly better
- 1= symptoms are moderately better
- 0= symptoms are markedly better

Visit 6 (Day 28 ± 1 day, final visit): The patient will have a repeat physical examination and nasal examination. The clinical labs will be repeated, the diary adverse event record will be reviewed, and the physician assessment and global evaluation will be done. For the female patient the pregnancy test will be repeated.

Study Medications

Each randomized patient will receive two bottles of study drug at visit 2 and at visit 4. Each dose will require patients to take 2 sprays per nostril, daily, from both bottles.

Metered dose nasal spray pumps will be used, each spray delivers 100 µl (containing 0, _____ and 50 µg/spray). Patients will be given detailed instructions on administration.

Treatment	Bottle A 2 sprays/nostril	Bottle B 2 sprays/nostril
Placebo	0 μ g TAA/spray	0 μ g TAA/spray
50 μ g TAA	— μ g TAA/spray	0 μ g TAA/spray
200 μ g TAA	— μ g TAA/spray	— μ g TAA/spray
400 μ g TAA	50 μ g TAA/spray	50 μ g TAA/spray

Blinding

The study placebo medication will be supplied in units identical to the active drug containers.

Early withdrawal criteria

- clinically significant abnormal laboratory value or one of uncertain clinical significance
- intolerable side effects
- patient non-compliance
- positive pregnancy test
- consent withdrawal
- investigator's judgement
- sponsor terminates study

Statistical Methods

Efficacy

Primary efficacy measure

Patient diary evaluation of symptom severity: intensity of symptom scores as rated by the patient for each of the symptoms specified in addition to the sum of symptoms defined as a composite nasal score (nasal congestion, rhinorrhea, and sneezing), are to be compared using the patient diary assessment of symptoms.

Baseline calculation: the average of the corresponding diary measurements for all days prior to the first dose of study medication.

Baseline: for patients with >7 days baseline data, the last 7 days were used in the calculation. For patients with \leq 7 days baseline data, all days were used; submission N (BM) dated 6/4/96.

Baseline: for patients with >7 days baseline data, the last 7 days were used in the calculation. For patients with \leq 7 days baseline data, all days were used; submission N

(BM) dated 6/4/96. According to this last submission, in 49% of patients the baseline was \leq 7 days and for the rest of the patients, the baseline period consisted of 8-19 days. A symptom severity index (SSI) will be calculated as the sum of three individual symptom severity scores (nasal congestion, rhinorrhea, and sneezing). The SSI has a minimum of 0 and a maximum of 12. Treatment group comparisons for each treatment week will be made using an ANCOVA model, adjusting for study site, with the corresponding baseline serving as the covariate in each model.

Secondary efficacy variables:

-For the physician's assessment, treatment group comparisons for individual symptoms for each treatment week and SSI scores, will be made using an ANCOVA model, adjusting for study site, with the corresponding baseline (Visit 2) serving as the covariate in the model.

- The physician's nasal exam will be rated using the following scale:

secretions and swelling:	0= within normal limits
	1= slight
	2= moderate
	3= great

Treatment group comparisons will be made using an ANCOVA model, adjusting for study site, with the corresponding baseline (Visit 2) serving as the covariate in the model.

-The patient's and physician's global evaluation will be analyzed for each treatment week using an ANOVA model adjusting for study site.

Concomitant medication: The frequency and percentages for the concomitant medications used will be calculated within treatment group. The number of patients not taking any concomitant medications during the double -blind phase study period will be tabulated. Treatment comparisons will be made controlling for study site.

Safety

Primary safety variables

Analysis of safety: All laboratory values, physical examination changes, and adverse reaction reports will be compared within groups and between groups.

- Adverse events will be analyzed individually and by body systems.
Number and % of patients will be displayed in the combined

TAA treatment group. Treatment groups will be compared with respect to number of patients who experienced the adverse event (by preferred name and by body system category) using the Cochran-Mantel-Haenszel test and controlling for study site.

-Changes in physical and nasal examination from baseline to final visit.

Shift in category (normal to abnormal etc.) will be compared among treatments, using the Cochran-Mantel-Haenszel test controlling for study site. For each vital sign parameter, treatment group comparisons will be made with respect to change from baseline using an ANOVA model adjusting for study site.

-Changes in clinical laboratory from baseline to final visit for hematology, blood chemistry and urinalysis. Treatment group comparisons with respect to final evaluation will be done using an ANOVA model adjusting for study site. For comparisons among treatments in category shift the Cochran-Mantel-Haenszel test controlling for study site will be used.

Reviewer's comments to the protocol:

The protocol does not specify what method will be used to randomize patients to treatment.

The protocol does not specify what measures will be used to assess patient's compliance with study medication.

Although the protocol states, under the section of diary record (4.2), that daily rain and pollen counts will be documented daily, the protocol does not specify by whom, where and how this is going to be done.

The protocol states that patients will be randomized to treatment within 5 days and that symptoms will be evaluated for enrollment during the start of the pollen season. However, the protocol does not specify how the start of the pollen season is going to be determined.

The reviewer could not find the patient's instruction for the use of the nasal spray in the protocol.

The unit pump to be used in the study was not specified.

The protocol does not justify the sample size selected.

The statistical plan does not include a statement of how missing data will be treated.

RESULTS

Blinding

To blind the Tri-nasal treatments, placebo was supplied in containers identical to the active drug. All evaluated medications were blind-labeled.

Randomization

The randomization was based on a total sample size of 312, four treatment groups, and it used a block size of four. The sponsor used a computer generated code.

Compliance

In the patient accounting and disposition sections, the study report mentions that the daily average weight of delivered study medication will be used to assess whether the patient can be considered to be evaluable for efficacy. A minimum weight of 0.72 grams is also mentioned to assess this parameter. This criteria was not part of the study protocol.

The reviewer could not find a listing of the used weight of study drug by individual patients.

The sponsor realized that the criterion for compliance used (83%) was not the one they had originally intended to use. The intent-to-treat analyses and conclusions do not change since this criterion was only applied for inclusion in the evaluable for efficacy subset, sponsor's correspondence dated 3/6/96.

Patient Numbers

The sample size calculation were made based on estimates from previous studies. It was estimated that a total of 60 patients per treatment group would provide greater than 80% power to detect a difference of 0.70 in symptom severity, based on a scale of 0-4 for nasal congestion.

There were 269 patients that enrolled in the study. The patients were studied at six study sites. Three of these sites were in California, from Table 1A, vol 4.31.

	Patients enrolled/site
Site 1: R.J. Dockhorn, Lenexa (KS)	51
Site 2: S. Spector, Los Angeles (CA)	48
Site 3: H.J. Schwartz, Cleveland (OH)	50
Site 4: G. Shapiro, Seattle (WA)	39
Site 5: B.M. Prenner, San Diego (CA)	35
Site 6: T. I. Chu, San Jose (CA)	46

Patient numbers by treatment from Table 1A, vol 4.31

	Placebo	50 μ g TAA	200 μ g TAA	400 μ g TAA	Total
Intent-to treat	66	68	69	66	269
Completed study	61	61	62	63	247
Did not complete study	5	7	7	3	22
Evaluable for efficacy	38 (58%)	44 (65%)	34 (49%)	36 (55%)	152 (57%)
Not evaluable for efficacy	23	24	35	30	117
Non-compliance study medication	11	15	23	17	66
use of restricted medication	15	12	16	13	56

There were more patients that were not considered to be evaluable for efficacy in the 200 and 400 μ g treatment groups. The two most common reasons for not been considered to be evaluable for efficacy were study medication non-compliance and restricted medication violation.

Study medication non-compliance was defined as those patients whose daily average weights of delivered study medication was less than 0.72 grams.

All 269 patients were evaluable for safety.

Discontinued patients

There were no statistical differences between treatment groups for the number of patients that discontinued the study, Table 1B, vol 4.31.

Twenty two patients discontinued the study after the baseline (Visit 2); according to the study report, data from these patients was included in the individual patient listings and in all applicable tables.

Of the 22 patients that discontinued the study, 8 patients did so due

to adverse events, according to the study report. Four of them were from the 200 μ g TAA treatment group, 1 from the 400 μ g TAA, 2 from the 50 μ g TAA and 1 from the placebo group. In only 2 of the patients, both from the 200 μ g TAA group, were the adverse events considered to be related to study drug. The cases of study discontinuation due to adverse events will be discussed in the safety section of the review.

After review of Table 1C, vol 4.31, the following patients classified as having discontinued the study due to other reasons, could also have been classified as discontinuing the study due to adverse events or inadequate treatment:

Placebo #307 -	"patient chose to drop out because of lack of decongestant and his consequently feeling "out of it"
Trinasal 50 μ g-	#116 "exacerbation of allergy and asthma symptoms, pt had to use prednisone" #216 "Pt lost to follow up due to URI. Pt discontinued on her own..."
Trinasal 200 μ g-	#115 "allergy symptoms too severe to continue, lost to follow up"

Demographics and patients characteristics at baseline

The mean age for the patients that participated in this study was 33-34 years of age. Fifty seven percent of the patients were female and the majority of the patients were Caucasian (82%). There were no statistical significant differences between treatment groups for age, gender and race, Table 2, vol 4.31.

Patients' past medical history. There were no statistical significant differences between treatment groups for the past medical history categories at baseline, Table 3, vol 4.31.

Physical exam. Of the vital signs and body systems evaluated, a statistical significant difference was found between treatment groups for respiratory rate. The range of means for the treatment groups was 15-16 (rpm). This is not a clinically significant difference.

The most frequently found abnormal findings were in the eyes (52 patients, 19%); throat (13 patients, 5%); skin (12 patients, 5%) and nose (8 patients, 3%).

Efficacy

The reviewer's comments will discuss the efficacy and safety results of the intent-to-treat population.

Intent-to-Treat Population

Even though the study protocol appeared to favor the analysis of all the patients' diary individual symptom scores over the SSI scores in the evaluation of the primary efficacy endpoint, in the study report the analysis of the SSI scores was selected as the most important parameter in the evaluation of the primary efficacy endpoint.

Symptom Severity Index (SSI)- Patient Diary

Baseline

It was stated in the study protocol that baseline would include at least 4 days of diary recordings prior to randomization to active treatment. In the study protocol's statistical plan it was stated that baseline would be calculated using the average of the corresponding diary measurements for all days prior to the first dose of study medication. However, in Table 5A1 describing the study results, it is stated that baseline includes 7 days of diary recording prior to active treatment.

Baseline: for patients with >7 days baseline data, the last 7 days were used in the calculation.

For patients with ≤7 days baseline data, all days were used; submission N (BM) dated 6/4/96.

According to this last submission, in 49% of patients the baseline was ≤ 7 days and for the rest of the patients, the baseline period consisted of 8-19 days.

No significant treatment-by-site interactions were reported at baseline, Table 5A1.

There were statistically significant differences at baseline for SSI scores. Both the placebo and the 400 µg TAA groups had statistically significant lower symptom scores than the other two active treatments. There were no statistically significant differences between the placebo and the 400 µg treatment group in symptom severity index scores at baseline, Table 5G1, vol. 4.31.

In view of the discrepancy in results of the higher dose formulation versus the lower dose formulations in terms of efficacy versus placebo (for SSI and individual symptoms), the statistical reviewer needs to assess whether the analyses used were adequate to differentiate whether the significant differences found in the study between the 50 and 200 µg formulations and placebo are real drug effects and not a carry-over effect from significant baseline differences.

Patient Diary- Adjusted Mean Symptom Severity Index (SSI), Intent-to-Treat, from Table 5A1, vol 4.31:

	Placebo	Tri-nasal 50 µg	Tri-nasal 200 µg	Tri-nasal 400 µg	P value

Baseline	6.29 N=66	6.92 N=68	6.90 N=69	6.02 N=64	0.001*
Week 1	5.64 N=66	4.72 N=65	4.66 N=69	5.29 N=65	0.010**
Week 2	4.89 N=64	4.07 N=64	3.93 N=66	4.68 N=63	0.022**
Week 3	4.75 N=61	3.88 N=62	3.79 N=64	4.28 N=64	0.049**
Week 4	4.65 N=61	3.68 N=60	3.59 N=63	3.81 N=63	0.026**

* Results are based on an ANOVA model with effects for treatment and site.

** Results are based on an ANCOVA model with baseline covariate and effects for treatment and site.

Summary of Symptom Severity Analyses for Symptom Severity Index (SSI),
from Table 5G1, vol 4.31:

	Placebo vs. Tri-Nasal 50 µg	Placebo vs Tri-Nasal 200 µg	Placebo vs. Tri-Nasal 400 µg	Tri-Nasal 50 µg vs Tri-Nasal 200 µg	Tri-Nasal 50 µg vs Tri-Nasal 400 µg	Tri-Nasal 200 µg vs. Tri-Nasal 400 µg
Baseline *	0.020	0.023	0.337	0.953	0.001	0.001
Week 1**	0.007	0.003	0.302	0.851	0.099	0.064
Week 2**	0.024	0.007	0.563	0.685	0.098	0.040
Week 3**	0.022	0.011	0.213	0.813	0.296	0.200
Week 4**	0.014	0.007	0.031	0.829	0.744	0.586

* Results are based on an ANOVA model with effects for treatment and site.

** Results are based on an ANCOVA model with baseline covariate and effects for treatment and site.

The symptom severity index score (SSI) improved in all treatment groups during the course of the study.

Biometrics was asked why there were more patients listed at week 1, N=65, than at baseline, N=64, for the 400 µg treatment group. The analysis was based on nonmissing data. For the patients in the 400 µg group, patients #219 and #310, had week 1 data but no baseline data. Patient #6, who had baseline data, did not have the week 1 observation; refer to Dr. Guo's review pages 7 and 8 in Appendix 3.

Patients receiving the Tri-Nasal 50 and the 200 μg treatment had greater improvement in the SSI scores than placebo for Weeks 1 through 4. This improvement was statistically significantly different from placebo at all treatment weeks.

No statistically significant differences were demonstrated between the SSI scores of the 400 μg treated group and placebo until Week 4.

There were statistically significant differences between the scores of the 200 and the 400 μg treated group for Week 2.

In Figure 9A, that depicts the patient diary evaluation for the severity of symptoms by treatment groups for the individual centers, pages 262 to 266, in volume 4.31, it is apparent that there is no good separation in the lines for those scores of patients on active treatment versus those on placebo during the treatment phase of the study.

Individual symptoms - Patient Diary

At baseline, the 400 μg Tri-nasal and the placebo group, had lower individual symptom scores for all individual symptoms, than the 200 and 400 μg Tri-nasal treatment groups.

For the Tri-Nasal 50 μg treatment group, there was a statistical significant improvement over placebo for the individual symptom score of nasal congestion from week 1 to week 4. A statistical significant improvement over placebo was also noted for sneezing (weeks 1-3) and rhinorrhea (weeks 1 and 4).

For the Tri-nasal 200 μg treatment group, there was a statistical significant improvement over placebo for the individual symptom scores of sneezing and nasal congestion from week 1 to week 4. A statistical significant improvement over placebo was also noted for rhinorrhea (week 1) and itchy N/T/P (week 1 to week 3).

For the Tri-nasal 400 μg treatment group, a statistical significant improvement over placebo for the individual symptom scores of rhinorrhea and nasal congestion was only demonstrated at week 4. No statistical significant improvement over placebo was noted for the individual symptoms of sneezing, itchy N/T/P or itchy R/W/eyes.

These results reflect the findings of the analysis for the SSI scores. A table giving the specific details follow.

Patient diary evaluation of individual symptom severity, intent-to-treat, adjusted mean scores, from Tables 5B1, 5C1, 5D1, 5E1, 5F1 and 5G1 from volume 4.31.

	Baseline	Week 1	Week 2	Week 3	Week 4
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Sneezing	[1]	[2]	[2]	[2]	
T 50	1.99*# (50vs400)	1.36*	1.11*	1.06*	1.03
T 200	2.07*# (200vs400)	1.28*	1.03*#(200vs400)	0.96*#(200vs400)	0.91*
T 400	1.65	1.48	1.35	1.25	1.07
Placebo	1.71	1.62	1.37	1.37	1.29
Rhinorrhea	[1]	[3]			
T 50	2.33# (50vs400)	1.62*	1.43	1.26	1.20*
T 200	2.42#(200vs400)	1.65*	1.34	1.29	1.26
T 400	2.08	1.79	1.56	1.47	1.22*
Placebo	2.23	1.93	1.62	1.55	1.55
Nasal Congestion	[1]	[2]			[2]
T 50	2.59*#(50vs400)	1.76*	1.52*	1.56*	1.45*
T 200	2.40	1.77*	1.60*	1.55*	1.44*
T 400	2.30	1.93	1.71	1.56	1.49*
Placebo	2.35	2.09	1.89	1.84	1.81
Itchy N/T/P	[1]		[2]	[2]	
T 50	1.95# (50vs400)	1.44	1.12	1.12	1.00
T 200	1.98# (200vs400)	1.24*#(200vs400)	0.93*#(200vs400)	0.84*#(200vs400)	0.93
T 400	1.59	1.54	1.34	1.29	1.15
Placebo	1.71	1.49	1.36	1.28	1.22
Itchy R.W/eyes	[1] [3]				
T 50	2.11*(50vs400)	1.76	1.31	1.37	1.28
T 200	1.99*(200vs400)	1.50	1.18#(200vs400)	1.09*#(200vs400)	1.03*
T 400	1.63	1.60	1.49	1.41	1.31
Placebo	1.65	1.48	1.42	1.44	1.45

[1] statistically significant differences between treatment groups, $p < 0.05$, analysis based on an ANOVA model with effects for treatment and site.

[2] statistically significant differences between treatment groups, $p < 0.05$, analysis based on an ANCOVA model with baseline covariate and effects for treatment and site.

[3] significant treatment by site interaction

* $p < 0.05$ between active treatment and placebo

$p < 0.05$ between active treatments

Patient diary evaluation of symptom severity

Dose-Response Analysis

The study report presents the dose-response relationship (as dose is increased from 0 to 400 μ g) for the patient diary evaluation of the adjusted mean SSI scores by treatment week in Figure 3A, vol. 4.31. A linear trend with p values ≤ 0.05 are reported for weeks 1, 3, and 4 and a cubic trend with p values ≤ 0.05 is reported for weeks 1 and 2. The study report does not discuss the meaning of these results in terms of the primary efficacy endpoint results where the effects of the 400 μ g dose were not found to be statistically significantly different from placebo until week 4. Further comments on the validity and meaning of the model used as it applies to this study, are deferred to the statistical reviewer.

Use of Rescue Medication

There were no statistical significant differences between the mean chlorpheniramine (mg) use during the study for patients on active treatment versus placebo, except for the Tri-nasal 400 μ g treatment group on week 2. The use of rescue medication by this group was significantly higher than placebo, Table 11A and 11B, vol 4.31.

The mean chlorpheniramine (mg) used per week was compared between active treatment groups. The mean (mg) used per week was statistically significantly higher in the Tri-nasal 400 μ g group versus the Tri-nasal 50 and 200 μ g groups for week 2, and versus the Tri-nasal 50 μ g group for week 4, Table 11A and 11B, vol 4.31.

A significant treatment-by-site interaction was found for these two weeks. These two interactions can be eliminated by removing patient #514, who ingested 192 mg of Chlorpheniramine maleate during treatment week 2, and 80 mg during treatment week 4, page 82, vol 4.30.

The number of patients on Tri-nasal 400 μ g that reported using chlorpheniramine during weeks 2 and 3, was lower than the number of patients using rescue medication, in the placebo and Tri-nasal 50 μ g treatment groups, during these two weeks.

Although there are no consistent statistically significant differences between active and placebo treated patients for this parameter, it is noted that the number of placebo patients using rescue medication during the treatment phase stayed at about the same level as week 1, and that the number of active treated patients using rescue medication by the end of treatment was less than at week 1.

Mean Chlorpheniramine (mg) taken during the study period by study week, intent-to treat, from Table 11A, vol 4.31.

	Placebo	Tri-nasal 50 μ g	Tri-nasal 200 μ g	Tri-nasal 400 μ g	P value [*]
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Week 1	15.03 N=20	14.00 N=19	13.16 N=15	14.67 N=19	0.988
Week 2	14.20 N=18	12.68 N=18	9.21 N=12	23.81 N=14	<.001[**]
Week 3	14.51 N=21	12.24 N=17	7.56 N=11	16.33 N=14	0.682
Week 4	14.47 N=20	5.89 N=12	9.07 N=12	12.36 N=13	0.176[**]

[*] Results are based on an ANOVA model with effects for treatment, site, and their interaction.

[**] significant treatment-by-group site interaction

Summary of chlorpheniramine usage (mg) analyses, intent-to-treat, from Table 11B, vol. 4.31.

	P vs 50 μ g	P vs 200 μ g	P vs 400 μ g	50 μ g vs 200 μ g	50 μ g vs 400 μ g	200 μ g vs 400 μ g
Week 1	0.972	0.761	0.906	0.761	0.880	0.851
Week 2	0.652	0.255	<.001	0.255	<.001	<.001
Week 3	0.843	0.550	0.476	0.550	0.384	0.247
Week 4	0.169	0.756	0.304	0.756	0.030	0.222

Other secondary efficacy parameters

Physician weekly assessment of symptom severity

There were statistically significant differences at baseline for SSI scores between the 50 μ g and 400 μ g Tri-nasal groups. The adjusted mean SSI scores in all Tri-nasal treatment groups were numerically lower than those of the placebo treated patients at each treatment week, Table 7A1, vol 4.31. The SSI symptom scores as assessed by the physicians, were statistically significantly better for patients treated with Tri-nasal 200 μ g versus placebo at weeks 3 and 4, and for patients receiving the Tri-nasal 400 μ g treatment, at weeks 1 and 4, versus patients treated with placebo, Table 7G, vol 4.31. However, these individual treatment differences were not large enough to show an overall statistically significant difference among treatments for the individual study weeks.

Patient global evaluation of symptom severity

Patients rated the Tri-nasal 50 and 200 μg treatments superior (statistically significant $p \leq 0.05$) to placebo at weeks 1, 2, and 4 and the Tri-nasal 400 μg at week 4. At other times the Tri-nasal scores were lower numerically (superior) than those of patients receiving placebo, but the results did not reach statistical significance, Tables 9A and 9B, vol 4.31.

Physician global evaluation of symptom severity

Physicians found the Tri-nasal treatments to be superior (statistically significant $p \leq 0.05$) to placebo at weeks 1 and 4, for all Tri-nasal treatment groups. The physicians rated the 200 μg treatment superior to placebo for all weeks of treatment ($p \leq 0.05$). The 50 μg treatment was rated superior ($p \leq 0.05$) to placebo on weeks 1, 2, and 4 of treatment. The Tri-nasal scores were lower numerically (superior) than those of patients receiving placebo, at all treatment weeks, Tables 10A and 10B, vol 4.31.

Nasal Examinations

There were no treatment differences with respect to differences in final examination between treatment groups with respect to nasal secretions or nasal swelling. All treatment groups improved from their examinations at baseline but there were no differences detected in terms of the extent of improvement in nasal secretions and nasal swelling across treatment groups, Tables 8A and 8B, vol 4.31.

Pollen count and frequency of rain during the study period

The sponsor included in the report the recorded tree, grass and total pollen count at the individual study centers. The report does not mention what method was used to record pollen counts at the individual study sites. The sponsor was asked to provide us with this information in teleconference dated 5/2/96. It should be noted that as part of the inclusion criteria, patients needed to be sensitive only to grass pollen, for study participation.

In Table 12 A, vol 4.31, the mean grass pollen counts/cubic meter are listed per center: Lenexa (KS):50.92; Los Angeles (CA):2.67; Cleveland (OH):64.80; Seattle (WA):15.92; San Diego (CA):4.56; San Jose (CA):18.33. Only one site, Cleveland, OH, had grass pollen counts consistently above 20 counts/ cubic meter, during the study duration. The Lenexa (KS) site had very low counts for the first 18 days that patients were enrolled, but thereafter the pollen counts were adequate, refer to Figure 7A, pages 237-242, vol 4.31.

Looking at the Figures that depict the mean patient diary evaluation of the symptom severity index (SSI) in placebo patients, at the individual study sites, Figure 8A pages 249-254 in vol 4.31, it is apparent that patients had symptom scores of 4 and above during the study duration at all centers except for the Los Angeles (CA) site. In this center, the

SSI scores were less than 4 during the last 14 days of study duration, however the daily grass pollen counts did not appear to change, that is, the pollen count was low throughout the study duration. The patient's mean SSI scores of 4 and above at this and other centers with low grass pollen counts may reflect exposure to allergens that these patients were sensitive to, that were not necessarily captured by the level of pollen count reported.

The sponsor does not report a statistical analysis on the frequency of rain days because of the large number of missing data of rainy days at individual centers.

Safety

Reviewer's comments:

Extent of exposure

A total of 269 patients were enrolled in the study. Of these:

66	received	Tri-nasal	400	µg
69	received	Tri-nasal	200	µg
68	received	Tri-nasal	50	µg
66	received	Placebo		

once daily for 4 weeks.

Adverse events

The number of patients with adverse events by treatment, intent-to-treat, was very similar, Table 13A, vol 4.31:

Placebo	75.8%	(50/66)
Tri-nasal 50 µg	70.6%	(48/68)
Tri-nasal 200 µg	75.4%	(52/69)
Tri-nasal 400 µg	69.7%	(46/66)

There were no statistically significant differences among treatment groups in the overall frequency of adverse events.

The total number of occurrences of adverse events by treatment, is reported in Table 13C, vol 4.31:

Placebo	188
Tri-nasal 50 µg	174
Tri-nasal 200 µg	190
Tri-nasal 400 µg	162

The treatment group with the lowest number of occurrences was the Tri-nasal 400 µg group.

Most adverse events were classified to be of mild to moderate severity, page 87, vol 4.30.

The list of the most common adverse events by treatment in decreasing order of percent of patients reporting these events by body system, is presented in Table 13A, vol 4.31. The most common adverse events listed were: headache, pharyngitis, application site reaction, asthma and rhinitis.

Adverse event	Placebo	Tri-nasal 50 μ g	Tri-nasal 200 μ g	Tri-nasal 400 μ g
Headache	44	46	51	42
Pharyngitis	8	12	20	12
Application site reaction	6	15	16	11
Asthma	9	7	6	6
Rhinitis	6	5	4	6

About twice as many patients on active drug reported application site reaction and pharyngitis versus those patients on placebo.

The following table, from Table 13A, vol 4.31, depicts the adverse experiences that were reported at a higher frequency in any of the active treatment groups compared to placebo and that were reported by more than 5% of the patients.

Number (%) of patients with adverse experiences by preferred term, intent-to-treat, from Table 13A, vol 4.31.

Adverse event	Placebo	Tri-nasal 50 μ g	Tri-nasal 200 μ g	Tri-nasal 400 μ g
Headache	44	46	51	42
Pharyngitis	8	12	20	12
Application site reaction	6	15	16	11
Back pain	2	4	7	6
Pain	5	4	3	6
Cough increased	3	3	3	6
Accidental injury	2	2	6	0
Dysmenorrhea	2	4	4	6
Conjunctivitis	2	0	6	5

All the adverse events listed in the above table were checked for relationship to study medication in Table 13C, vol 4.31. The following table depicts the percent of occurrences, by treatment, that were classified as drug related, at least possibly related. The adverse events from the above table that are not shown were not classified in the report as related to study drug. The adverse event, taste perversion, was added because even though it had been reported with a frequency of <5% all cases reported were classified as at least possibly drug related.

Percent of adverse event occurrences that were classified as drug related, from Table 13C, vol. 4.31.

Adverse event	Placebo	Tri-nasal 50 μ g	Tri-nasal 200 μ g	Tri-nasal 400 μ g
Headache	0	3	2	1
Pharyngitis	0	0	1	0
Application site reaction	2 (4/188)	9 (15/174)	7 (14/190)	5 (8/162)
Cough increased	0	1	0	0
Taste perversion	0	0	2	1

As can be seen from the above table, application site reaction was the adverse event reported at the highest frequency versus placebo that was considered to be related to study drug. It is not clear from the report what terms were grouped under the preferred term application site reaction. The sponsor was asked to provide us with this information on the teleconference dated 5/2/96.

In the same listing 13C one occurrence of tachycardia (moderate severity), in a patient receiving Tri-nasal 200 μ g, was classified to be drug related and a report of a mild episode of GI hemorrhage in a patient receiving Tri-nasal 200 μ g was classified as of unknown etiology. The study report does not include a brief clinical description of these cases. The sponsor was asked to provide us with this information, in teleconference dated 5/2/96.

Drop-outs due to adverse events

There were 8 patients that were reported to have discontinued the study due to adverse events: placebo:1, Tri-nasal 50 μ g:2, Tri-nasal 200 μ g:4, and Tri-nasal 400 μ g:1. Of these, two patients in the 200 μ g Tri-nasal group, had the adverse event classified as drug related.

Tri-nasal 50 μ g:

#220- 33 y/o Caucasian male, D/C after one week in the study due

to an URI that exacerbated asthma; the patient was treated with prednisone, ipratropium bromide, albuterol, and antibiotics.

#242- D/C 39 y/o Black female, D/C after 3 weeks of treatment due to an URI that exacerbated asthma symptoms. The patient was treated with prednisone, Tylenol, antibiotics and ear drops.

Tri-nasal 200 μ g

#150- 54 y/o Caucasian, D/C after 2 weeks of treatment due to severe headaches, classified as of unknown relationship to study drug. The headaches resolved with treatment.

#201- 35 y/o Caucasian female, D/C after 3 weeks of treatment due to severe annular tear at the L-3, L-4 level, classified of an other, known relationship to study medication in page 095 vol 4.31. This is probably a typographical error and the event is not related to study drug.

#231- 36 y/o Caucasian male, D/C study after two weeks of treatment due to severe burning (application site). The event was rated as definitely related to study medication. The event lasted two weeks and resolved after therapy was discontinued.

#408- 45 y/o Caucasian female, D/C after 3 days of treatment due to severe pharyngitis, that was rated as definitely related to study drug. The event resolved after discontinuation of therapy.

Tri-nasal 400 μ g

#233- 26 y/o Caucasian female, D/C after one day of treatment due to URI of moderate severity and of another known cause not related to study drug. The condition lasted three weeks, and at study closure the patient was listed as recovered.

Deaths

There were no deaths during the course of the study.

Clinical Laboratory evaluations

Hematology

There were no statistically significant changes when between treatment groups comparisons were made taking baseline as a covariate (Table 14, vol 4.31). There were numerically small changes in % eosinophil counts, that were significant when the within group comparisons were made from final evaluation to baseline, see following table. Although the degree of change in % eosinophil counts is not clinically significant by itself, it does correlate with the study's efficacy results.

Change in mean % Eosinophils from baseline to final evaluation, intent-to-treat, from Table 14, vol 4.31.

	Placebo	Tri-nasal 50 µg	Tri-nasal 200 µg	Tri-nasal 400 µg
Baseline	2.81 N=66	3.28 N=68	2.73 N=68	2.58 N=65
Final Value	2.64 N=66	2.35 N=63	2.00 N=67	2.23 N=65
Within-group p value*	0.326 N=66	0.000 N=63	0.001 N=66	0.218 N=64

* Within group p-value based on a paired t-test on the change from baseline

Chemistry

When the changes in mean values from baseline were evaluated there were a few statistically significant changes that are depicted in pages 99-100 of volume 4.30. These changes are not clinically significant (Table 15, vol 4.31). These were mean decreases in total protein (<0.15 g/dl), albumin (<0.10 g.dl), calcium (0.20 mg/dl), SGOT (<3 U/L), SGPT (<2 U/L) and alkaline phosphatase (<4 U/L).

In the chemistry lab individual patient results (Data Listing 19A, volumes 4.89 and 4.90) there are numerous instances of unexpected high values for creatinine kinase both at screening and at final evaluation. The study report does not mention it or explains this fact. The sponsor was asked to provide us with an explanation in the teleconference dated 5/2/96.

The study report does not discuss any individual abnormal lab value. Labs from all treatment groups were reported. The following abnormal lab reports from patients on active treatment were obtained from the Data Listing 19A in volumes 4.89 and 4.90:

**APPEARS THIS WAY
ON ORIGINAL**

Test	Screening	Final	Treatment	Pt. #	Sex	DOB
creatine kinase U/L	142	356 no retest done	Tri-nasal 200	109	M	
creatine kinase U/L	122	247 no retest done	Tri-nasal 200	228	M	
creatine kinase U/L	91	419 82 (Retest 3 weeks later)	Tri-nasal 50	406	F	
creatine kinase U/L	140	441 no retest done	Tri-nasal 400	426	M	
creatine kinase U/L	596 no retest done	949 no retest done	Tri-nasal 400	626	M	
creatine kinase U/L	77	1320 no retest done	Tri-nasal 50	646	F	
creatine kinase U/L	135	1950 no retest done	Tri-nasal 200	632	M	
creatine kinase U/L	249 no retest done	500 no retest done	Tri-nasal 200	637	M	
SGOT U/L	32	46	Tri-nasal 50	528	M	
SGPT U/L	74 79, 82- (Retest 3 days later)	114	Tri-nasal 50	528	M	
SGOT U/L	27	57	Tri-nasal 400	405	F	
SGPT U/L	34	64	Tri-nasal 400	405	F	
Total bilirubin mg/dl	0.8	1.7 (7/9/93) 1.4 (Retest 20 days later)	Tri-nasal 200	437	M	

- * early study termination
- * *Total bilirubin normal, patient terminated study early

From Data Listing 16 B in volume 4.86:

Patient #437 had Phenergan for nausea and acute gastroenteritis on 6/24/93. Patient #405 used aspirin for a total of 5 days during the study and was also on Proventil for asthma. Patient #528 was on either aspirin or acetaminophen for a total of 5 days for headache and on acetaminophen for 3 days for flu.

Patient # 406 was on acetaminophen or ibuprophen through out the study for sinus headaches, and 3 days specifically for sore muscles. This patient was on Lo-ovral. Pt # 426 had psoriasis and was on acetaminophen trough out the study for pain. He was also using triamcinolone ointment. Pt #632 is listed as using ibuprophen for 3 days for headaches. Pt # 228 used ibuprophen 1 day, and aspirin 1 day for headache. Pt # 646 is listed as usigg ortho-novum.

Patients 637, 109 and 626 are not listed as taking any concomitant medication.

The sponsor was asked to provide us with a brief clinical history and follow up of the patients reported in the above table in the teleconference dated 5/2/96.

Urinalysis

There were no statistically significant differences in pH, specific gravity at baseline or final evaluation within or among groups. For categorical parameters there were no statistically significant differences between treatment groups at either baseline or final evaluation, Table 16A, vol 4.31.

Physical examination

There were no statistical differences in weight at baseline or at final evaluation within groups or among groups (Table 17A, volume 4.31). There were statistically significant differences among groups for systolic or diastolic blood pressure. However, there were statistically significant within-group differences for both parameters. Systolic blood pressure in the 50 μ g group increased from 114 to 117 (mm Hg) and the diastolic blood pressure increased from 70 to 75 mm Hg (50 μ g) and 70 to 74 mm Hg (200 μ g). These changes are not clinically significant.

The physical examination of the lungs also showed statistical significant differences among treatments. There were 3 placebo treated patients that were found to have abnormal findings at final evaluation that had normal lung evaluation at screening, and 4 Tri-nasal 50 μ g treated patients that were found to have abnormal findings at screening and normal findings at final evaluation, Table 17A, volume 4.31.

Concomitant medications

Rescue medication was allowed in this study. Its use in the study was discussed in a previous section, under efficacy comments.

Patients taking the most common concomitant medications at a >10% frequency from Table 18 in volume 4.31. Only one medication of each type is counted for each patient.

	Placebo N=66	Tri-nasal 50 μ g N=68	Tri-nasal 200 μ g N=69	Tri-nasal 400 μ g N=66
Concurrent meds.	43 (65%)	52 (77%)	50 (73%)	43 (65%)
Anilides	26 (40%)	27 (40%)	24 (35%)	22 (33%)
Propionic acid derivatives	13 (20%)	17 (25%)	18 (26%)	11 (17%)
Progesterones and estrogens, fixed combinations	12 (18%)	9 (13%)	15 (22%)	10 (15%)
Selective beta-2-agonists	6 (9%)	8 (12%)	6 (9%)	8 (12%)

The study report does not include the necessary linking tables or figures for the reviewer to make the assessment as to whether the use of the most commonly used concurrent medications had any clinical interactions with the study drugs, particularly as it refers to adverse events. In the review of specific abnormal labs there were no particular safety concerns raised with the use of the above concomitant medications.

Overall conclusions

This was a double-blind, parallel, multicenter study that compared the efficacy and safety of Trinalasal at dosages of 50 μ g, 200 μ g and 400 μ g q.d. versus placebo for 4 weeks in the treatment of seasonal allergic rhinitis due to grass pollen in adults 18-65 years of age.

There were 269 patients enrolled in 6 centers. Patients had a minimum baseline period of 4 days. Patients evaluated treatment keeping a daily diary of symptom severity. Physicians evaluated the effect of the treatment on symptoms at weekly clinic visits. Chlorpheniramine 4 mg was allowed as a rescue medication during the treatment phase of the study.

The formulation used for the Tri-nasal treated patients is the to-be

marketed formulation. The intended dose delivered by actuation for the 50 and 200 μg doses were a — $\mu\text{g}/\text{spray}$ and — $\mu\text{g}/\text{spray}$ respectively, and for the 400 μg dose, it was 50 $\mu\text{g}/\text{spray}$. The study used the to-be-marketed formulation but did not use the to-be marketed pump. The characteristics of the to be marketed pump need to be supported by comparative data from the unit pump(s) used in this and other pivotal clinical studies.

The study results using the intent to treat population, support the efficacy of the 50 and 200 μg formulations. The study results do not support the efficacy of the 400 μg formulation but they do support its safety.

In view of the discrepancy in results of the higher dose formulation versus the lower dose formulations in terms of efficacy versus placebo (SSI scores and individual symptoms), the statistical reviewer needs to assess whether the analyses used were adequate to differentiate whether the significant differences found in the study between the 50 and 200 μg formulations and placebo are real drug effects and not a carry-over effect from significant baseline differences. From the draft Biometrics's review, it appears, that the efficacy with the 50 and 200 μg doses is not a carry-over effect from significant baseline differences.

In this study the results of other secondary efficacy endpoints does not clearly support in terms of statistical significant differences the superiority of the active formulations over placebo.

Efficacy

SSI scores

Patient derived symptom severity index (SSI) scores (rhinorrhea, nasal congestion and sneezing) was selected as the primary end-point for efficacy in the study report.

There were statistically significant differences for SSI scores at baseline. Both the placebo and the 400 μg TAA groups had statistically significant lower symptom scores than the other two active treatments. There were no statistically significant differences between the placebo and the 400 μg treatment group in symptom severity index scores at baseline.

Patients receiving the Tri-Nasal 50 and the 200 μg treatment had greater improvement in the SSI scores than placebo for Weeks 1 through 4. This improvement was statistically significantly different from placebo at all treatment weeks. There were statistically significant differences between the scores of the 200 and the 400 μg treated group for Week 2.

No statistically significant differences were demonstrated between the SSI scores of the 400 μg treated group and placebo until Week 4.

Individual symptoms

At baseline, the 400 μg Tri-nasal and the placebo group, had lower individual symptom scores for all individual symptoms, than the 200 and 400 μg Tri-nasal treatment groups.

For the Tri-Nasal 50 μg treatment group, there was a statistical significant improvement over placebo for the individual symptom score of nasal congestion from week 1 to week 4. A statistical significant improvement over placebo was also noted for sneezing (weeks 1-3) and rhinorrhea (weeks 1 and 4).

For the Tri-nasal 200 μg treatment group, there was a statistical significant improvement over placebo for the individual symptom scores of sneezing and nasal congestion from week 1 to week 4. A statistical significant improvement over placebo was also noted for rhinorrhea (week 1) and itchy N/T/P (week 1 to week 3).

For the Tri-nasal 400 μg treatment group, a statistical significant improvement over placebo for the individual symptom scores of rhinorrhea and nasal congestion was only demonstrated at week 4. No statistical significant improvement over placebo was noted for the individual symptoms of sneezing, itchy N/T/P or itchy R/W/eyes.

Rescue medication use

There were no statistical significant differences between the mean chlorpheniramine(mg) use during the study for patients on active treatment versus placebo, except for the Tri-nasal 400 μg treatment group on week 2. The use of rescue medication by this group was significantly higher than placebo, during week 2.

The mean chlorpheniramine(mg) used per week was compared between active treatment groups. The mean(mg) used per week was statistically significantly higher in the Tri-nasal 400 μg group versus the Tri-nasal 50 and 200 μg groups for week 2, and versus the Tri-nasal 50 μg group for week 4. A significant treatment-by-site interaction was found for these two weeks. These two interactions can be eliminated by removing patient #514, who ingested 192 mg of Chlorpheniramine maleate during treatment week 2, and 80 mg during treatment week 4.

The number of patients on Tri-nasal 400 μg that reported using chlorpheniramine during weeks 2 and 3, was lower than the number of patients using rescue medication, in the placebo and Tri-nasal 50 μg treatment groups, during these two weeks.

Although there are no consistent statistically significant differences between active and placebo treated patients for this parameter, it is noted that the number of placebo patients using rescue medication during the treatment phase stayed at about the same level as week 1, and that the number of active treated patients using rescue medication by the end of treatment was less than at week 1.

Physician symptom scores

For the physician rated assessments of symptom severity, there were statistically significant differences at baseline for SSI scores between the 50 μg and 400 μg Tri-nasal groups. There were no overall statistically significant differences between the active treatment groups and placebo for the 4 study weeks. The adjusted mean SSI scores in all Tri-nasal treatment groups were numerically lower than those of the placebo treated patients at each treatment week. The SSI symptom scores as assessed by the physicians, were statistically significantly better for patients treated with Tri-nasal 200 μg versus placebo at weeks 3 and 4, and for patients receiving the Tri-nasal 400 μg treatment, at weeks 1 and 4, versus patients treated with placebo. However, these individual treatment differences were not large enough to show an overall statistically significant difference among treatments for the individual study weeks.

Patient global scores

Patients rated the Tri-nasal 50 and 200 μg treatments superior (statistically significant $p \leq 0.05$) to placebo at weeks 1, 2, and 4 and the Tri-nasal 400 μg at week 4. At other times the Tri-nasal scores were lower numerically (superior) than those of patients receiving placebo, but the results did not reach statistical significance.

Physician global scores

Physicians found the Tri-nasal treatments to be superior (statistically significant $p \leq 0.05$) to placebo at weeks 1 and 4, for all Tri-nasal treatment groups. The physicians rated the 200 μg treatment superior to placebo for all weeks of treatment ($p \leq 0.05$). The 50 μg treatment was rated superior ($p \leq 0.05$) to placebo on weeks 1, 2, and 4 of treatment. The Tri-nasal scores were lower numerically (superior) than those of patients receiving placebo, at all treatment weeks.

Nasal examination

There were no treatment differences with respect to differences in final examination between treatment groups with respect to nasal secretions or nasal swelling.

Safety

The study results support the safety of the three doses of Tri-nasal used once/day for the four weeks of treatment.

A total of 269 patients were enrolled in the study and they were all evaluable for safety. Of these 66 received Tri-nasal 400 μg , 69 received Tri-nasal 200 μg and 68 received Tri-nasal 50 μg once daily for 4 weeks.

The percent of patients reporting adverse events in all treatment groups ranged from 70-76%. Patients treated with Tri-nasal 200 μg had

the highest frequency of adverse events and largest number of occurrences. The majority of the patients experienced adverse events that were mild or moderate in severity. The most common adverse event considered to be at least possibly related to study medication and that at the same time were reported at a higher frequency in active groups than in placebo were: application site reaction, headache and pharyngitis.

It is not clear from the report what terms were grouped under the preferred term application site reaction. The sponsor was asked to provide us with this information on the teleconference dated 5/2/96.

There was one occurrence of tachycardia (moderate severity), in a patient receiving Tri-nasal 200 μg , it was classified to be drug related. There was a report of a mild episode of GI hemorrhage in a patient receiving Tri-nasal 200 μg that was classified as of unknown etiology. The study report does not include a brief clinical description of these cases. The sponsor was asked to provide us with this information, in teleconference dated 5/2/96.

There were 8 patients that were reported to have discontinued the study due to adverse events: placebo:1, Tri-nasal 50 μg :2, Tri-nasal 200- μg :4, and Tri-nasal 400 μg :1. Of these, two patients in the 200 μg Tri-nasal group, had the adverse event classified as drug related.

#231- 36 y/o Caucasian male, D/C study after two weeks of treatment due to severe burning (application site). The event was rated as definitely related to study medication. The event lasted two weeks and resolved after therapy was discontinued.

#408- 45 y/o Caucasian female, D/C after 3 days of treatment due to severe pharyngitis, that was rated as definitely related to study drug. The event resolved after discontinuation of therapy.

There were no reported deaths.

There were no clinical significant differences in the mean changes from baseline to final evaluation for the hematology, u/a or chemistry laboratories obtained in this study.

In the chemistry lab individual patient results, there are numerous instances of unexpected high values for creatinine kinase both at screening and at final evaluation. The study report does not mention it or explains this fact. The sponsor was asked to provide us with an explanation in the teleconference dated 5/2/96. During the same teleconference, the sponsor was asked to provide us with a brief clinical history or the CRFs, for eight patients that have normal screening creatinine kinase values followed by abnormal values at final evaluation and for three patients that had either an abnormal serum transaminase value at final evaluation or total bilirubin value without a retest report.

10.e. Study No. 1-0501

Title: Relative potency of Nasal Triamcinolone Aqueous Solution on adrenal function in volunteers with allergic rhinitis.

Objective: To determine the potency of nasally applied triamcinolone acetonide solution on adrenocortical responsiveness in adult subjects with allergic rhinitis.

Study Protocol: Appendix A.2 in volume 15

Design

This is 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 μg , 400 μg , and 800 μg bid) on the HPA-axis in comparison to placebo and 10 mg/day of prednisone.

Population

The study plans to enroll a total of 28 volunteers (men and women), ages 18-50, in one study site.

Inclusion criteria

A clinical history of seasonal allergic rhinitis not optimally responsive to antihistamines/or decongestants and sensitive to tree and/or grass pollen. To corroborate allergy history, positive skin tests to the relevant allergen.

Minimal collateral allergic disease, otherwise healthy.

Women that are menopausal or surgically sterilized can participate.

Exclusion criteria

Asthma, infection, perforated nasal septum or polyposis, hypertension, cataracts or glaucoma, abnormal labs, use of inhaled, topical or nasal corticosteroid within the previous 3 mo or oral corticosteroids for the previous 6 mo, abnormal HPA-axis function during baseline.

Early withdrawal criteria

Development of an adverse clinical sign or symptom
Abnormal laboratory value, if clinically significant on retest
Deviation from protocol
Uncooperative patient
Lost to follow up
Levels of morning serum cortisol ($\leq 2.5\mu\text{g/dL}$) or urinary free

cortisol ($\leq 20 \mu\text{g/day}$), indicating substantial adrenal suppression.

Study Plan

Screening visit: medical history, physical exam and clinical labs.

Baseline visit: approx. one week following the initial screening, to assess pre-treatment patient response to cosyntropin. Twenty four hours prior to baseline, a 24-hour urine collection will be started. In the baseline visit to the Clinical Research Center (CRC), zero-time blood samples will be obtained followed by a 6 hr infusion of cosyntropin 0.25 mg (0.040 mg/hr). Blood samples q half hr, during infusion and 2 hrs after infusion. A 24 urine collection will be started at the time of cosyntropin infusion.

Serum will be assayed for cortisol, and urine for free cortisol and total 17-hydroxycorticosteroids.

Treatment phase: two weeks after baseline, patients with a normal serum level in response to cosyntropin, begin treatment phase for 42 days. They will come to the CRC for dosing each morning and evening. Patients will collect 24-hour urines on Days 7, 28, 35 and 42. Blood samples will be collected on Days 8, 29, 36 and 43.

Blood samples will be assayed for serum cortisol. A 24 urine sample will be assayed for free cortisol and total 17-hydroxycorticosteroids.

On Days 8, 29, 36 and 43, patients will undergo a brief physical exam, including blood pressure and nasal cavity examination.

Final visit (Day 43): HPA axis assessment same as in baseline visit.

Study medication

Patients will be randomized (5/group on active, 2 on placebo) to four treatment groups:

Group A: Prednisone 10 mg orally 7-8 am every morning, Deltasone tablets for 6 weeks or placebo

Group B: Triamcinolone 400 $\mu\text{g/day}$ (200 bid) or placebo

Group C: Triamcinolone 800 $\mu\text{g/day}$ (400 bid) or placebo

Group D: Triamcinolone 1600 $\mu\text{g/day}$ (800 bid) or placebo

Patients will be provided with Bromfed capsules- brompheniramine 12 mg with pseudoephedrine HCL 120 mg: 1 capsule bid. Patients

will record all relief medication used, date and quantity.

Triamcinolone acetonide will be supplied at a concentration of 0.5 mg/mL, using a _____ pump unit; each 100 μ l spray delivered will contain 50 μ g of the drug. Due to the volume of drug to be administered and the potential for study medication loss, the nasal sprays will be spaced, giving total volumes of 400 μ l at 30 min intervals (200 μ l/nostril). Instructions as to how to administer the nasal drug will be supplied to the investigator. Actual time of each dosing will be recorded.

Blinding

In the study, identical bottles and pumps delivering 100 μ l will be used for the nasal placebo. Prednisone will be concealed in a hard gelatin capsule. All drugs will be blind labeled.

HPA-axis assessment

Cortisol assay: Serum and urine cortisol will be analyzed by both _____ assay. The method for _____ assay is described in the protocol. The intra-day and inter-day coefficient of variation is _____ and the lower limit of steroid detection is _____

Normal range: Serum cortisol: 5-20 μ g/dl
urine free cortisol: >50 μ g/day but <150 μ g/day

Cosyntropin stimulation

Normal range: serum cortisol increase, not <7 μ g/dl, and typically 2-3 fold above baseline

Total 17-hydroxycorticosteroids assays for urine: _____ as well as the _____ will be used.

Normal range: total hydroxycorticosteroids (urine): >75 μ g/day but <200 μ g/day

Reviewer's comment:

The sponsor clarified in telephone conversation (2/23/96), that only _____ method was used to assay serum cortisol samples. This assay was performed in the study samples by _____. The sponsor agreed to provide us with the specifications for this method.

In the telephone facsimile dated 3/6/96 the sponsor provided us with the available information on _____ methods used to assay urine and serum cortisol and 17-OHCS in _____. _____ method used for urine and serum cortisol was a commercially bought kit purchased by _____, which is _____ and for which they have no further information, except _____

what is provided in the fax. The normal ranges for this assay are included. The laboratory normals used during the analysis of samples from this study were: AM serum cortisol, low limit of normal= _____ high limit of normal= _____ PM serum cortisol=low limit of normal _____ and high limit of normal= _____ However, the detectable limits and the coefficients of variation were not given. The _____ method was used to assay 17-OHCS. A list of drugs interfering with this assay was included as well as the ranges of detection and corrections on a known standard.

Safety evaluation

Adverse events: On Days 8, 29, 34 and 43, patients will be asked, without suggesting specific adverse events, to describe any adverse event that they may have experienced during the previous weeks. These will be recorded in the CRF.

Corticosteroid systemic effects: Serum cortisol and urine for free cortisol and 17-hydroxycorticosteroids will be obtained according to the study plan. If a patient has lab values suggesting substantial adrenal suppression, then the patient will be discontinued and subsequent visits will be scheduled until values normalized towards baseline.

Brief physical exam with blood pressure and nasal cavity examination will be done on Days 8, 29, 36 and 43. If there is suggestive evidence of monilia infection present, a culture will be obtained.

Statistical Plan

A minimum of 20 patients is required to give 80% power to show a 20% difference, using _____ assay. Patients that discontinue due to adrenal suppression will not be replaced.

Repeated measures analysis of the variance will be used to determine if adrenal suppression is occurring over time by comparison of morning cortisol, % increase in serum cortisol as a result of Cosyntropin stimulation, 24 hour urinary free cortisol, and 24 hour 17-hydroxycorticosteroids.

Between treatment group comparisons will also be made by analysis of percent change from baseline in each patient from each dose level of triamcinolone acetonide and prednisone.

The predetermined value for which a statistical difference will be assigned is when alpha is less than or equal to 0.05. When a difference is found to be significant, a multiple comparison test will be applied to determine the source of the difference. Grouped data will be analyzed with descriptive statistics.

Reviewer's comments on the protocol: