

- 3) sneezing
- 4) itching of the nose, throat, or palate

- positive "prick" skin test to mountain cedar, defined as 5 mm or greater than diluent

- 2 hours of outdoor exposure daily, expected

Exclusion criteria:

Asthma requiring use of steroids or Cromolyn

Restriction in medications prior to baseline:

- topical corticosteroids (nasal/oral inhaled), oral corticosteroids, Cromolyn sodium, for 4 weeks
- systemic corticosteroids and astemizole for 12 weeks
- other antihistamines for 1 week

The following medications were not allowed during baseline or during treatment phase:

- topical corticosteroids (nasal/oral inhaled), oral or systemic corticosteroids, Cromolyn sodium, antihistamines other than chlorpheniramine

Study plan:

On visit 1: Medical history, physical exam, vital signs, clinical labs(including pregnancy tests for females) and skin testing (if skin test had been done prior to 11/1/92) would be obtained.

Baseline period: for a period of 4-21 days after visit 1, patients will keep a daily diary of symptoms that will be used as part of the inclusion criteria. Chlorpheniramine is not allowed during the baseline period. The time of the day when symptoms are going to be recorded during the baseline period is not specified in the protocol. The period of time that this assessment will evaluate is not specified in the protocol.

After treatment is begun on visit 2, symptoms will be recorded in the diary before dosing, 7-10AM, to evaluate symptoms in the preceding 24 hours. Quantity and type of concomitant medication used, hours and type of outdoor exposure would be documented as well as any adverse events.

The protocol also notes that rain and pollen count would be documented in the diary record.

The five symptoms to be evaluated during the baseline and treatment periods are:

- nasal congestion
- rhinorrhea
- sneezing
- itchy nose/throat/palate
- itchy/red/watery eyes

The symptom rating scale:

- 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

The number of hours symptoms were present during the previous 24-hr period will be recorded in the daily diary.

The use of decongestants would be allowed up to baseline but restricted during baseline and treatment phase.

A physician assessment using an identical symptom scoring to the one used by the patients will be used at visit 2, 3, 4, 5, and 6. The symptoms to be evaluated are the same as previously described.

On visit 2 (Day 1, start of treatment) medications will be dispensed and IM medication administered.

On visits 3, 4, 5 and 6 the weekly IM medication will be administered. Patient's Trinasal and placebo bottles will be weighed for compliance and recorded in the case report form.

On visits 3,4, 5, and 6 in addition to the physician assessment, a global evaluation will be obtained by the patient, comparing the present treatment week to the baseline phase. The scale to be used:

- 6= symptoms were markedly worse
- 5= symptoms were moderately worse
- 4= symptoms were slightly worse
- 3= symptoms were the same
- 2= symptoms were slightly better (slight relief)
- 1= symptoms were moderately better (moderate relief)
- 0= symptoms were markedly better (marked relief)

A repeat physical examination, lab studies and pregnancy test will be done at the final visit.

The flow charts note a physician global evaluation at the last visit, Visit 6.

#### Study medication

This study uses the to be marketed formulation: 39-050-2. The study uses the ~~\_\_\_\_\_ pump~~. The to-be marketed pump is the ~~\_\_\_\_\_~~ Nasal Actuator. Page 053 in volume 4.1.

Nasal TAA and placebo supplied in an amber 15 ml glass bottle with a manual nasal pump unit; each spray delivers 100  $\mu$ l.

Tri-nasal treated patients will receive either 50 mcg of nasal TAA (using a  $\text{---}$   $\mu$ g/spray) or 400  $\mu$ g of nasal TAA by using a 50  $\mu$ g/spray.

To deliver 400  $\mu$ g of TAA, patients would be instructed to use 2 sprays in each nostril in the morning from 2 bottles containing 50 mcg TAA per spray. To deliver 50 mcg, patients would be asked to use  $\text{---}$  sprays in each nostril of a  $\text{---}$  mcg/spray solution, plus 2 sprays of the placebo TAA, also containing 100  $\mu$ l/spray. Since each spray delivers 100  $\mu$ l, the total volume delivery to each nostril would be 400  $\mu$ l/nostril/morning (0.4 ml). Patient's instructions for the use of the nasal pumps are included in the protocol's Appendix 2.

IM Kenalog-40 and placebo. The IM volume to be administered weekly was of 0.01 ml for a total of 4 mg/week.

Chlorpheniramine 4 mg, to be used up to qid, would be allowed as a rescue medication.

#### Blinding

The placebo medication will be supplied in units identical to the active drug. The person administering the medications will have no role in patient evaluation. All randomized patients will receive both the nasal spray and an IM injection during the treatment period.

#### Efficacy evaluation

##### Primary

Primary efficacy variable was defined in the protocol as the patient's diary evaluation of symptom severity consisting of: intensity of symptom scores 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, sneezing).

#### Secondary

-Physician weekly evaluation of symptom severity, using as a time frame the period of the week prior to the visit on which the assessment was made [N(BM)-6/4/96]: mean scores from physician evaluation of nasal symptoms and nasal physical examination are to be compared within and between groups.

-Global (overall) control of symptoms: patient and physician evaluation will be compared within and among groups.

- Concomitant therapy: use of chlorpheniramine will be compared within and between groups.

#### Safety evaluation

##### Primary

Analysis of safety: all lab values, physical examination changes, and adverse reaction reports are to be compared within and between groups.

All adverse reactions will be followed and reported

Cultures of fungal infections of the mucous membranes will be obtained if suspected.

#### Discontinuations

Patients will be discontinued from the study if any of the following criteria is met:

- clinically significant abnormality during screening or interim lab testing that is confirmed by a retest
- intolerable adverse events
- non compliance in study visits or fail to complete diary cards
- positive pregnancy test during study
- withdrawn consent
- for the patient's best interest as assessed by the investigator
- study is terminated by the sponsor

#### Statistical Plan

Sample size estimation: It was estimated that with a sample size of 60 patients per treatment group the study would provide greater than 80% power to detect a 0.70 difference in symptom severity for nasal congestion (using a scale of

0-4 with a two tailed test).

All treatment comparisons will be declared statistically significant at the 5% alpha level using two tailed tests.

For the patient diary assessments: individual symptom severity and duration of symptoms over the preceding 24 hours will be recorded. In addition a symptom severity index (SSI) will be calculated as the sum of the three individual symptoms severity scores for nasal congestion, rhinorrhea and sneezing. The SSI score has a minimum of 0 and a maximum of 12.

Baseline is defined as the average of all daily diary recordings prior to first dose of treatment.

Descriptive statistics will be presented for baseline and each week of active treatment for the severity of individual symptoms and SSI. Treatment group comparisons for each week of active treatment will be made on each individual symptom and the SSI, using an ANCOVA model adjusting for study site, with baseline serving for a covariate in each model.

Additional treatment group comparisons will be made using the DESIAPA model (daily effect scores after the second day, individually adjusted to the placebo average), proposed by the Pilot Drug Division for individual symptom severity and SSI scores.

Descriptive statistics will be done for the weekly physician assessments of individual symptoms and SSI scores (nasal congestion, runny nose and sneezing). The SSI score also has a minimum of 0 and a maximum of 12. Treatment group comparisons will be done using an ANCOVA model, adjusting for study site, with baseline assessment (Visit 2) serving as a covariate in each model.

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

Comparison of individual symptoms in terms of symptom duration. Descriptive statistics will be presented for each week of active treatment. Treatment group comparisons on each individual symptom will be done using an ANCOVA model, adjusting for study site, with baseline as a covariate. Graphical plots will be used to present mean duration of individual symptoms for each day in the study, by treatment.

Adverse events will be tabulated by body systems and treatment route. Percent of patients within body system

category, number of patients with each individual adverse event, and the number of patients with at least one adverse event will be compared among treatments, controlling for study site. Adverse events will also be tabulated by body system and maximum symptom severity.

Descriptive statistics will be done for each clinical lab for baseline (Visit 1), final evaluation, and change from baseline. Between group comparisons will be made with respect to change from baseline for each parameter using an ANOVA model adjusting for study site. Categorical changes (normal to abnormal, no change, abnormal to normal) will be tabulated, and percentages calculated for each treatment group. Comparisons between group will be done, controlling for study site.

Categorical changes in physical exam from baseline Visit 1 will be tabulated and calculated for each treatment group; between group comparisons will also be made. For each vital sign parameter, descriptive statistics will be given for baseline, final visit and change from baseline. Between group comparisons for change from baseline will be made, adjusting for study site.

#### **Reviewer's comment to the protocol**

Account for the use of rescue medication in the primary efficacy parameter: although the protocol specifies that the use of concomitant medication would be accounted for in the analysis as a secondary endpoint, and the statistical plan proposes to compare its use within and between treatment groups, the efficacy analysis plan does not take into account the fact that the reported patient's symptom scores, may have been directly affected by the use of concomitant medication in the preceding 24 hours.

Handling of missing data in the statistical analysis: The statistical plan does not specify how missing data is going to be handled in the analysis.

The minimum number of diary records/study week necessary for the evaluation of the primary efficacy variable was not specified.

The protocol does not specify how the individual centers are going to validate the pollen exposure. The protocol specifies that rain and pollen count will be documented daily. However, this statement is included in the paragraph that discusses the daily diary. No specific part of the CRF is designed to include this information. The protocol does not specify that the study centers should collect this information or how they should do it.

The protocol specifies that the patients in this study will receive 4 sprays of 100  $\mu$ l each, in each nostril, in the mornings. From clinical practice observations, it is very likely that part of this volume, particularly from the sprays applied last, would drain out of the nose. This raises the concern that: patients may on their own omit the last doses. Particularly, if patients receiving the Trinasal 400, are not receiving the appropriate dose, then we would not be evaluating the safety of a 400  $\mu$ g dose but that of a smaller dose.

According to the protocol, the study bottles would be weighted at the clinic visits and compared to the weight of a bottle that had been used according to the protocol. The protocol does not define what relative scale would be used to assess whether the patient had been compliant at each visit. A graphical representation and analysis of the mean used weight per individual bottle A or B, per treatment group, per week, is not planned for the statistical analysis.

Although the protocol specifies that the method used for physician weekly evaluation of symptom severity is identical to the one used for the patient's diary it does not specify what role or input the patient is going to have.

The CRF for the protocol asks the physician to classify adverse events as definite, possibly or probably related to study medication. However, the study protocol does not specify what these terms would be, and whether any relation to rescue medication will be considered.

Even though the protocol clearly states that all adverse events will be followed and reported, it appears that the adverse event recording will only take place at the weekly clinic visits. According to the submitted CRF, the daily diary will not include a space or instructions for adverse event recording. This may underestimate the incidence of adverse events for this study.

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## RESULTS

A revised final report for study 100-204 was submitted on 4/1/96. The revised report states: "Both the intent to treat and evaluable for efficacy diary analysis were rerun. None of the efficacy conclusions were affected. The p-values for pairwise comparisons changed minimally (in most instances only the decimal point was affected)."

The results and discussion that follows are based on the data included in the original submission dated 10/31/95, except where indicated. The MO review for this study had been completed prior to the 4/1/96 submission, and the intent-to-treat analyses and conclusions did not change.

Efficacy analysis involving patient diary assessments were done in both intent-to-treat and efficacy evaluable patient groups. Patients who were randomized to treatment at visit 3 were considered part of the intent-to treat population. The analysis based on this group was considered primary.

The patients that were found to be non-compliant by the following criteria were excluded from the evaluable efficacy subset:

- randomized patients that violated the criteria for diagnosis of SAR to mountain cedar as described in the protocol

In the correspondence dated 3/6/96 the sponsor stated that after revising the data in this study they found that the investigators had used a criterion based on the outside air exposure variable instead of the one based on patient symptoms as originally intended. This criterion for inclusion in the evaluable for efficacy subset was removed from the revised final report of this study, as is indicated in page 001 of the 4/1/96 submission.

- patient that had: severe deviated septum, structural defect or nasal polyps; rhinosinusitis during baseline or developed while on study medication; clinically significant neuropsychiatric disorders; a history excessive alcohol or drug abuse

- patients whose daily average weights of delivered study medication were less than 0.72 grams

After reviewing the calculations used for non-compliance in terms of usage of study medication, as a criteria for inclusion in the evaluable for efficacy subset, the sponsor realized that they had done a mistake and that a more restrictive criteria than was intended had been chosen (correspondence dated 3/6/96). A revised final report for this study was submitted 4/1/96. The sponsor's revised comments are included in the MO reviewer's comments for the population enrolled/analyzed section, that follows.

- use of restricted pre-study or concomitant medication

All descriptive analyses of patient characteristics at baseline were performed in the intent-to-treat patient group.

#### Population enrolled/analyzed

Two hundred and ninety seven patients were enrolled in 5 centers, with the following investigators:

William Howland, III, MD, Austin TX  
 Bruce Martin, MD, San Antonio, TX  
 Robert Jacobs, MD, San Antonio, TX  
 Paul Ratner, MD, San Antonio, TX  
 Joseph Diaz, MD, San Antonio, TX

Patient were randomized to one of four treatment groups:

50 mcg - 74 patients  
 400mcg - 75 "  
 4 mg IM - 74 "  
 placebo - 74 "

Of 297 patients enrolled, 269 completed the study. All 297 patients were evaluable for safety and 120 (40.4%) were evaluable for efficacy.

Patients randomized to treatment - (from Table 1A, vol 17)

| Patients               | Placebo | Trinasal 50 | Trinasal 400 | Kenalog 4mg |
|------------------------|---------|-------------|--------------|-------------|
| assigned to Rx         | 74      | 74          | 75           | 74          |
| completed study        | 67      | 63          | 72           | 67          |
| Not completing study   | 7       | 11          | 3            | 7           |
| evaluable efficacy     | 29      | 28          | 30           | 33          |
| non evaluable efficacy | 45      | 46          | 45           | 41          |

The most frequent reason reported for not been evaluable from the

efficacy standpoint was non compliance with study medication.

Reported reasons for not been evaluable for efficacy, from Table 1A, volume 17:

118 (39.7%) non compliance with respect to study medication

31 - placebo  
32 - Trinasal 50  
25 - Trinasal 400  
30 - Kenalog 4

42 (14.1%) inadequate exposure to mountain cedar at baseline

9 - placebo  
12 - Trinasal 50  
17 - Trinasal 400  
4 - Kenalog 4

16 (5.4%) use of restricted medication  
10 (3.4%) had rhinosinusitis at baseline or while on study  
3 (1.0%) clinically significant neuropsychiatric disorder  
2 (0.7%) structural defect in the nose  
1 (0.3%) excessive alcohol or drug intake

In the placebo group 7 patient developed rhinosinusitis during baseline or treatment.

The following listing, in Table 21B, vol 4.79, corresponds to patients terminated at the time of the final visit, by investigator, patient number, treatment, at the time of final visit:

|         | Placebo   | Trinasal 50                        | Trinasal 400          | Kenalog 4                     |
|---------|---|------------------------------------|-----------------------|-------------------------------|
| Howland | 105, 117,<br>140                                | 104, 145                           |                       | 102, 113, 145                 |
| Martin  | 218, 230  |                                    | 233                   | 250, 231                      |
| Jacobs  |   | 334, 358                           |                       |                               |
| Ratner  | 409, 404,<br>416, 436,<br>445, 452,<br>456, 460 | 437, 420,<br>447, 449,<br>454, 458 | 401, 415,<br>443, 446 | 406, 421,<br>441, 455,<br>459 |
| Diaz    |   | 530, 552                           | 507                   | 522                           |

**Reviewer's comments:** Although the distribution of non evaluable efficacy patients does not differ between treatment groups, the

number of efficacy evaluable patients is below the planned sample size calculations for the study to have adequate power to detect significant differences among treatments.

The listed number of patients that were considered to be non-compliant with study medication was 39.7% of the patients enrolled. However, there are no apparent differences in the proportion of these patients between treatment groups.

It is also noticeable the number of patients that were not considered to be evaluable for efficacy for the last visit, particularly in Dr. Ratner's study site. The case report forms for these patients is not included in the submission unless the patient had been discontinued due to an adverse event. We asked the sponsor for the CRFs from patients that are listed under Dr. Ratner's as not considered evaluable for efficacy in the last visit. These CRFs were submitted [N(BZ)-2/12/96] and reviewed for safety. No further safety concerns were elicited.

The sponsor had been asked to clarify the criteria for non-evaluable for efficacy due to non-compliance with study medication use, in a teleconference dated February 23, 1996. After reviewing the calculations used to determine compliance for the Tri-nasal groups, the sponsor concluded that the weight chosen resulted in a compliance criterion of 83% and not 67% as intended and reported. The use of the 83% value resulted in a more stringent criterion of compliance that they had originally intended; correspondence dated 3/6/96. Even though the intent-to-treat analyses and conclusions did not change, the sponsor chose to submit a revised report [N(BZ)-4/1/96], to correct the evaluable for efficacy analyses.

The following table depicts the percentage of non-compliant patients by treatment group (as a percent of the treatment group totals), for the 83% and 67% weight criteria for inclusion in the evaluable for efficacy subset, from page 04 in the correspondence dated 3/6/96.

| Compliance Criteria | Placebo | Tri-nasal 50 | Tri-nasal 400 | Kenalog |
|---------------------|---------|--------------|---------------|---------|
| 67% usage           | 20%     | 11%          | 11%           | 11%     |
| 83% usage           | 31%     | 28%          | 23%           | 23%     |

Using the less restrictive criteria for noncompliance, patients in the Tri-nasal group show greater compliance than placebo treated groups.

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## Discontinuations:

| Patients                  | Placebo | Trinasal 50 | Trinasal 400 | Kenalog 4 |
|---------------------------|---------|-------------|--------------|-----------|
| Not completing study      | 7       | 11          | 3            | 7         |
| Terminated visit 3        | 0       | 0           | 0            | 1         |
| Terminated Visit 6        | 7       | 11          | 3            | 6         |
| Reason: AE                | 1       | 1           | 1            | 0         |
| Medication non compliance | 1       | 1           | 0            | 2         |
| Other                     | 5       | 9           | 2            | 5         |

Narratives from patients discontinued due to adverse events (volume 16, pages 90-92):

### Placebo:

Pt.117 (Howland)

38 y/o w, female, burning of the nose and gagging (moderate severity), lasted for two weeks, resolved after drug was d/c. Patient was terminated early from the study on the final visit.

### Reviewer's comments:

CRF (vol 150): This patient complained 2 weeks after starting treatment that the "medication burned too much and dosage caused gagging." The patient's global for the first week of treatment was that symptoms were markedly better. However, for the second week the patient's global evaluation was that the symptoms were slightly worse. This patient rated as severe, sinus headache during two days of the baseline period. On two separate days during active treatment this adverse event recurred and was rated as moderate.

Nose burn, throat burning usually lasting for 5 minutes, nausea and gagging from quantity of medication delivered per dose.

Review of the study medication weight record reveals that the patient did not use the expected volume of study meds for the two weeks of treatment. The patient did not record using Chlortrimetron. The reviewer, after reading the CRF, concurs with the investigator that the adverse event is most likely related to

study medication.

Tri-Nasal 400:

Pt.401 (Ratner)

57 y/o, w, female, nosebleed (mod), lasted 1 hour after 2 weeks of treatment, resolved after drug was d/c.

**Reviewer's comments:**

CRF (vol 150): This patient had a nosebleed after two weeks of treatment and discontinued study medication. No recurrences were recorded after medication was d/c. The patient was taking daily Chlortrimetron tables and complained that these caused thirst continuously. The symptoms most helped was congestion, the eyes continued to be itchy and watery through out. This patient was on Premarin and Provera.

The contribution to this adverse event by the use of concomitant rescue medication and its common side effect, dryness of the mucosa, cannot be ruled out.

Tri-nasal 50:

Pt.454 (Ratner)

62 y/o, w, female, hives (mod), after one week of treatment. Resolved with medication. Patient on concomitant ASA, Relafen and Premarin.

**Reviewer's comments:**

CRF (vol 150): One day after starting treatment the patient developed hives. The patient had continued the previous meds, Relafen and Premarin. Initially, in the first days that the hives appeared, the patient had taken acetaminophen for headaches. ASA was started 4 days after hives had started. Chlortrimetron was started the same day that the hives were noted. It is not clear whether the hives began before or after the first dose of chlortrimetron was taken. The next day the patient received what appears to be an ?oral steroid (CFR photocopy -not clear). This patient had no previous history of urticaria recorded. The patient had been on the Relafen and Premarin for more than 1 yr.

Since the CRF records are not clear as to when the patient started using the rescue medication in relation to the first appearance of the hives, the role that the study drug may have had in this adverse event cannot be completely ruled out.

From the discontinued patient listing in Table 21B, volume 79, some patients that were listed as having discontinued the study early due to



#### Study conduct

According to the study report the original protocol was followed and there were no amendments made.

#### Compliance

Patients who failed to meet the weight usage criterion for Tri-nasal were considered to be non-compliant. According to the protocol the study bottles would be weighted at the clinic visit and compared to the weight of a bottle that had been used according to the protocol.

#### Database management

"The data from the CRFs were double data entered using \_\_\_\_\_ for DOS, version 4.5. The database was audited by generating a random 10% sample of the patients and comparing the CRF to database listings. An error rate of — % was used for safety and efficacy files; an error rate of — % was used for all other study files. The error rate was determined by dividing the number of error by the total number of datapoints and multiplying by 100. For those files that did not meet the error rate specification, a 100% manual verification of the CRF versus database listing was completed and all updates integrated prior to locking the database."

#### Reviewer's comments:

The report does not mention the results of the audited 10% of CRFs, specifically what listing if any failed. It is not clear whether after the audit of the 10% sample was done, the 100% manual verification of the CRFs was limited only to the affected fields in the 10% sample or if it included these affected fields found to have problems, for all CRF records.

Although the sponsor was not asked specifically about the details of the internal audit, a revised final report for study 100-204 was submitted on 4/1/96, due to the sponsor's mistake made in the inclusion criteria for the evaluable for efficacy subset. As stated in the report when the re-analyses of the efficacy subset was done, some database errors were discovered. These are included in the 4/1/96 submission and as stated in page 002 of that submission none of the efficacy conclusions were affected.

#### EFFICACY RESULTS:

Only the results of the intent to treat population: 297 patients, will be discussed.

"The data from the 28 patients that discontinued the study after baseline (visit 2) was included in the individual patient listings and in all applicable tables."

#### **Demographics and baseline characteristics**

The study reports finds no significant differences between treatment groups with regards to patient age, sex or race. In the intent to treat group, 43.4% were male. The majority of the patients were Caucasian. The percentage of other races: Hispanic (26.9%; 80/297), Black (2.4%; 7/297), Oriental (1%; 3/297), and other (0.3%; 1/297).

The patient's medical history data at screening across treatment groups did not show statistical differences in terms of abnormalities by body systems, including: EENT, pulmonary, and use of tobacco (vol 17, Table 3).

There were no significantly different abnormalities reported between treatment groups with respect to the physical examination: body system abnormality or vital sign. A significant group-by-site interaction was noted at baseline for diastolic blood pressure (Table 4A, vol 17, page 013) but there was no significant treatment interaction (appendix B, part 2.1 pages 022-024, vol 18). The mean values for diastolic blood pressure by treatment group follow: P (76.05); T-50 (75.62); T-400 (76.35); K-4 (76.88)-Table 4A, vol 17.

#### **Baseline symptoms**

##### **Patient derived diary scores**

##### **Baseline Patient Diary Evaluations and SSI scores:**

For the intent-to-treat (ITT), the adjusted mean baseline SSI scores in the active treatments, were numerically lower than in the placebo group. Tri-nasal, (TAA) 400 µg: 7.41, TAA 50 µg: 7.72 and Kenalog 4 mg:7.81, and placebo 8.30.

According to Table 5A1, vol 4.17 (intent-to-treat) the comparison of the treatment groups at baseline is statistically significant  $p=0.006$  based on an ANOVA model with effects for treatment, site and their interaction. The SSI scores at baseline for the placebo group, were statistically significantly different from the Tri-nasal 50 µg ( $p=0.025$ ), Tri-nasal 400 µg ( $p<0.001$ ) and the Kenalog 4 mg ( $p=0.051$ ) treatment groups (Table 5G1, vol 4.17).

In the ITT group, there is a significant group-by-site interaction for SSI scores ( $p=0.051$ ). Of the randomized treatment groups at baseline, two sites have significant

differences in the scores. Site 2, Dr. Howland (p=0.008), and site 5, Dr. Diaz (p=0.024)-Appendix E, Table E.01, vol 29, page 230. At site 2, P vs 400 (p=0.001), P vs 50 (p=0.024), 400 vs 4 (p=0.025). At site 5, P vs 4 (p=0.002).

### Baseline Individual symptom scores

Summary of symptom severity analysis at baseline from Table 5G1 (Intent to Treat), vol 17.

| symptom          | overall p value | P vs 50 | P vs 400 | P vs 4 | 50 vs 400 | 50 vs 4 | 400 vs 4 |
|------------------|-----------------|---------|----------|--------|-----------|---------|----------|
| sneezing         | 0.018 *         | 0.183   | 0.002    | 0.047  | 0.075     | 0.506   | 0.263    |
| rhino-rhea       | 0.012           | 0.021   | 0.001    | 0.032  | 0.375     | 0.862   | 0.289    |
| nasal congestion | 0.229           | 0.139   | 0.130    | 0.950  | 0.975     | 0.155   | 0.145    |
| itchy NTP        | 0.141*          | 0.047   | 0.043    | 0.288  | 0.972     | 0.353   | 0.334    |
| itchy/Eyes       | 0.042           | 0.028   | 0.007    | 0.067  | 0.625     | 0.711   | 0.390    |

\* significant treatment-by-site interaction at 0.10 Level

### Duration of individual symptoms at baseline

At baseline, (intent-to-treat), the mean duration of individual SAR symptoms was consistently numerically greatest in the placebo group. The duration of sneezing was significantly longer in the placebo group versus the other three treatment groups.

Adjusted mean:, (Table 6A1, vol 17)

P=8.89 hrs  
T 50=6.10 hrs  
T 400=6.35 hrs  
K 4=6.13 hrs

The recorded duration for rhinorrhea was statistically significantly longer in the placebo group than in the Tri-nasal treated groups.

Adjusted mean, (Table 6B1, vol 17)

|       |            |
|-------|------------|
| P     | 12.63 hrs  |
| T 50  | 9.65 hrs   |
| T 400 | 9.54 hrs   |
| k 4   | 10.87 hrs. |

### Physician evaluations

#### Baseline SSI scores and individual symptom scores

There were no significant treatment differences with respect to physician evaluations of SSI or individual symptoms at baseline (Table 7G, vol 17). The adjusted mean scores ranged from 8.21 in the Tri-nasal 50 group to 8.34 in the placebo group.

### Analysis of efficacy variables

#### Patient Diary Evaluation of Symptom Severity

##### Reviewer's comments:

The results displayed in the following tables for the SSI scores (sneezing, rhinorrhea and nasal congestion) in the intent to treat population, support the efficacy of the Tri-nasal 400  $\mu$ g over placebo at all four weeks of treatment. The statistical analyses (by week) used to evaluate the differences across treatments for SSI scores, took into account baseline as a covariate. However, it is not clear to the reviewer if these analyses would be the only ones that need to be done when these covariate values at baseline are statistically significantly different among themselves. The statistical reviewers are aware of this issue and will be looking into it.

All treatment groups, including placebo, had an improvement in the SSI scores from baseline to the last week scores. When the adjusted mean SSI scores by treatment groups for week 4, are subtracted from the baseline score, the difference appears to be almost the same for all treatment groups: 3.62 for placebo, 3.57 for Trinasal 50, 3.62 for Trinasal 400 and 3.78 for Kenalog 4. It is the rate of improvement over these 4 weeks that appears to be different among treatment groups.

The Tri-nasal 50  $\mu$ g and Kenalog 4 treatment groups failed to show adequate consistent efficacy versus placebo in the by week analyses. Kenalog 4 treated group had significant lower adjusted mean SSI scores than placebo, for weeks 2 and 3; Trinasal 50  $\mu$ g only for week 3. It would be important to demonstrate a significant difference in the first week of

treatment for an active treatment versus placebo to receive the indication to treat seasonal allergic rhinitis.

The consistent decrease in symptoms demonstrated in placebo treated patients could be the result of low pollen exposure.

The following tables show pertinent adjusted mean SSI scores and individual symptom scores from the patient's daily diary.

**Symptom severity index (adjusted mean SSI scores, Intent-to-Treat)** Adjusted mean Scores for SSI index from Table 5A1, vol 17.

| Week | Placebo | Trinasal 50 | Trinasal 400 | Kenalog 4 |
|------|---------|-------------|--------------|-----------|
| 0    | 8.30    | 7.73        | 7.41         | 7.80      |
| 1    | 7.07    | 6.97        | 6.24         | 7.11      |
| 2    | 6.60    | 5.92        | 5.05         | 5.81      |
| 3    | 5.71    | 4.71        | 4.30         | 4.59      |
| 4    | 4.68    | 4.16        | 3.79         | 4.02      |

Summary of symptom severity analysis (SSI scores), from Table 5G, vol 17, referring to the above table.

| week | overall p value | P vs 50 | P vs 400 | P vs 4 | 50 vs 400 | 50 vs 4 | 400 vs 4 |
|------|-----------------|---------|----------|--------|-----------|---------|----------|
| 0    | 0.006 *         | 0.025   | <.001    | 0.051  | 0.208     | 0.769   | 0.121    |
| 1    | 0.017           | 0.733   | 0.009    | 0.915  | 0.019     | 0.651   | 0.006    |
| 2    | <.001*          | 0.065   | <.001    | 0.032  | 0.019     | 0.769   | 0.038    |
| 3    | 0.003           | 0.011   | <.001    | 0.005  | 0.291     | 0.768   | 0.448    |
| 4    | 0.185           | 0.218   | 0.034    | 0.115  | 0.369     | 0.737   | 0.575    |

Results for Weeks 1, 3, and 4 are based on an ANOVA model with a baseline covariate and effects for treatment and site. Results for Week 2, are based on an ANCOVA model with a baseline covariate and effects for treatment, site and their interaction.

\* significant treatment-by-site interaction at the 0.10 Level.

Biometrics was asked to comment on the significant treatment-by site interaction at baseline and at week 2 in the above table. They referred to their previous response to a similar question in Study 100-309; Dr. Guo's review, page 6 and 3, Appendix 3. Biometrics considers the sponsor's approach to be correct. The

sponsor notes that there is a significant interaction, follows the protocol and does a by-site analyses of treatment effect.

The endpoint mean SSI scores are displayed in Figure 2, vol 4.17. Endpoint was considered to be the last available non-missing post baseline measure. A statistical analysis of this parameter was not included in the study report. The reported results were: Tri-nasal 400  $\mu$ g:3.57; Tri-nasal 50  $\mu$ g:4.41; Kenalog 4:4.03 and Placebo: 5.11.

#### **Individual symptom scores (intent-to-treat)**

The results of the individual symptom scores in the intent-to-treat population follow. The results are presented using the reported adjusted mean scores for the week, followed by the summary results from the statistical analyses.

There were statistical significant differences at baseline for placebo versus the active treatments for the following symptoms : sneezing -all except the Trinasal 50; rhinorrhea-all; nasal congestion-all; itchy/nose/throat/palate and itchy /red/watery eyes- all except Kenalog 4. The statistical analyses used baseline as a covariate.

Only Trinasal 400  $\mu$ g demonstrated consistent and statistically significant efficacy over placebo for the 4 weeks of treatment, for sneezing and rhinorrhea. For nasal congestion, it was significantly different from placebo in weeks 1, 2, and 3. For the symptom complex of itchy/nose/throat/palate, it was significantly better than placebo for weeks 1, 2, and 3 of treatment and for itchy/red/watery eyes symptom complex, on weeks 2 and 3.

It is important to note that treatment with Kenalog 4, a systemic steroid, did not show significant differences on itchy/red/watery/eyes, over placebo, except for week 2 and 3. Kenalog 4's effect versus placebo was demonstrated on sneezing for weeks 3 and 4, for rhinorrhea on week 3, nasal congestion for weeks 2, 3, and 4, and for the symptom complex itchy/nose/throat and palate for week 2 and 3.

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## Sneezing (adjusted mean scores, intent-to-treat) from Table 5B1

|                          | Week 0 | Week 1 | Week 2 | Week 3 | Week 4 |
|--------------------------|--------|--------|--------|--------|--------|
| Placebo                  | 2.61   | 2.19   | 1.93   | 1.66   | 1.40   |
| Tri-nasal 50<br>$\mu$ g  | 2.44   | 2.06   | 1.66   | 1.32   | 1.12   |
| Tri-nasal<br>400 $\mu$ g | 2.21   | 1.71   | 1.43   | 1.10   | 0.89   |
| Kenalog 4 mg             | 2.36   | 2.13   | 1.69   | 1.28   | 1.09   |

## Summary of symptom severity analysis from Table 5G1

## Sneezing

| week | overall<br>p value | P vs 50 | P vs 400 | P vs 4 | 50 vs 400 | 50 vs 4 | 400 vs 4 |
|------|--------------------|---------|----------|--------|-----------|---------|----------|
| 0    | 0.018*             | 0.183   | 0.002    | 0.047  | 0.075     | 0.506   | 0.263    |
| 1    | 0.002 *            | 0.337   | <.001    | 0.652  | 0.010     | 0.610   | 0.002    |
| 2    | 0.010              | 0.069   | <.001    | 0.101  | 0.114     | 0.853   | 0.075    |
| 3    | 0.002              | 0.019   | <.001    | 0.008  | 0.123     | 0.744   | 0.223    |
| 4    | 0.007              | 0.065   | <.001    | 0.040  | 0.117     | 0.845   | 0.167    |

\* significant treatment-by-site interaction at the 0.10 Level.

Results for Weeks 0, and 1 are based on an ANOVA model with effects for treatment, site and their interaction. Results for weeks 2 and 3 are based on an ANCOVA model with a baseline covariate and effects for treatment and site. Results for week 4 are based on an ANOVA model with effects for treatment and site.

## Rhinorrhea (adjusted mean scores, intent-to-treat) from Table 5C1

| Treatment               | Week 0 | Week 1 | Week 2 | Week 3 | Week 4 |
|-------------------------|--------|--------|--------|--------|--------|
| Placebo                 | 2.83   | 2.39   | 2.29   | 1.93   | 1.62   |
| Tri-nasal 50<br>$\mu$ g | 2.58   | 2.39   | 2.00   | 1.57   | 1.45   |

|                          |      |      |      |      |      |
|--------------------------|------|------|------|------|------|
| Tri-nasal<br>400 $\mu$ g | 2.48 | 2.08 | 1.65 | 1.42 | 1.20 |
| Kenalog 4 mg             | 2.60 | 2.42 | 2.03 | 1.58 | 1.41 |

Summary of symptom severity analysis from Table 5G1

#### Rhinorrhea

| week | overall<br>p value | P vs 50 | P vs 400 | P vs 4 | 50 vs 400 | 50 vs 4 | 400 vs 4 |
|------|--------------------|---------|----------|--------|-----------|---------|----------|
| 0    | 0.012              | 0.021   | 0.001    | 0.032  | 0.375     | 0.862   | 0.289    |
| 1    | 0.013              | 0.954   | 0.012    | 0.749  | 0.009     | 0.791   | 0.004    |
| 2    | <.001*             | 0.032   | <.001    | 0.055  | 0.010     | 0.804   | 0.005    |
| 3    | 0.004              | 0.012   | <.001    | 0.016  | 0.300     | 0.912   | 0.252    |
| 4    | 0.057*             | 0.273   | 0.007    | 0.181  | 0.112     | 0.817   | 0.172    |

\* significant treatment-by-site interaction at the 0.10 Level.

Results for Week 4 are based on an ANOVA model with effects for treatment, site and their interaction. Results for weeks 1 and 3 are based on an ANCOVA model with a baseline covariate and effects for treatment and site. Results for week 2 are based on an ANCOVA model with effects for treatment, site and their interaction. Results for week 0 are based on an ANOVA model with effects for treatment and site.

#### Nasal Congestion (adjusted mean scores, Intent-to-treat) from Table 5D1

| Treatment                | Week 0 | Week 1 | Week 2 | Week 3 | Week 4 |
|--------------------------|--------|--------|--------|--------|--------|
| Placebo                  | 2.87   | 2.61   | 2.44   | 2.14   | 1.85   |
| Tri-nasal 50<br>$\mu$ g  | 2.72   | 2.53   | 2.20   | 1.82   | 1.60   |
| Tri-nasal<br>400 $\mu$ g | 2.72   | 2.36   | 1.89   | 1.75   | 1.59   |
| Kenalog 4 mg             | 2.86   | 2.52   | 2.11   | 1.72   | 1.48   |

## Summary of symptom severity analysis from Table 5G1

## Nasal Congestion

| week | overall p value | P vs 50 | P vs 400 | P vs 4 | 50 vs 400 | 50 vs 4 | 400 vs 4 |
|------|-----------------|---------|----------|--------|-----------|---------|----------|
| 0    | 0.229           | 0.139   | 0.130    | 0.950  | 0.975     | 0.155   | 0.145    |
| 1    | 0.137           | 0.485   | 0.023    | 0.403  | 0.111     | 0.892   | 0.146    |
| 2    | 0.001*          | 0.094   | <.001    | 0.020  | 0.024     | 0.520   | 0.103    |
| 3    | 0.011           | 0.021   | 0.006    | 0.003  | 0.644     | 0.518   | 0.848    |
| 4    | 0.116           | 0.124   | 0.097    | 0.019  | 0.932     | 0.423   | 0.462    |

\* significant treatment-by-site interaction at the 0.10 Level.

Results for Week 2 are based on an ANOVA model with effects for treatment, site and their interaction. Results for week 0 are based on an ANOVA model with a baseline covariate and effects for treatment and site. Results for week 1, 3 and 4 are based on an ANCOVA model with effects for treatment and site.

Itchy/nose /throat/ palate (adjusted mean scores, intent-to-treat)

## Summary of symptom severity analysis from Table 5E1

| Treatment             | Week 0 | Week 1 | Week 2 | Week 3 | Week 4 |
|-----------------------|--------|--------|--------|--------|--------|
| Placebo               | 2.60   | 2.25   | 2.05   | 1.71   | 1.31   |
| Tri-nasal 50 $\mu$ g  | 2.34   | 2.13   | 1.73   | 1.34   | 1.08   |
| Tri-nasal 400 $\mu$ g | 2.33   | 1.85   | 1.48   | 1.18   | 1.05   |
| Kenalog 4 mg          | 2.46   | 2.12   | 1.68   | 1.32   | 1.12   |

| week | overall p value | P vs 50 | P vs 400 | P vs 4 | 50 vs 400 | 50 vs 4 | 400 vs 4 |
|------|-----------------|---------|----------|--------|-----------|---------|----------|
| 0    | 0.141*          | 0.047   | 0.043    | 0.288  | 0.972     | 0.353   | 0.334    |

|   |        |       |       |       |       |       |       |
|---|--------|-------|-------|-------|-------|-------|-------|
| 1 | 0.013  | 0.360 | 0.002 | 0.307 | 0.023 | 0.919 | 0.030 |
| 2 | 0.003* | 0.035 | <.001 | 0.016 | 0.108 | 0.777 | 0.183 |
| 3 | 0.005  | 0.016 | <.001 | 0.011 | 0.316 | 0.902 | 0.380 |
| 4 | 0.357  | 0.153 | 0.098 | 0.242 | 0.849 | 0.782 | 0.634 |

Results for weeks 1, 2, 3 and 4 are based on an ANCOVA model with baseline covariate and effects for treatment and site. Results for week 0 are based on an ANOVA model with effects for treatment and site.

\* significant treatment-by-site interaction at the 0.10 Level.

**Itchy/red /watery eyes (adjusted mean scores, intent-to-treat)**

| Treatment        | Week 0 | Week 1 | Week 2 | Week 3 | Week 4 |
|------------------|--------|--------|--------|--------|--------|
| Placebo          | 2.64   | 2.23   | 2.02   | 1.69   | 1.29   |
| Tri-nasal 50 µg  | 2.32   | 2.30   | 2.01   | 1.67   | 1.37   |
| Tri-nasal 400 µg | 2.25   | 2.01   | 1.66   | 1.36   | 1.09   |
| Kenalog 4 mg     | 2.37   | 2.19   | 1.69   | 1.38   | 1.06   |

Summary of symptom severity analysis from Table 5G1

| week | overall p value | P vs 50 | P vs 400 | P vs 4 | 50 vs 400 | 50 vs 4 | 400 vs 4 |
|------|-----------------|---------|----------|--------|-----------|---------|----------|
| 0    | 0.042           | 0.028   | 0.007    | 0.067  | 0.625     | 0.711   | 0.390    |
| 1    | 0.098           | 0.576   | 0.070    | 0.757  | 0.016     | 0.380   | 0.127    |
| 2    | 0.021           | 0.945   | 0.020    | 0.032  | 0.023     | 0.036   | 0.842    |
| 3    | 0.055           | 0.902   | 0.038    | 0.054  | 0.048     | 0.069   | 0.882    |
| 4    | 0.145           | 0.621   | 0.206    | 0.153  | 0.074     | 0.054   | 0.857    |

Results for week 1, 2, 3 and 4 are based on an ANCOVA model with a baseline covariate and effects for treatment and site. Results for week 0 are based on an ANOVA model with effects for treatment and site.

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Biometrics was asked why baseline was not used as a covariate for the individual symptoms of sneezing-week 1; rhinorrhea-week 4; and nasal congestion-week 2, noting that there had also been a treatment by-site interaction at these weeks. The sponsor followed the method specified in the protocol when there is a treatment by-site interaction and it is acceptable. When there is a treatment by-site interaction one cannot describe the magnitude of the baseline adjusted mean difference between the drugs or dose levels without considering that it differs depending of which center is considered. The measurements of the treatment effect are not comparable to baseline-adjusted measurements, refer to Dr. Guo's review, Appendix 3.

## Patient evaluation of symptom duration

### Reviewer's comments:

The mean week scores for the duration of individual symptoms as well as the change from baseline within treatment groups are depicted in Tables 6A1 to 6E2. There are only few instances where there are demonstrated significant differences between placebo and the active treatments in the duration of individual symptoms. Only the statistically significant differences will be noted.

In all the following cases the symptoms were recorded as lasting significantly longer in the placebo treated group vs the active treatments.

From Table 6F, vol 17, statistically significant differences of active treatments vs placebo  $p \leq 0.05$  were:

Sneezing: Trinasal 50 at baseline

Trinasal 400 at baseline

Kenalog 4 at baseline

Rhinorrhea: Trinasal 50 at baseline

Trinasal 400 at baseline and at weeks 2 and 3

Nasal congestion: Trinasal 50 at baseline

Kenalog 4 at week 3

Itchy nose/throat/palate: Trinasal 400 at baseline and at weeks 2, 3; and 4

Trinasal 50 at weeks 2 and 3

Itchy/red/watery/eyes: Trinasal 50 at baseline

Trinasal 400 at baseline.

From the above by week comparisons among treatment groups for individual symptoms the most frequent statistically significant differences ones are the ones at baseline. The other statistically significant comparisons between treatment groups are not consistent or persistent during the study duration.

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## Physician weekly assessment for symptom severity

### SSI scores

No significant differences were detected among treatment groups at baseline.

At baseline the scores ranged from 8.21 to 8.34 in the different treatment groups. The Trinasal 400 adjusted mean scores for weeks 1-4 were statistically significantly lower ( $p \leq 0.05$ ) than placebo. Trinasal 50 scores were statistically significant lower than placebo at week 2, and 3. Kenalog 4 scores were statistically significantly lower than placebo on weeks 2 and 3; Tables 7A1 and 7G in vol 17. At week 2 there was a significant group-by-site interaction.

### Individual symptom scores

No significant differences were detected among treatment groups at baseline for each individual symptom score.

Summary of statistically significant results ( $p \leq 0.05$ ) vs placebo from Table 7G in vol 17, for adjusted mean scores in a by week analysis:

Sneezing: Trinasal 400 at weeks 1-4  
Trinasal 50 at weeks 2 and 3  
Kenalog 4 at weeks 2, 3, and 4

Rhinorrhea: Trinasal 400 at weeks 1-4  
Trinasal 50 at week 2

Nasal Congestion: Trinasal 400 at weeks 1-4  
Trinasal 50 at week 2  
Kenalog at weeks 1-4

Itchy Nose/throat/palate: Trinasal 400 at weeks 1-4  
Trinasal 50 at weeks 1, 2, and 3  
Kenalog 4 at weeks 1, 2, and 3

Itchy/red/ watery eyes: Trinasal 400 at weeks 1-4  
Trinasal 50 at week 3  
Kenalog 4 at weeks 1, 3, and 4

When the post treatment-by week adjusted mean scores for individual symptoms were compared to their own group baseline score, all groups including placebo, had a statistically significant difference from baseline ( $p \leq 0.05$ ) for sneezing, nasal congestion, rhinorrhea, and itchy nose/throat/palate. For itchy/red/watery eyes, the Trinasal and Kenalog treatment groups the statistically significant differences were found at all treatment weeks but for the placebo group, statistically significant differences from baseline were only demonstrated on weeks 2-4.

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## Reviewer's comments:

The results of the physician assessment of symptoms described above in terms of the adjusted mean SSI scores and individual symptoms support the result that Trinasal 400 is superior to placebo through out the 4 weeks of treatment. The results for Trinasal 50 and Kenalog 4 demonstrate efficacy vs placebo only for weeks 2 and 3 for SSI scores, and sporadically for individual symptom scores at different weeks.

The effect that the use of rescue medication prior to the physician's assessments at the clinic visit may have had on the symptom scores is unknown since there were no restrictions in its use prior to these visits.

## Patient global evaluation of therapy

Patients (intent-to treat) rated their therapy in a range of 1.61 to 3.31 for the active treatments vs 2.77 for placebo, during the first week of treatment for all treatments. By week 4, the range was 0.94 to 1.27 for the active treatments and 1.75 for the placebo group. Table 8A in volume 17

Score 1 =moderately better and a Score 2 =slightly better.

When the active treatments were compared versus placebo in a by week analysis, the two Trinasal treatment groups had statistically significant lower scores than placebo for all weeks. Kenalog scores were statistically significantly lower than placebo at weeks 1, 2, and 4; Table 8B in volume 17.

## Physician global evaluation of therapy

The physicians rated the three active therapy groups at week 4 for the intent to treat population with lower scores (better) than the placebo group. The scores ranged from 1.08 to 1.59 in the active groups versus 3.31 for the placebo treated group; Table 9A, volume 17. The score of 1=moderately better and a score of 2=slightly better. These scores were statistically significant ( $p < 0.05$ ) different for the three active treatments vs placebo.

## Use of rescue medication

Descriptive statistics were done for the amount of chlorpheniramine (mg taken=# tabs x 4mg) taken during each treatment week. Inferential comparison between treatments were made.

Reported mean (mg) of chlorpheniramine taken during the study period from Table 10A, in volume 4.17.

|        | Placebo | Trinasal 50 | Trinasal 400 | Kenalog 4 |
|--------|---------|-------------|--------------|-----------|
| Week 1 | 3.55    | 2.81        | 1.63         | 3.05      |

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|        |      |      |      |      |
|--------|------|------|------|------|
| Week 2 | 3.09 | 2.14 | 1.02 | 2.01 |
| Week 3 | 1.60 | 1.13 | 0.92 | 0.96 |
| Week 4 | 1.26 | 0.96 | 0.42 | 0.79 |

There is a statistically significant difference reported for the use of rescue medication in the Trinasal 400 and Kenalog 4 treatments group versus the placebo group for week 2 and for Trinasal 400 vs placebo for week 4. Although there is a statistical difference between Trinasal 400 and placebo at week 1 there is also a significant treatment group-by site interaction.

### Reviewer's comments:

Although the frequency and percentages for concomitant medication may have been calculated within treatment group this information is not readily accessible from the referenced tables, listing and appendices. Treatment comparisons were made, as it is referenced in Tables 10A. However, we do not know how were the chlorpheniramine use means calculated.

As referenced in the report, vol 16, page 085, after a careful look at the individual patient listing for use of concomitant medication, Data Listing 14A and 14B in vol 69, it is noted that only a few patients recorded chlorpheniramine use. According to these listings, most of the use of the rescue medication was done during the screening period and in general two sites, Dr. Ratner's and Dr. Diaz', had the majority of the listed patients. In teleconference with the sponsor dated 7/16/96 it was clarified that they had incorrectly cited Tables 14A and 14B as the source Data Listings for Table 10A, it should had been Data Listing 10 titled "Patient Diary Evaluation and Rescue medication usage". The listing was originally submitted in the 10/31/95 submission and re-submitted with corrections on 4/1/96. The numbers provided in the submission dated 3/6/96 are correct.

In a teleconference dated 2/23/96, the sponsor was asked to provide us with the proportion of patients who took chlorpheniramine by treatment week. The following table was provided in the correspondence dated 3/6/96.

Proportion of patients who took chlortrimetron by treatment week and overall: numerator represents patients who took any chlortrimetron during the given time period, denominators represent the number of patients in the study for the given time period.

| Week (P Value)   | Placebo | Tri-nasal 50 | Tri-nasal 400 | Kenalog |
|------------------|---------|--------------|---------------|---------|
| Week 1 (P=0.051) | 55/73   | 48/74        | 41/75         | 51/74   |
| Week 2 (P<0.001) | 51/73   | 41/73        | 25/74         | 38/73   |

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|                      |       |       |       |       |
|----------------------|-------|-------|-------|-------|
| Week 3 (P=0.032)     | 38/69 | 25/71 | 24/73 | 26/70 |
| Week 4 (P=0.026)     | 30/67 | 19/65 | 15/72 | 21/68 |
| OVERALL<br>(P=0.024) | 63/73 | 58/74 | 49/75 | 58/74 |

P- value for Cochran-Mantel-Haenzel analysis controlling for site

In the revised final report table above, the number of patients using rescue medication is in the range of what would be expected in this type of study.

## Pollen count and frequency of rain during the study period

Mountain cedar pollen counts were recorded daily by site, for each seven day period from the first baseline date to the last patient treatment week 4 date at that site. Descriptive statistics were done by site. A second analysis was done, using descriptive statistics, in which the average daily patient exposure to pollen was calculated during baseline and each treatment week.

The pollen count, type of allergen and type of weather was recorded by study site and is reported in Data Listing 13, volume 69.

The data on pollen count and frequency of rain overall, by study week, and by study site is reported in Table 11A.

Mountain cedar pollen counts were reported to be similar across study sites when analyzed by individual study week and over the entire study period. They ranged from  $\text{---}/\text{m}^3$  to  $\text{---}/\text{m}^3$  at week 2.

Table 11 in volume 17, summarizes patient pollen exposure. The mean pollen counts recorded were:

Baseline      6471.5  $\pm$  3309/ $\text{m}^3$   
week 1        6886.5  $\pm$  2203.7/ $\text{m}^3$   
week 2        5091.1  $\pm$  2860/ $\text{m}^3$   
week 3        1873.2  $\pm$  2779.2/ $\text{m}^3$   
week 4        1160.4  $\pm$  947.6/ $\text{m}^3$

The large standard deviation observed in the pollen counts are attributed to wide day-to-day variations.

## Reviewer's comment:

The method used to collect this data is not reported in the protocol or in the study report. In the correspondence dated 3/6/96, the sponsor

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reports that pollen counts were done by 3 of the 5 investigators. Two investigators used ~~\_\_\_\_\_~~ sampler (Howland and Martin) and the other (Ratner) a ~~\_\_\_\_\_~~ device \_\_\_\_\_.

From the mean overall pollen data it appears that for week 3 and 4 the patients were exposed to less pollen than during the first two weeks.

There are differences by week at different study centers: Week 1, Dr. Martin's center had the lowest recorded pollen count of the 5 study sites; for weeks 2, 3 and 4 it was Dr. Howland's site that had the lowest counts. It would be of interest to see what would happen to the analysis of efficacy if the scores from Dr. Howland's patients are not included in the analysis.

The review of Data Listings 13 in volume 69, also shows that in many instances the individual centers did not record the type of weather at that center. However, after looking at the recorded pollen counts it appears that for the most part if it had rain at the center it was recorded, even though not all low counts had recorded the type of weather for that day.

## **Efficacy conclusions**

Provided that the statistical reviewers find the statistical analyses used adequate to eliminate the residual effect of baseline differences in the analysis, then this study would support the efficacy of Trinasal 400 $\mu$ g versus placebo.

The results of the intent-analysis of the patient's daily diary, using a retrospective 24 hr assessment, for SSI scores and individual symptoms (sneezing, rhinorrhea) for all study weeks; nasal congestion, itchy/nose/throat/palate and itchy/red/watery eyes, for weeks 1-3, support the efficacy of Trinasal 400  $\mu$ g versus placebo.

In addition, from the physician's weekly assessment, the SSI scores and individual symptoms for all 4 weeks also support this conclusion. It should be noted that there were no significant differences in symptom scores at baseline for the physician's assessments. Although, it is not clear by the protocol what was the contribution from the patient to this assessment.

The results of the study in the intent-to treat population, patient's diary assessment, support the superiority of the topical Trinasal 400 $\mu$ g over Kenalog 4 mg IM at weeks 1 and 2 for SSI scores, and individual symptoms (sneezing (wk1), rhinorrhea (wk 1 and 2), and itchy nose/throat/palate (wk 1)).

Although the scores for the Trinasal 50 were lower than placebo, the results did not show significant differences versus placebo except for week 3 (SSI scores, sneezing, rhinorrhea, nasal congestion and itchy nose/throat and palate).

A topical effect for Tri-nasal 400  $\mu$ g vs Kenalog 4 mg IM was not

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demonstrated in this study.

Patients on Kenalog 4 mg IM demonstrated a statistically significant improvement in SSI scores (primary endpoint) versus placebo only for weeks 2 and 3. Kenalog 4 mg improved the following individual symptoms compared to placebo: sneezing (week 3 and 4), rhinorrhea (week 3), nasal congestion (week 2, 3, and 4), itchy nose/throat/palate (weeks 2 and 3), itchy red/watery eyes (weeks 2 and 3). Tri-nasal 400  $\mu$ g qd was superior to placebo for all weeks of treatment (SSI scores) and significant improvement versus placebo was demonstrated during all study weeks for sneezing and rhinorrhea, and during weeks 1-3 for nasal congestion. Trinasal 440  $\mu$ g was superior to Kenalog 4 mg IM q week for the first 2 weeks of treatment in terms of SSI scores. It was also superior to Kenalog improving sneezing during week 1; rhinorrhea during week 1 and 2; itchy nose/throat/palate during week 1; and it was not found to be different from Kenalog for nasal congestion or itchy/red/watery eyes.

The selected dose and route of administration of 4 mg Kenalog IM q week is not considered to be an adequate comparator to assess the topical effect of the Tri-nasal solution. Blood levels for the drug were not obtained in study 100-204, but the results of the single dose pharmacokinetic study, 100-104, comparing Tri-nasal 400  $\mu$ g to Kenalog 4 mg IM, suggest that a weekly dose of Kenalog 4 mg would produce much lower systemic levels than what would be expected with daily doses of Tri-nasal 400  $\mu$ g in terms of C<sub>max</sub> and AUCs. Therefore, the efficacy of Tri-nasal could be considered to be secondary to higher systemic exposure rather than to a local topical effect.

Study 100-104, page 067, vol 4.1

|           | Trinasal 400  | Kenalog 4 mg IM |
|-----------|---------------|-----------------|
| C max     | 1.91 ng/ml    | 0.40 ng/ml      |
| AUC 0-168 | 33.22 ng·h/ml | 44.89 ng·h/ml   |
| AUC 0-12  | 6.92 ng·h/ml  | 3.22 ng·h/ml    |
| T max     | 0.36 h        | 18.67 h         |

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

This study does not support the to-be marketed nasal spray pump. The to be marketed unit pump, ~~nasal~~ nasal actuator is not the same pump that was used in this study. The characteristics of the to be marketed pump need to be supported by comparative data from the unit pump used in this and other pivotal clinical studies.

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## Safety

### Extent of exposure

The report states that 297 patients were enrolled in the study. Of these 74 patients received Trinasal 50, 75 were treated with Trinasal 400, and 74 patients each receive either 4 mg of Kenalog 40 or placebo. According to the tables in this section all were considered evaluable from the safety stand point.

### Adverse events:

#### Overall Occurrences

These were tabulated by COSTART body system and by individual COSTART preferred terms. Total number of patients with at least one adverse experience were compared across treatments. Inferential comparisons of the number of patients with each individual adverse event were only presented if this was experienced by 5% or more of the patient sample.

There were no differences between treatment groups in the overall frequency of adverse events. From Table 12A, the individual group frequency of adverse events was:

|              |       |
|--------------|-------|
| Trinasal 400 | 68.0% |
| Trinasal 50  | 68.9% |
| Kenalog 4 mg | 71.6% |
| Placebo      | 66.2% |

The most commonly reported adverse events at a frequency greater than placebo were:

#### Headache:

#### Pharyngitis:

|              |               |       |
|--------------|---------------|-------|
| Trinasal 400 | 49.3% (37/75) | 14.7% |
| Trinasal 50  | 45.9% (34/74) | 16.2% |
| Kenalog 4 mg | 60.8% (45/75) | 6.8%  |
| Placebo      | 52.7% (39/74) | 12.2% |

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From Table 12A, volume 17, the number of patients reporting other adverse events recorded at a higher frequency than placebo by individual treatments are:

|                    | Placebo<br>N=74 | Trinasal 50<br>N=74 | Trinasal 400<br>N=75 | Kenalog 4<br>N=74 |
|--------------------|-----------------|---------------------|----------------------|-------------------|
| epistaxis          | 2.7%            | 8.1%                | 2.7%                 | 0%                |
| cough<br>increased | 2.7%            | 1.4%                | 1.3%                 | 5.4%              |
| ear pain           | 2.7%            | 2.7%                | 1.3%                 | 6.8%              |
| myalgia            | 0%              | 4.1%                | 6.7%                 | 2.7%              |

From Table 12B, volume 17, the myalgia was reported as mild or moderate. One episode of epistaxis was reported as severe in the Trinasal 400 treatment group. The other reports of epistaxis were recorded as mild for Trinasal 50. Ear pain was reported as moderate in 3, and as severe in 2 patients treated with Kenalog 4 mg. Four patients on the Kenalog group reported cough increase of moderate severity and in the placebo group one patient reported a severe cough increase.

From Table 12C, volume 17, 7 reports of mild epistaxis associated with the use of Trinasal 50 were considered to be drug related.

The number of adverse experiences was tabulated by individual COSTART body system and preferred term for maximum severity.

The incidence of severe pharyngitis was 1.4% in the placebo group, 0% in the Trinasal 50, 2.7% (2/75) in the Trinasal 400 group and 1.4% in the Kenalog 4 mg group.

The number of occurrences of each individual event was tabulated by body system.

The total number of adverse event and the ones with the highest number of occurrences by treatment were:

Trinasal 400 - 162 events -  
most common: headache, 59.3% (96/162)

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Trinasal 50 - 169 events -

most common: headache, 53.8% (91/169)

Kenalog 4 - 194 events -

most common: headache, 61.3% (119/194)

Placebo - 221 events - most common: headache, 45.7% (101/221)

## Reviewer's comments:

Headache was an adverse event that was more frequently reported in the active treatment groups than in placebo. This was true for both the number of patients that reported this adverse event as well as for the number of occurrences. The Kenalog 4 treatment group had the highest number of patients reporting this event, and the largest number of occurrences per patient. It is not uncommon to see this adverse event reported with a high frequency in allergic rhinitis trials. However, the rate of reports per patient is higher than expected compared to the two other active treatments and placebo. The number of occurrences ÷ number of patients reporting the adverse event was 2.6, 2.5, 2.6 and 3.8 for placebo, Trinasal 50, Trinasal 400 and Kenalog 4 respectively.

Pharyngitis was reported with a higher frequency in the patients using the nasal sprays than in those patients treated with Kenalog 4. There were no obvious differences in the frequency of this adverse event or in its severity among those patients treated with Trinasal 400 vs those receiving Trinasal 50.

Rhinitis was rated by a majority of the patients reporting this adverse event as been drug related. It was reported with a higher incidence in placebo patients than in the active treatments, placebo: 10/74 (13%), Trinasal 50: 2/74 (3%), Trinasal 400: 1/75 (1%) and Kenalog 4: 3/74 (4%) in Table 12A, volume 17. For all the reports it was rated as mild or moderate in Table 12B, vol 17. It appears that although the placebo patients may have interpreted having rhinitis symptoms as been drug related, this symptom could have been the normal expected response in the untreated rhinitic mucosa.

## Clinical Laboratory

### Hematology

#### Reviewer's comments:

There were statistically significant differences between treatment groups for WBCs, when the values from the final evaluation were compared to baseline values. The WBC increased for Kenalog 4 treated patients from 6.74 to 7.17/ $\mu\text{L}$  ( $\times 10^3$ ), Table 13, vol 17. Placebo patients did not have a statistically significant change from baseline.

For eosinophilia the statistically significant changes noted were: a decrease in eosinophilia in the Kenalog 4 group [from 2.78 to 2.09/ $\mu\text{L}$  ( $\times 10^3$ )] and an increase in eosinophil counts in the placebo group

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[from 3.08 to 3.66 / $\mu$ L ( $\times 10^3$ )], Table 13, vol 17.

The two examples shown above reflect known systemic steroid effects of Kenalog 4 compared to placebo in an allergic rhinitis population exposed to seasonal allergens.

There were other differences from baseline in the hematology parameters studied that were also statistically significant. They were quantitatively small and not considered to be of clinical significance or specific interest.

## Blood chemistry

### Reviewer's comments:

There were statistically significant differences between treatment groups, when the lab values from the final evaluation were compared to those at baseline. In general the differences in numerical values were small and not considered clinically significant, Table 14, vol 17.

The BUN increased in the Kenalog 4 group from 11.92 to 12.82 mg/dl, without any significant changes in the other treatment groups. There were no significant changes among treatment groups with respect to serum creatinine.

Glucose increased in the Trinasal 50 group from 86.7 to 91.4 mg/dl but there were no other significant changes in the other treatment groups.

Phosphorous increased from 3.46 to 3.64 mg/dl in the Kenalog 4 group but the changes in the other treatment groups were even smaller.

Triglycerides decreased in the Kenalog 4 group (141 to 125 mg/dl) and in the Trinasal 400 group (173 to 150 mg/dl) and there were no significant changes in the Trinasal 50 or in the placebo groups. There were no treatment related differences in cholesterol values.

Three placebo patients had a shift from normal at baseline to abnormal at final evaluation in total bilirubin. For blood chemistry values, with exception of total bilirubin, shifts in all other parameters were similar between treatment groups.

## Urinalysis

### Reviewer's comments:

In the urinalysis, the only statistically significant difference between treatment groups was the presence of blood in the urine at the final evaluation. Among the four diagnostic categories: "+", "++", "+++" and "trace", there was a decline in the number of patients in the ++ and +++ categories except for the placebo treatment group.

In the "+" and "trace" categories, the number of patients increased at final evaluation for the Kenalog group (from 5 to 11 patients) and for Trinasal 400 (from 6 to 10 patients). The report notes that the

hematuria was considered to be due to menstrual bleeding and not of clinical significance.

#### **Other Safety Assessments**

##### **Physical Examination**

##### **Reviewer's comments:**

There were no clinical significant changes in the parameters studied and reported in Tables 16A and 16B, vol 17.

##### **Concomitant Medications**

##### **Reviewer's comments:**

Approximately 75-80% of patients in all treatment groups used a concomitant medication during the study, other than rescue medication. The most frequent medications used were the anilides (acetaminophen and derivatives for headache), Trinasal 50: 32%, Placebo: 43%, Trinasal 400: 44%, and Kenalog 4: 46%.

Propionic acid derivatives (i.e. ibuprophen) were also commonly used, Placebo: 23%, Trinasal 50: 23%, Trinasal 400: 19%, and Kenalog 4: 28% in Table 17, volume 17; Data Listing 16A, 16B and 16C in volume 70.

#### **Safety Conclusions**

The major concern in this study in terms of both safety and efficacy is whether the randomized patients were fully exposed to the full dose of study medications, particularly Trinasal 400  $\mu$ g, on a daily basis, for the study duration. There were problems in terms of compliance for all treatment groups; 118 patients (39.5%) were non compliant with respect to study medication, however, there was no apparent differences between treatment groups. The study report does not include a distribution of used weights/bottle per week according to treatment. We should ask the sponsor to provide us with this information.

The large number of patients that were considered not evaluable from the efficacy standpoint, particularly during the last study visit, is of concern. The sponsor was asked (via telephone facsimile) to provide us with the CFRs from those patients that were enrolled in Dr. Ratner's site for review.

Assuming that the exposure to study medication was adequate, the another safety concern is whether the adverse event frequency was under reported or underestimated because patients did not record adverse events in their daily diary. These were recorded at the weekly clinic visit. Although in general, this practice would not likely affect the report of a severe event, it would tend to minimize the report of local, mild adverse events.

The reported frequency of adverse events is 66-72% for all treatment groups. The report of pharyngitis in the Kenalog treated group was 7%, and all other treatment groups treated with nasal sprays had at least twice that amount, including placebo.

There were no other unexpected clinical significant differences in clinical laboratory, blood chemistry, u/a, or physical exam between the active groups and placebo described in the study report. The increase in WBC count and the decrease in eosinophil counts in the Kenalog treated group are expected changes due to systemic activity. Although physical exams were done before and after treatment, it is not likely that eye tonometry was part of this exam, as it is not stated in the protocol. Particularly in this clinical study with a systemic steroid arm, it would have been valuable to obtain this information.

The study protocol states that cultures of suspected fungal infections would be obtained, however, the study report does not indicate whether there were any cultures obtained. This could be clarified via telephone conversation or fax to the sponsor.

**APPEARS THIS WAY  
ON ORIGINAL**

**10.c. Study No. 0501**

**Title:** A double blind, randomized, comparative study of triamcinolone acetonide and placebo in subjects ages 18 to 65 years with seasonal allergic rhinitis (spring hay fever).

**Objective:** To compare the efficacy of nasal triamcinolone acetonide at a dose of 200  $\mu$ g twice daily versus placebo in the treatment of spring hay fever in subjects 18-65 years of age and to compare the incidence of adverse experience with both.

**Study Protocol:** Appendix A.1 in volume 4.46

**Design**

This is a six week (2 week baseline, 4 week active treatment), double-blind, stratified, randomized, five center study in patients 18-65 years with spring hay fever that compares the efficacy and safety of nasal 200  $\mu$ g triamcinolone bid or placebo.

All patients will start baseline one week prior to the anticipated onset of the grass pollen season. Patients would be allowed to take pre-assigned concomitant medication (Seldane, Ceeon-A, Afrinol and Afrin) and they will keep a daily diary of symptom severity and duration. Physician weekly assessments will also be done.

**Population**

The study plans to enroll 125 patients in 5 study sites.

**Inclusion criteria**

18-65 years of age, male or female

Meet criteria for diagnosis of allergic rhinitis secondary to grass and/or tree pollen allergy (hx of typical recurring sx during the season, 2/3 sx: sneezing, nasal congestion, or rhinorrhea, and positive skin tests).

Patient must be significantly symptomatic during the baseline period.

**Exclusion criteria**

Disease hx or condition that may interfere with the evaluation of safety or efficacy (infections, nasal obstructions, asthma, uncontrolled DM, HBP >140/90, thrombophlebitis)

Medications that may interfere with the evaluation of efficacy or safety (systemic steroids-past 3 mo, topical steroids within one month of enrollment)

## Study Plan

Visit 1: medical hx, physical exam, clinical labs and skin testing.

Visit 2 and weekly visits (Visit 3, 4, 5, 6, and 7): physical exam of the nasal cavity, record spontaneous recount of adverse events.

Visit 3: Treatment started, patients will be given a diary to record daily symptoms severity and duration as well as the use of all concurrent medication for the past 24 hr period. Patients will record their symptoms once/day at 7PM.

The patient will evaluate the severity of the following individual symptoms for the preceding 24 hours: sneezing, stuffy nose, nasal secretions, itchy nose, throat, palate, itch and eye symptoms (sample CRF, Appendix A.2, vol 46).

The following scale will be used:

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

The duration of symptoms will be scored using the following rating scale:

- 0= no symptoms present between treatments
- 1= symptoms present 1-2 hours
- 2= symptoms present 2-6 hours
- 3= symptoms present 6-12 hours
- 4= symptoms present after > 12 hrs

In addition, the physician will make an assessment of physical signs of the nose using a scale 0-3 for color, secretions and swelling during Visit 3 and at the following weekly clinic visits.

Visit 4 and at the following weekly visits to the physician (5, 6, and 7): the physician will evaluate the severity of symptoms by asking the patient to describe the individual symptoms (previously discussed, with the addition of eye itch instead of eye symptoms) and making use of the same scale. Both the patient and the physician will give an overall assessment of the ability of the medication to control symptoms, using the following scale:

- 0= symptoms worse (worse)
- 1= no control over symptoms (no relief)
- 2= minor control of symptoms (slight relief)
- 3= moderate control over symptoms (moderate relief)

- 4= substantial control over symptoms (marked relief)
- 5= total control over symptoms (complete relief)

In addition, the patient will be ask to recount any unusual events that may have affected symptoms:

- A=exposed to unusually large amounts of grass pollen
- B=any acute infections
- C= exposed to unusual environmental conditions
- D= out of the area for a protracted period of time
- E=changes in lifestyle that might affect symptoms
- F= use of any other medication

At every clinic visit, clinical evidence suggestive of monilia will be looked for and if present it will be cultured.

Visit 7: Clinical labs will be repeated.

#### Study medication

Drug canisters will contain: Triamcinolone acetonide —  
mg/ml (50 µg/spray) or placebo.

Patients will also be given 60 tablets of Seldane, 60 tablets of Afrinol Repetabs, 2 (15 ml ) Afrin Nasal Spray, and 2 (15 ml) Opcon-A.

#### Blinding

All drugs will be coded. To assure blinding, the test and control drug will appear identical, except for the randomized patient code.

#### Efficacy evaluation

In the protocol the following efficacy measurements are discussed (see above):

1. Patient's evaluation of severity of symptoms by diary
2. Patient's evaluation of symptom duration by diary
3. Physician's evaluation of symptom severity at physician visits
4. Patient's overall assessment of the ability of the medication to control symptoms at physician visits
5. Physician's overall assessment of the ability of the medication to control symptoms.
6. At the physician's visit the patient will recount any unusual events that may have had an effect on the usual pattern of

symptoms.

#### Safety evaluation

Medical hx and physical exam and clinical labs at screening and at Visit 7. Weekly physical exam of the nasal cavity. Weekly review of adverse events and patient evaluation of nasal stinging and irritation at the clinic visits. Cultures for monilia will be obtained if suspected.

For the patient evaluation of nasal stinging or irritation the patient will be asked to assess the severity of nasal stinging or irritation according to the following scale:

0=absent, 1=mild present but not annoying, 2=moderate; present and annoying but not sufficient to stop spray, 3=severe; present and severe enough to stop spray.

#### Discontinuations

The protocol indirectly refers to conditions that could have an effect on the usual pattern of symptoms and in reference to serious adverse events.

#### Statistical Plan

The patient's diary of mean intensity of symptoms and concomitant medication from the two weeks of baseline will be compared to those on treatment. Between group comparisons will be made for each time period.

Investigator's weekly evaluation of symptoms and results from nasal cavity examination from the two weeks of baseline will be compared to the weeks on treatment. Between and within group comparisons will be made.

Patient's and physician's overall global scores on Day 28 will be compared within and between groups.

All laboratory data will be compared within and between groups.

#### Reviewer's comments on the protocol:

A primary endpoint for efficacy is not clearly defined.

The protocol does not define what is meant by significant symptoms during the baseline period, one of the inclusion criteria into the treatment phase of the study.

In the protocol's Section IX. Data analysis, it describes the comparison of patient diary data from weeks -2 and -1 to weeks +1

to +4. By looking at the Data Listings in volume 93 and the telecon with the sponsor dated 3/13/96, it was clarified that the patients began recording their daily symptoms in their diaries after the screening visit even though the protocol does not clearly specify this.

The protocol is not clear as to how many individual symptoms are going to be evaluated by patients in their diaries, 5 or 7. The study sample case report form in Appendix A.2, and the study report list 5 symptoms, it reports itchy nose, throat and palate as one symptom complex.

The protocol does not clearly specify how the baseline scores for patient and physician assessments are going to be calculated. In telecon with sponsor dated 3/13/96 this was clarified. "Baseline severity scores were calculated for each patient first by calculating an average for each of the two weeks of the baseline period and then calculating the average of the weekly averages to arrive at a baseline average score."

The sample case report form for the patient diary specifies an area where the patient will keep record of the Chlortrimetron tablets used. The protocol does not include the use of this drug as a rescue medication. No protocol amendments are included in vol 49. The use of Seldane as a concurrent medication is described in the submitted study protocol. The statistical summary analysis (Appendix B, vol 49) also includes the analysis of the results of the use of Chlortrimetron as a concurrent therapy. The sponsor clarified this issue in telecon dated 3/13/96. Seldane was the antihistamine used in this study. There is an error in the sample draft CRF submitted (Appendix A.2, vol 46) and in the statistical report (Appendix B, vol 46), where it states Chlortrimetron, it should state Seldane.

The study protocol does not clearly specify the criteria that will be used for study discontinuation.

The study protocol does not include a sample size calculation for power estimation.

The specific analyses that will be used to compare efficacy and safety measurements are not specified.

In the study protocol, under the sections Study Design and Treatment Definition, it states that the study will be stratified. The protocol does not specify what stratification will be done or when.

The protocol does not define what type of randomization will be used or when it will be used.

The protocol does not define how missing data is going to be

handled. In telecon with the sponsor dated 3/13/96 it was clarified that missing values were not replaced and averages were calculated using the non missing symptom scores.

The protocol does not describe how compliance will be monitored.

Patients are not going to record adverse events in their daily diary.

The protocol does not specify what will be done with the adverse event data collected to compare the incidence of adverse events between treatments.

The protocol does not define what method will be used by the individual centers to determine the day of anticipated onset of the grass pollen season needed to determine the start of baseline. The protocol does not specify whether this day will be the same or different for different study sites. The protocol does not define whether patients sensitive only to tree pollen will be entered at different dates from those sensitive to grasses. It was clarified in telecon with the sponsor dated 3/13/96 that the individual centers made the decision on their own on when to start the study according to the predicted pollen onset. At least two centers were measuring pollen counts. It is not clear to the sponsor how the other centers made their decision. According to the sponsor a big effort was made to enter patients in the study in the individual centers on the same calendar date.

The protocol does not specify whether the individual study centers will collect data on pollen exposure during the study duration. It was clarified in telecon with sponsor dated 3/13/96 that at the time that the study was conducted, FDA did not require to have information about pollen exposure during the study duration by the individual centers.

## **RESULTS**

### **Reviewer's comments**

The sponsor used a computer-generated randomization list to assign patients to treatment. The randomization code appears in p.4 vol 93.

### **Population enrolled/analyzed**

One hundred and eighteen patients were randomized into two treatment groups. Fifty-nine patients were assigned to receive triamcinolone acetonide (TAA) and 59 were assigned to receive placebo. The following are the participating investigators, with the corresponding number of randomized patients per study site:

Elliot Ellis, M.D., Jacksonville, FL