Nasacort, as the positive control, was not blinded. In study 100-204, even though the patients in the positive-control group received intramuscularly administered Kenalog, however, the blindness was maintained, because all the patients received both nasal spray and intramuscular injection. In study 0501, patients treated with 200 µg Tri-Nasal twice daily actually received a daily dose of 400 µg.

Five allergic symptoms were considered efficacy measures: sneezing, rhinorrhea, nasal congestion, itchy nose/throat/palate and itchy/red/watery eyes. This review is focused on the first three symptoms: sneezing, rhinorrhea, and nasal congestion. These symptoms were measured by scores ranked 0-4, representing the least severe to the most severe cases. A symptom severity index (SSI) was defined in the protocol as the total scores for sneezing, rhinorrhea, and nasal congestion.

The sponsor applied the statistical procedures of analysis of variance (ANOVA) and analysis of covariance (ANCOVA) to analyze the allergic symptom scores for each treatment week separately. The individual symptom severity scores or the SSI scores measured prior to treatment were treated as the baseline scores. To test the true drug effect, these baseline measures were needed for adjustment. This way, the influence by the difference among the treatment groups prior to treatment was reduced. According to the protocol, the statistical procedure followed the following order.

First, the significance of baseline-(treatment) group interaction at significance level of α=0.1 was tested.

- If the baseline-(treatment) group interaction was not statistically significant, then an ANCOVA model was fit with baseline, treatment, site, and treatment-site interaction. This way, the baseline variation was adjusted while comparing the treatment differences.

  Test the significance of treatment-site interaction at α=0.1.

  - If the treatment-site interaction was not significant, fit an ANCOVA model with baseline, treatment, and site. Then test baseline at α=0.1.

  - If the treatment-site interaction was significant, fit the by-site ANCOVA models with baseline, treatment. Then test baseline at α=0.1.

- If the baseline-(treatment) group interaction was significant, then fit an ANOVA model with treatment, site, and treatment-site interaction.

  Test the significance of treatment-site interaction at α=0.1.

  - If the treatment-site interaction was not significant, then fit an ANOVA model with treatment, and site.

- If the treatment-site interaction was significant, then fit the by-site ANOVA models with treatment.

The definitions of the primary and secondary endpoints varied from study to study. The physician's evaluation at patient visits, the patient's global evaluation of the therapeutic effect, and other measurements were also included as endpoints. The following Table 3 gives a summary of endpoint definitions by the study protocols.

Table 3. Sponsor' Definitions of Endpoint

Endpoint	Study 100-309	Study 100-204	Study 100-305	Study 0501
Overall symptom: SSI	Primary	Primary	Primary	NA
Sneezing	secondary	Primary	Primary	Primary
Rhinorrhea	secondary	Primary	Primary	Primary
Nasal congestion	secondary	Primary	Primary	Primary
Itchy nose/throat/palate	secondary	Primary	Primary	Primary
Itchy/red/watery eyes	secondary	Primary	Primary	Primary
Physician's evaluation on individual symptoms	secondary	secondary	secondary	Primary
Physician's global evaluation		secondary	secondary	Primary
Patient's global evaluation	secondary	secondary	secondary	Primary
Use of rescue medication	NA	secondary	secondary	NA
Nasal examination	NA	NA	secondary	NA

This review treats the SSI as the primary efficacy measure for the studies. Also, the measures on sneezing, rhinorrhea and nasal congestion were evaluated individually.

Sponsor's Results and Reviewer's Comments

To better understand and summarize the statistical results on the efficacy studies, this reviewer uses a graphical interpretation here to describe the symptom-severity-score changes from baseline values across time, using the sponsor's data. The statistical interpretations based on p-values will follow.

The change from baseline is obtained by subtracting the baseline mean value from that of the observed values at a selected time point. Because the more the patient improves, the lower the symptom score would become, we expect to see a decrease in SSI scores. In this case, such a change from baseline should be negative values.

Symptom Severity Index (SSI)

The following Figures 1-4 depict the changes from the baseline in mean SSI scores for studies 100-309, 100-204, 100-305, and 0501.

Figure 1 depicts the changes in mean SSI scores from the baseline by treatment group, for study 100-309. The patients in the Tri-Nasal 200 or 400 µg dose groups showed greater reductions in SSI than those in the placebo group. The patients in the Nasacort group improved as much as those in the Tri-Nasal 400 group.

Figure 2 depicts the changes in mean SSI scores from the baseline by treatment group, for study 100-204. The Tri-Nasal 400 µg dose group showed a somewhat greater reduction in symptom severity scores than the placebo, the Tri-Nasal 50 µg group and the Kenalog group. Kenalog appeared to be as effective as the Tri-Nasal at 50 µg daily dose. Both were more effective than the placebo starting week 2, but were less effective than the placebo at week 1.

Figure 3 depicts the changes in mean SSI scores from the baseline by treatment group, for study 100-305. Contradicting the results in studies 100-309 and 100-204, the reductions in symptom severity scores in the highest dose (400 µg) of Tri-Nasal were not as great as those in the 50 µg and 200 µg doses, which demonstrated clear reductions compared to the placebo.

Figure 4 depicts the changes in mean SSI scores from the baseline by treatment group, for study 0501. The patients treated with Tri-nasal 200×2 µg daily improved more than those in the placebo group. The SSI scores were not defined and reported in this study. This reviewer calculated the SSI scores using the same definition as that in the other studies.

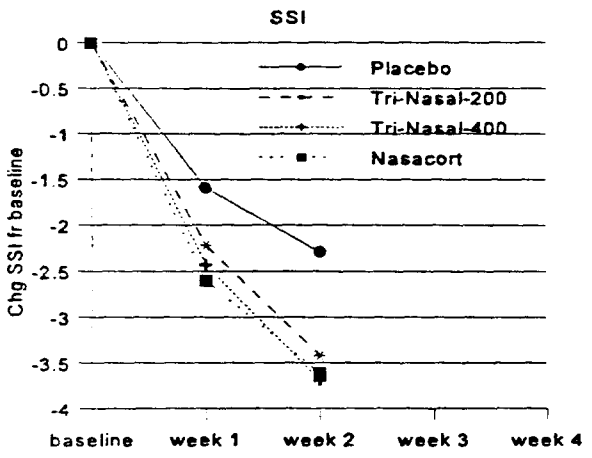

Figure 1. Study 100-309

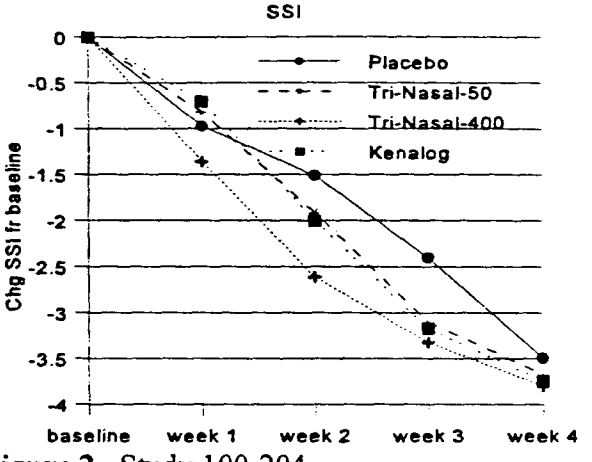

Figure 2. Study 100-204

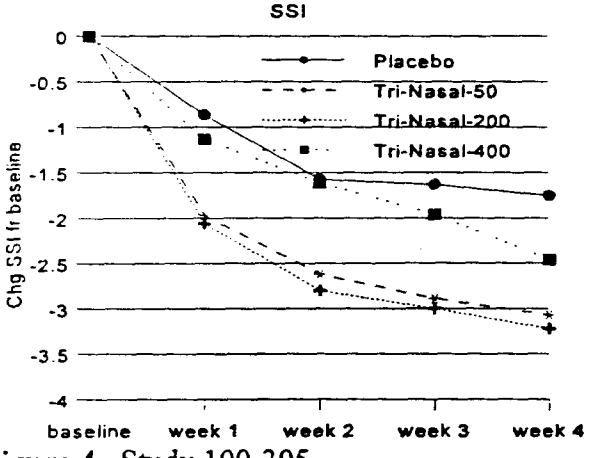

Figure 4. Study 100-305

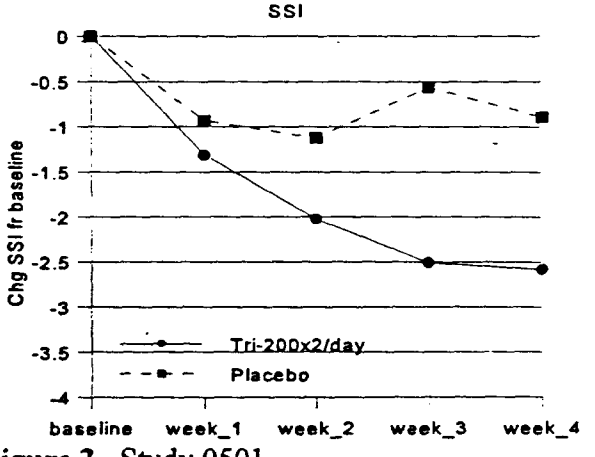

Figure 3. Study 0501

The above Figures 1 and 3 showed that Tri-Nasal at 200 µg daily dose was more effective than the placebo in improving SSI. Figures 2 and 4 showed that Tri-Nasal at 400 µg daily dose also was more effective than the placebo in improving SSI. Nasacort was as effective as Tri-Nasal 400.

It may be useful to visualize the treatment effect on a particular allergic symptom instead of the overall effect indicated by SSI. For this purpose, this reviewer depicted the changes from baseline for the three individual symptom severity scores on which the SSI was based. These individual symptoms, sneezing, rhinorrhea, and nasal congestion are described in the following groups of figures: Figures 5-8, Figures 9-12, and Figures 13-16, respectively. For each selected symptom, the severity scores from the four studies (studies 100-309, 100-204, 100-305, and 0501) are compared. For example, Figures 5-8 show the changes from baseline in sneezing-severity scores across time, by treatment groups.

Individual Symptoms

Sneezing

Figures 5-8 depict the changes from baseline in mean severity scores for sneezing by treatment group, for the four studies. For sneezing, the severity-score changes from baseline had a similar pattern as that for the SSI scores. Studies 100-309, 100-204 and 0501 showed that the patients on Tri-Nasal 400 µg daily dose showed greater reductions in sneezing than those on the placebo. However, study 100-305 did not demonstrate the superiority of Tri-Nasal at 400 µg to its lower doses. Tri-Nasal 200 µg appeared to be very effective from studies 100-309 and 100-305. A dose level of 50 µg daily was shown to be too low to be effective, based on study 100-204.

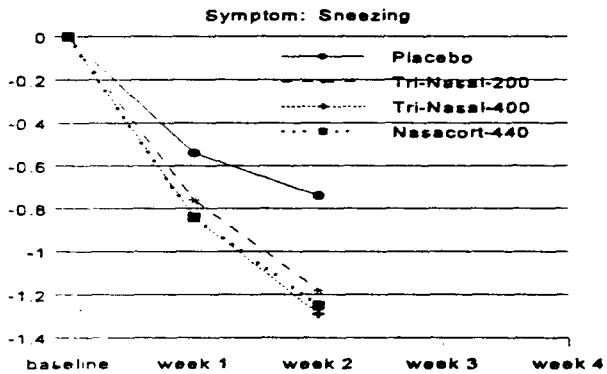

Figure 5. Study 100-309

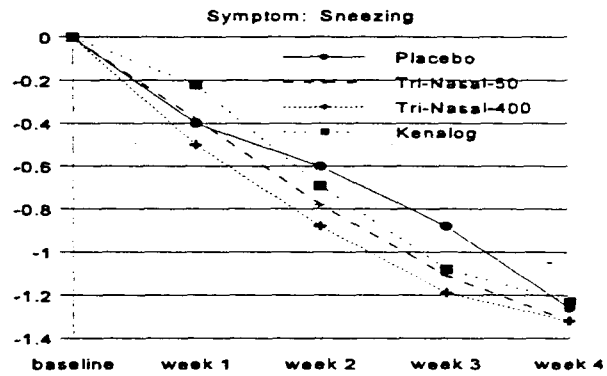

Figure 6. Study 100-204

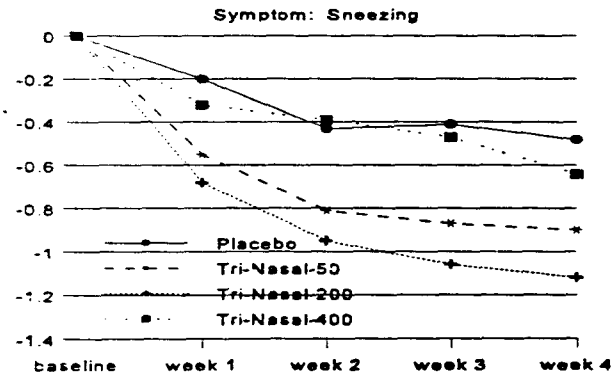

Figure 7. Study 100-305

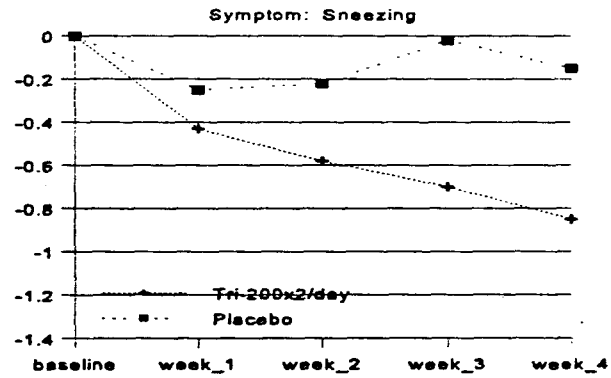

Figure 8. Study 0501

The above Figures 5 and 7 showed that Tri-Nasal at 200 µg daily dose was more effective than the placebo in relieving sneezing. Figures 6 and 8 showed that Tri-Nasal at 400 µg daily dose also was more effective than the placebo in relieving sneezing. Nasacort was as effective as Tri-Nasal 400.

Rhinorrhea

Figures 9-12 depict the changes from baseline in mean severity scores for rhinorrhea by treatment group, for the studies. For rhinorrhea, the severity-score changes from baseline presented similar patterns as those for the SSI and sneezing scores. In other words, the treatment effect on sneezing and rhinorrhea appeared to be similar.

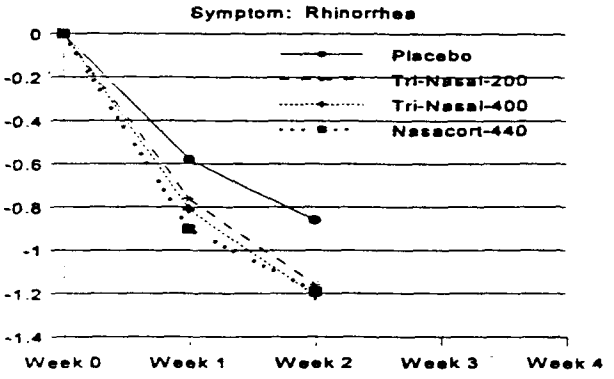

Figure 9. Study 100-309

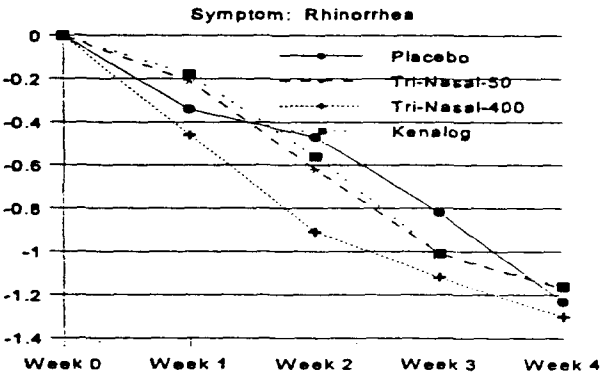

Figure 10. Study 100-204

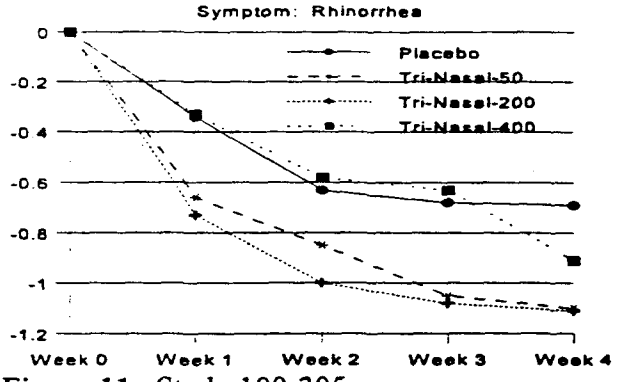

Figure 11. Study 100-305

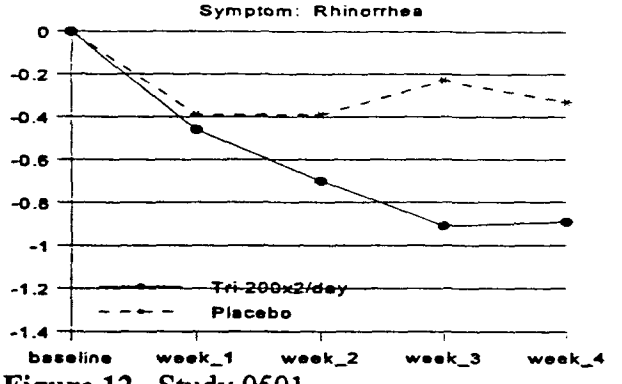

Figure 12. Study 0501

The above Figures 9 and 11 showed that Tri-Nasal at 200 µg daily dose was more effective than the placebo in relieving rhinorrhea. Figures 10 and 12 showed that Tri-Nasal at 400 µg daily dose also was more effective than the placebo in relieving rhinorrhea. Nasacort was as effective as Tri-Nasal 400.

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In summary, the above Figures 5-16 have shown the following results:

Note: "✔" represents that the drug appears to be superior to the placebo.
"✖" represents that the drug does not show enough superiority to the placebo.

Symptom	Study	Tri-Nasal 200	Tri-Nasal 400
Sneezing	100-309	✔	✔
	100-204	Not apply	✔
	100-305	✔	×
	0501	Not apply	✔
Rhinorrhea	100-309	✔	✔
	100-204	Not apply	✔
	100-305	✔	×
	0501	Not apply	✔
Nasal Congestion	100-309	✔	✔
	100-204	Not apply	✔
	100-305	✔	✔
	0501	Not apply	✔

For the symptoms of sneezing and rhinorrhea, Tri-Nasal at 200 and 400 µg daily doses is superior to the placebo, except that study 100-305 fails to demonstrate a superiority of Tri-Nasal at 400 µg daily dose to the placebo. However, study 100-305 has shown that Tri-Nasal at 400 µg appears to be more effective in reducing the symptom of nasal congestion than the symptoms of sneezing and rhinorrhea. These conclusions hold in the following statistical comparisons as well.

Statistical Comparisons of Individual Symptoms

The reviewer reanalyzed the data using the same statistical methods and procedures as the sponsor's, and demonstrated that the sponsor accurately applied the statistical procedures specified in the protocols. In studies 100-309 and 100-204, the sponsor used univariate ANOVA and ANCOVA and proved that Tri-Nasal at 400 µg daily was more efficacious than either the placebo or the positive controls: Kenalog or Nasacort. The same statistical method was used in study 100-305 and 0501. The ANCOVA was used to adjust for the baseline values that might significantly confound the true treatment effect. The ANOVA and ANCOVA were done for every time point (week) in evaluating the efficacy. The reviewer's results were consistent with the sponsor's. However, study 100-305 which compared the three dose levels of Tri-Nasal, failed to show that the 400 µg dose was more effective than the other two lower doses, 50 µg and 200 µg.

Nasal Congestion

Figures 13-16 depict the changes from baseline in mean severity scores for nasal congestion by treatment group, for the studies. For nasal congestion, the severity-score changes from baseline had similar patterns as those for the SSI scores, sneezing and rhinorrhea scores. In contrast to Figure 7 and Figure 11, in Figure 15 (100-305), Tri-Nasal at 400 µg appears to be more effective in reducing the symptom of nasal congestion than the symptoms of sneezing and rhinorrhea.

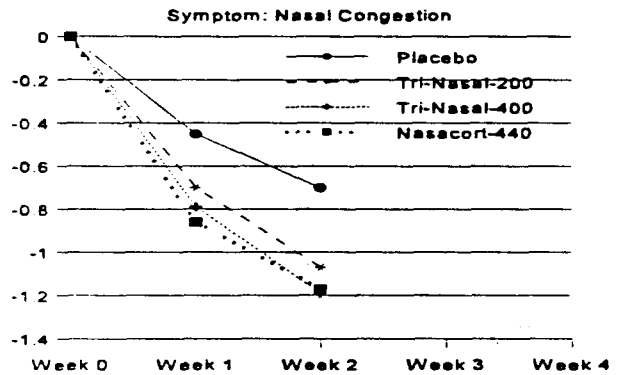


Figure 13. Study 100-309

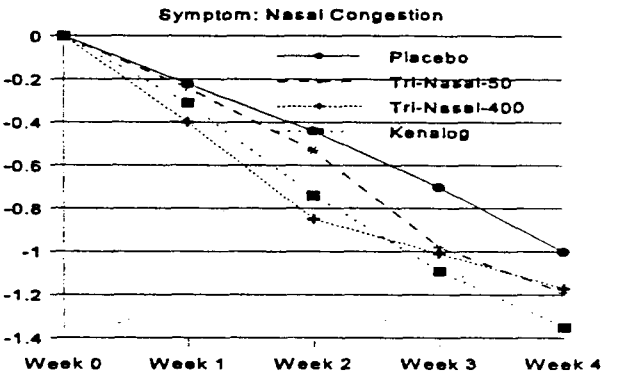


Figure 14. Study 100-204

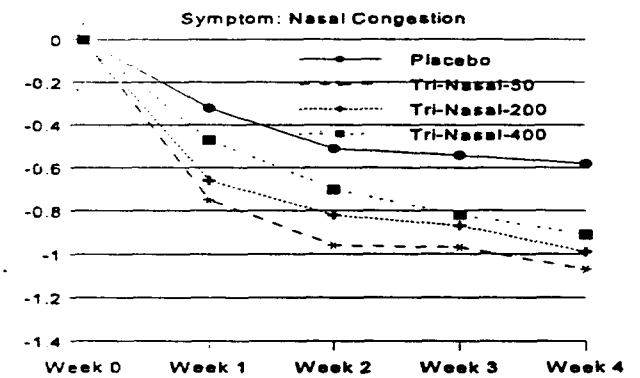


Figure 15. Study 100-305

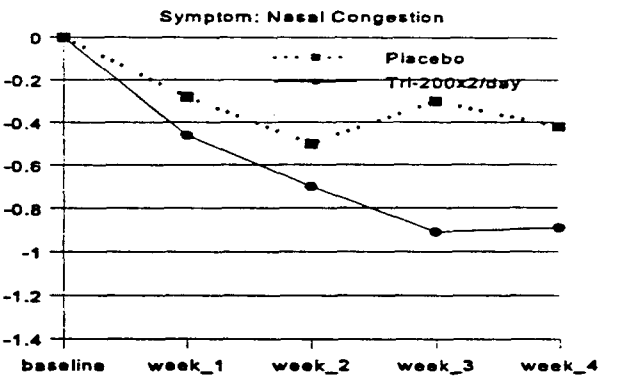


Figure 16. Study 0501

The above Figures 13 and 15 showed that Tri-Nasal at 50 and 200 µg daily dose was more effective than the placebo in relieving nasal congestion. Figures 14 and 16 showed that Tri-Nasal at 400 µg daily dose also was more effective than the placebo in relieving nasal congestion. Nasacort was as effective as Tri-Nasal 400. It is noteworthy to point out the following finding: In contrast to Figure 7 and Figure 11, in Figure 15 (100-305), Tri-Nasal at 400 µg appears to be more effective in reducing the symptom of nasal congestion than the symptoms of sneezing and rhinorrhea.

The following Table 4 describes the statistical results of the comparisons between the treated groups and the placebo in terms of p-values, for each of the individual allergic symptoms. The p-values less than 0.05 are in bold. Since the efficacy tests were done at each time point (week), each entry of the following table gives a minimum and maximum of the p-values for the entire study period. The details of the tests are described in the appendices. This table provides an overall picture of the efficacy.

Table 4. Comparisons between Treated groups and the Placebo

Symptom	Study #	Tri-Nasal 50 µg	Tri-Nasal 200 µg	Tri-Nasal 400 µg	Nasacort	Kenalog
Sneezing	100-309	NA	**.001-.036**	**.001-.004**	**.001**	NA
	100-204	**.019**-.337	NA	**<.001**	NA	**.008**-.652
	100-305	**.034-.072**	**.006-.01**	.119-.880	NA	NA
	0501	NA	NA	**<.01**	NA	NA
Rhinorrhea	100-309	NA	.1 (wk1)	**.008 (wk1)**	**.002 (wk1)**	NA
	100-204	**.012**-.954	NA	**.001-.012**	NA	**.016**-.749
	100-305	**.024**-.2	**.034**-.086	**.032**-.701	NA	NA
	0501	NA	NA	**.01**	NA	NA
Nasal Cong	100-309	NA	**.003-.019**	**.001-.004**	**.001**	NA
	100-204	**.021**-.485	NA	**.001**-.097	NA	**.003**-.403
	100-305	**.009-.052**	**.010-.043**	**.035**-.191	NA	NA
	0501	NA	NA	**<.01**	NA	NA
Itchy nose...	100-309	NA	**.002-.042**	**.001-.028**	**.002-.045**	NA
	100-204	**.016**-.360	NA	**.001**-.098	NA	**.011**-.370
	100-305	.085-.713	**.002-.068**	.642-.967	NA	NA
	0501	NA	NA	**.02**	NA	NA
Itchy... eyes	100-309	NA	.226-.869	.053-.244	.102-.147	NA
	100-204	.576-.945	NA	**.020**-.206	NA	**.032**-.757
	100-305	.105-.646	**.011**-.907	.385-.837	NA	NA
	0501	NA	NA	**<.01**	NA	NA

Treatment-Center Interaction

Note that when there was a significant treatment-center interaction at a particular time point, it is difficult to assess the overall treatment effect across centers. In such a case, the above table only reports the p-values at the time point (e.g., week 1) at which such treatment-center effect was negligible.

In the efficacy study for rhinorrhea for the second treatment week in the two-week study 100-309, the treatment-center interaction was found to be statistically significant. The following graphs and analyses are intended to explain why it is difficult to assess the overall (across-centers) treatment effect.

For the symptom of rhinorrhea, this reviewer chose to present the differences between the change from baseline in symptom severity scores for a selected dose level and the same change for the placebo, for all centers. As a general trend, the more effective a treatment dose is, the greater difference between the two changes (from baseline) would appear. By the definition specified in the sponsor's protocol, the larger value of the score represent the more severe symptom. The changes from baseline are negative. Therefore, the smaller negative values in the difference between the active dose and the placebo indicates a greater improvement in symptom. Ideally, all the trial centers should show negative differences.

For the symptom of rhinorrhea at week 2 of study 100-309, the following Figures 17-20 describe the differences in mean rhinorrhea scores between the changes: the change in symptom severity scores from baseline for a selected treatment (from Tri-Nasal 200, Tri-Nasal 400 and Nasacort) and the same change for the placebo. The differences are plotted on the Y axis and the centers by center numbers are plotted on the X axis. Figure 17 depicts the differences in means between the changes, i.e., the change from baseline for Tri-Nasal 200 and the change from baseline for the placebo, for week 2. Note that only at centers 3 and 7, Tri-Nasal 200 was significantly more effective than the placebo, according to the test done by the sponsor and confirmed by this reviewer. For centers 6, 9, 12, 13, and 14, at which the tests were not significant, the difference in means were negative. These negative numbers indicated that Tri-Nasal 200 was somewhat better than the placebo. For center 2, 4, 5, 8, 10, and 11, the placebo appeared to cause greater changes from baseline than did Tri-Nasal 200 µg daily dose.

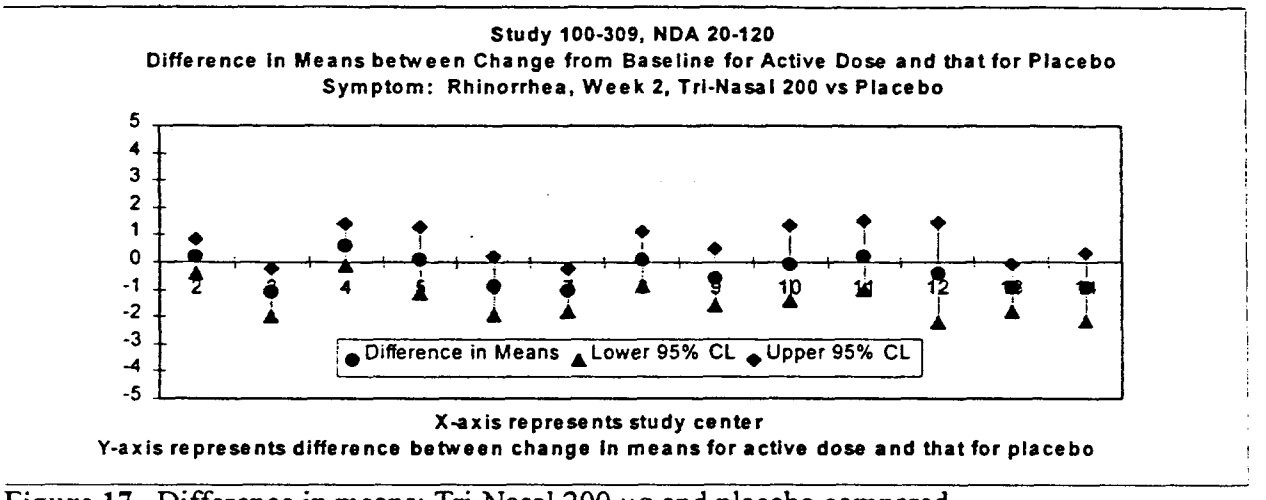


Figure 17. Difference in means: Tri-Nasal 200 µg and placebo compared

Figure 18 depicts the differences in means between the changes: the change from baseline for Tri-Nasal 400 and the change from baseline for the placebo, for week 2. Note that only at centers 3 and 7, Tri-Nasal 400 was significantly more effective than the placebo, according to the test done by the sponsor and confirmed by this reviewer. For centers 6, 8, 9, 10, 12, 13 and 14, at which the tests were not significant, the difference in means were negative. These negative numbers indicated that Tri-Nasal 400 was somewhat better than the placebo. For center 2, 4, 5, and 11, the placebo appeared to cause greater changes from baseline than did Tri-Nasal 400 µg daily dose.

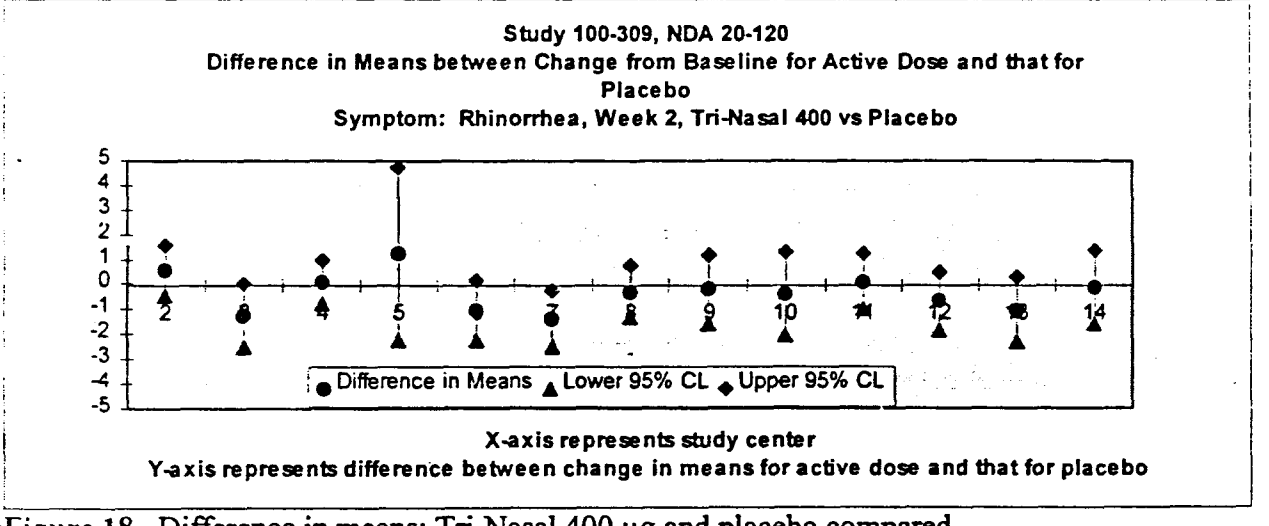
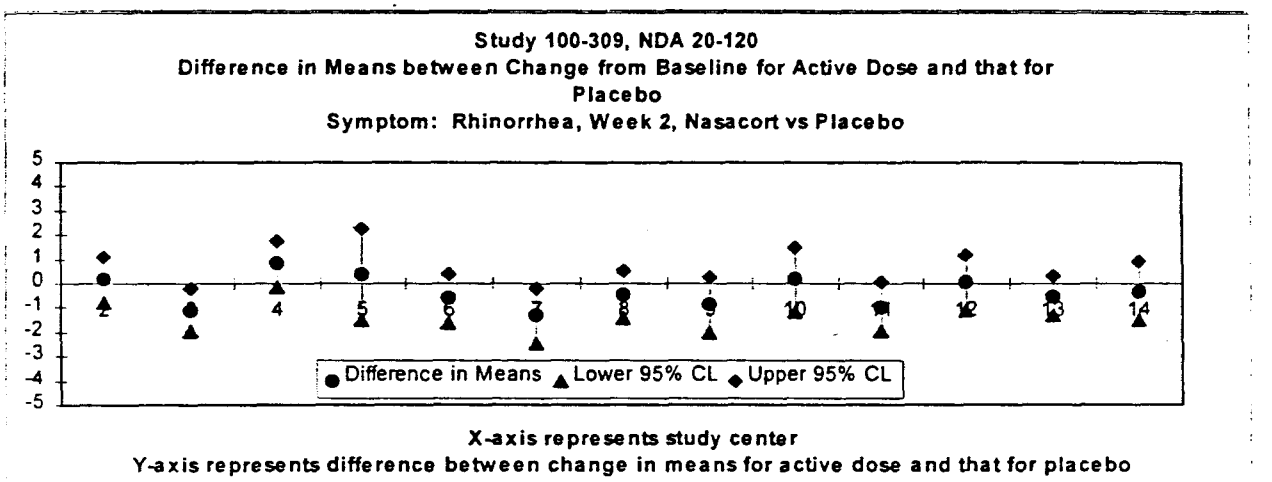


Figure 18. Difference in means: Tri-Nasal 400 µg and placebo compared

Figure 19 depicts the differences in means between the changes: the change from baseline for Nasacort and the change from baseline for the placebo, for week 2. Note that only at centers 3 and 7, Nasacort was significantly more effective than the placebo, according to the test done by the sponsor and confirmed by this reviewer. For centers 6, 8, 9, 11, 13 and 14, at which the tests were not significant, the difference in

means were negative. These negative numbers indicated that Nasacort was somewhat better than the placebo. For center 2, 4, 5, 10 and 12, the placebo appeared to cause greater changes from baseline than did Nasacort at 440 µg daily dose.



In summary, Figures 17-19 showed that, two (#3, Bronsky and #7, Lumry) out-of-fourteen centers, Tri-Nasal at 200 and 400 µg daily doses and Nasacort were superior to the placebo in improving rhinorrhea. This was not demonstrated for the remaining twelve centers. The number of participating patients by treatment group at each center is described in the following Table 5. Note that the numbers of participating patients at each center is small. Therefore, there might not be enough statistical power to detect the existing treatment differences.

Table 5. Number of Participating Patients by Treatment by Center

Center #/Name	Placebo	Tri-Nasal 200	Tri-Nasal 400	Nasacort 440	Total
2/ Berger	9	8	8	8	33
3/Bronsky	7	8	8	7	30
4/Dockhorn	8	8	8	8	32
5/Korenblat	5	5	4	4	18
6/Lampl	8	8	8	8	32
7/Lumry	7	7	7	6	27
8/Pollard	8	8	8	8	32
9/Raphael	8	8	8	8	32
10/Rohr	6	6	6	6	24
11/Rosenthal	8	7	7	7	29

Center #/Name	Placebo	Tri-Nasal 200	Tri-Nasal 400	Nasacort 440	Total
12/Velentine	7	7	8	7	29
13/Wanderer	7	7	7	7	28
14/Sharprio	8	7	8	8	31
Total	96	94	95	92	377

The above table also appears in Appendix 1.

Reviewer's Additional Analyses

In addition to the univariate ANOVA and ANCOVA methods used by the sponsor for each time point, the reviewer applied the repeated measures analysis of variance. Because a patient in a treatment group was evaluated by the physician and by the patient himself/herself multiple times during the trial, there are correlations among the measurements on the same patient. Therefore, the time effect or dose effect over time should be taken into account. One way to handle these correlated data was to create a statistical model in which the responses, say SSI formed a *nxp* response matrix. Here, *n* represents the number of patients, and *p*, the number of measurements on the same patient. The pretreatment measures as baseline values were treated as the covariate. Such a multivariate analysis of covariance, MANCOVA was used to analyze the same data. This analysis concluded the following.

- The MANCOVA based on study 100-309 data found that Tri-Nasal at 200, 400 µg and Nasacort were more effective than the placebo. The differences between Tri-Nasal doses and Nasacort were not significant. According to the sponsor, the treatment of Nasacort was not blinded.

- The MANCOVA based on study 100-204 data found that Tri-Nasal at 400 µg was more effective than Tri-Nasal at 50 µg, placebo and Kenalog. Tri-Nasal at 50 µg was not as significantly effective as in 400 µg.

- The MANCOVA based on study 100-305 data found that Tri-Nasal at 400 µg was not as effective as its two lower dose groups, 50 µg and 200 µg, as anticipated.

- The MANCOVA based on study 0501 data found that Tri-Nasal at 200 µg twice daily (equivalent to 400 µg per day) worked better than the placebo in relieving the following symptoms: sneezing, nasal secretion, nasal congestion, itching, and eye symptoms. The efficacy was also measured by the number of rescue medication pills taken. Patients who were treated with Tri-Nasal 200 µg twice daily took much less rescue

medication than those in the control group.

The statistical results obtained from MANCOVA were consistent with the univariate by-week ANOVA's or ANCOVA's.

The above conclusions were drawn based on the SSI data. The results from the analyses of individual symptoms were not consistent with one another: Tri-Nasal was efficacious in relieving most, but not all the symptoms. Details of the analyses of individual symptoms for each study may be found in the appropriate appendix at the end of this review.

Discussion

During the review, this reviewer requested that the sponsor provide an explanation for some conflicting results between the symptom scores and the physician evaluations. For example, in study 100-305, on Table 5G1 (page 53, Volume 4.31), the baseline differences in SSI among the treatment groups were found to be statistically significant with p=0.001, based on the patients' diaries. The same test did not show the statistical significance because of p=0.203 (Table 7G, page 92, volume 4.31), based on the physicians' evaluations. Another example was chosen from study 100-204. The test of no baseline difference based on the patients' diaries showed a significant baseline difference in SSI among the treatment groups with p=0.006 (Table 5G1, page 53, volume 4.17), but the same test based on the physicians' evaluations was not significant with p=0.962 (Table 7G, page 95, volume 4.17). This phenomenon can be found in other cases. The sponsor responded to this inquiry on May 29, 1996 in a FAX to this reviewer.

The sponsor's points were:

- *". . . While the general trends are similar between the two efficacy measures, the raw treatment differences are, for the most part, smaller for the physician assessment scores."*
- *". . . the variability was consistently greater in the weekly physician assessment scores as compared to the weekly patient diary means."*
- ". . . [therefore,] *the effect sizes* [mean difference divided by the variability] *are generally much smaller for the physician assessment scores."* [This lead to larger p-values when the physician evaluations were used.]
- *". . . the sample size for this study* [100-305] *was determined based on* [the patient] *diary SSI variances obtained from previous studies. Since the physician assessment measurements are more variable, it can be argued that the sample is not large enough to detect treatment differences for that efficacy measure* [SSI]."

The sponsor's argument is valid. After consultation with the reviewing medical officer, Dr. Ana Marie Saavedra Delgado, this reviewer is convinced that the symptom severity scores based on the patients' diaries are more reliable and informative in determining the efficacy. The statistical results based on the physicians' evaluations were useful as references.

Conclusion

This review concludes that three studies (100-309, 100-204 and 0501) have demonstrated that Tri-Nasal at 200 and 400 µg daily doses is superior to the placebo in relieving the symptoms of selected seasonal allergic rhinitis, such as sneezing, rhinorrhea, and nasal congestions, also to some extent, itchy nose/throat/palate and itchy/red/watery eyes. These two doses of Tri-Nasal are proven to be more effective in improving the SSI than the placebo. However, study 100-305, which compared Tri-Nasal at 50, 200 and 400 µg daily doses, does not conform with the above three studies: Tri-Nasal at 400 µg daily dose fails to show a significant difference from the placebo in improving the SSI. However, the sponsor's studies, taken as a whole, provide statistical evidence that Tri-Nasal (200 and 400 µg) is efficacious.

/S/

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

Concur: Steve Wilson, Ph.D. /S/ 9/3/96
S. Edward Nevius, Ph.D. /S/ 9-4-96

cc:
Archival NDA 20-120

HFD-570/Division file
HFD-570/SBarnes
HFD-570/JJenkins,
HFD-570/MHimmel
HFD-570/ASaavedra
HFD-715/Division file, Chron
HFD-715/ENevius
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Appendix 1 (Study No. 100-309)

NDA 20-120

Objectives of the trial

The purpose of this trial was to compare the efficacy and safety of triamcinolone acetonide (TAA) nasal spray solution (Tri-Nasal) in doses of 200 µg and 400 µg per day against the placebo and NASACORT 440 µg per day, in treating seasonal allergic rhinitis (SAR) during the grass pollen season.

Emphasis of this statistical review

This statistical review was focused on the efficacy aspect of the drug on the intent-to-treat (ITT) patients. The statistical analyses were based on the total and individual symptom severity scores. These rhinitis symptoms were recorded by the participating patients on a daily bases.

Study design

This two-week study was conducted at 13 centers. It was a double-blind, randomized, parallel, placebo-controlled, multicenter study. The NASACORT treatment was not blinded. The baseline observations lasted 1-3 weeks followed by a two-week treatment period.

Participating patients

Three hundred seventy seven (377) patients were enrolled in this study. These patients comprised both sexes and were 18-65 years of age.

Treatment groups

Control Group:	Treated with the placebo
Dose Group 1:	Treated with 200 µg Tri-Nasal daily
Dose Group 2:	Treated with 400 µg Tri-Nasal daily
Active control Group:	Treated with 440 µg NASACORT daily

Patient accountability

	Completed	Not completed	Total
Evaluable			260 (69%)
Not evaluable			117 (31%)
Total	355 (94%)	22 (6%)	377 (100%)

Of the 117 non-evaluable patients, 96 (82%) were non-compliant with respect to study medication.

Patients by treatment by center

Center #	Placebo	Tri-Nasal 200	Tri-Nasal 400	Nasacort 440	Total
2	9	8	8	8	33
3	7	8	8	7	30
4	8	8	8	8	32
5	5	5	4	4	18
6	8	8	8	8	32
7	7	7	7	6	27
8	8	8	8	8	32
9	8	8	8	8	32
10	6	6	6	6	24
11	8	7	7	7	29
12	7	7	8	7	29
13	7	7	7	7	28
14	8	7	8	8	31
Total	96	94	95	92	377

Statistical procedure

The statistical procedure followed the following order.

Test the significance of baseline-(treatment) group interaction at significance level of $\alpha=0.1$.

- If the baseline-(treatment) group interaction was not significant, then fit an ANCOVA model with baseline as a covariate, treatment, site, and treatment-site interaction.

  Test the significance of treatment-site interaction at $\alpha=0.1$.
  - If the treatment-site interaction was not significant, fit an ANCOVA model with baseline, treatment, and site. Then test baseline at $\alpha=0.1$.

- If the treatment-site interaction was significant, fit the by-site ANCOVA models with baseline, treatment. Then test baseline at α=0.1.

- If the baseline-(treatment) group interaction was significant, then fit an ANOVA model with treatment, site, and treatment-site interaction.

  Test the significance of treatment-site interaction at α=0.1.
  - If the treatment-site interaction was not significant, then fit an ANOVA model with treatment, and site.

  - If the treatment-site interaction was significant, then fit the by-site ANOVA models with treatment.

Efficacy variables

- Primary endpoint:
  Symptom severity index (SSI), which is the sum of the individual scores of sneezing, rhinorrhea, and nasal congestion.

- Secondary endpoints:
  - Individual symptoms
    1. Sneezing
    2. Rhinorrhea
    3. Nasal congestion
    4. Itchy nose/throat/palate
    5. Itchy/red/watery eyes
  - Physicians' evaluations on the above 5 individual rhinitis symptoms at patients' visits
  - Patients' global evaluations

Sponsor's results and reviewer's comments

The sponsor's results were verified and summarized in the following context. In most cases, the reviewer agreed upon the sponsor's conclusions. Otherwise, the disagreements were noted and discussed.

Analysis of baseline symptoms

There was no statistically significant (treatment) group-by-site interaction at baseline for the SSI scores (p=.4). The SSI scores were similar among the treatment groups at baseline (p=.76). Namely, the difference in scores at the beginning of the treatment among the treatment groups was not statistically significant.

There was no statistically significant (treatment) group-by-site interaction at baseline for any of the individual symptom severity scores. There were no statistically significant differences among the treatment groups at baseline for any of the individual symptoms.

Analysis of efficacy

The analyses based on physicians' evaluations were quoted in parentheses in the following tables for comparison purposes.

Analysis of the primary endpoint, SSI

Treatment effect

Time point	Baseline	Week 1	Week 2
	.822 (.596)	.002 (<.001)	<.001 (.002)

Comment: The results based on the physicians' evaluations were consistent with those based on the patients' diaries.

Pairwise comparisons

	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	NASACORT 440 µg vs Placebo
Week 1	.026 (<.001)	.002 (<.001)	<.001 (<.001)
Week 2	<.001 (.032)	<.001 (<.001)	<.001 (.002)

Comment: Besides the above tests, the reviewer also examined the sponsor's comparisons between Tri-Nasal at two different doses and NASACORT. There were no statistically significant differences among the two Tri-Nasal doses and NASACORT. The analysis of the SSI as a primary endpoint variable showed that the Tri-Nasal at doses, 200 µg and 400 µg was as efficacious as was the NASACORT.

Analysis of the secondary endpoints
Items numbered 1-5 represent the individual symptoms.

1. Sneezing

Treatment effect

Time point	Baseline	week 1	week 2
	.247 (.342)	.004 (<.001)	<.001 (<.001)

Pairwise comparisons

	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	NASACORT 440 µg vs Placebo
Week 1	.036 (<.001)	.004 (.003)	<.001 (<.001)
Week 2	<.001 (.069)	<.001 (<.001)	<.001 (<.001)

2. Rhinorrhea

Treatment effect

Time point	Baseline	week 1
	.412 (.519)	.009 (<.001)

Pairwise comparisons

	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	NASACORT 440 µg vs Placebo
Week 1	0.1 (0.002)	.008 (.002)	.002 (<.001)
Week 2*			
Site: Bronsky	.030 (.027)	<.001 (<.001)	.002 (<.001)
Site: Lumry	.006 (.003)	.002 (.019)	.006 (.074)

* Comment: The treatment-by-site interaction was statistically significant with a p-value of 0.0897 (less then the cutoff point p-value 0.1). Therefore, by-site analysis was done. The analysis of rhinorrhea based on the week-2 data showed that the efficacy was not consistent across the centers: Only two out of 13 centers showed that Tri-Nasal at 200 and 400 µg daily doses and NASACORT are equally superior to the placebo. The centers where the testing results were not significant are listed as follows:

2	4	5	6	8	9
Berger	Dockhorn	Korenblat	Lampl	Pollard	Raphael
10	11	12	13	14	
Rohr	Rosenthal	Velentine	Wanderer	Sharprio	

Note that, in analyzing the effects of Tri-Nasal 200 µg against the placebo at week 1, the analyses based on the patients' diaries and that based on the physicians' evaluations lead to opposite conclusions: p=0.1 based on the patients' diaries and p=0.002 based on the physicians' evaluations.

3. Nasal congestion

Treatment effect

Time point	Baseline	week 1	week 2
	.766 (.855)	.003 (.019)	<.001 (.092)

Pairwise comparisons

	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	NASACORT 440 µg vs Placebo
Week 1	.019 (0.017)	.004 (0.013)	<.001 (0.005)
Week 2	.003 (0.110)	<.001 (0.016)	<.001 (0.061)

4. Itchy nose/throat/palate

Treatment effect

Time point	Baseline	week 1
	.704 (.776)	.088 (<.001)

Pairwise comparisons based on the patients' diaries

	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	NASACORT 440 µg vs Placebo
Week 1	.042	.028	.045
Week 2	.002	<.001	.002

Pairwise comparisons based on the physicians' evaluations

	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	NASACORT 440 µg vs Placebo
Week 1	<.001	.003	.002
Week 2*			
Site: Bronsky	.07	<.001	.003
Site: Dockhorn	.522	.116	.062
Site: Lampl	.173	<.001	.464

* The treatment-by-site interaction was significant with a p-value of 0.0194 (less than the cutoff point p-value of 0.1).

5. Itchy/red/watery eyes

Treatment effect

Time point	Baseline	week 1	week 2
	.277 (.883)	.264 (.009)	.225 (.138)

Pairwise comparisons based on the patients' evaluations

	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	NASACORT 440 µg vs Placebo
Week 1	.869*	.244*	.147*
Week 2	.226*	.053*	.102*

* Neither Tri-Nasal nor NASACORT was effective in relieving this symptom.

Pairwise comparisons based on the physicians' evaluations

	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	NASACORT 440 µg vs Placebo
Week 1**			
Site: Bronsky	0.031	0.001	<.001
Week 2***			
Site: Bronsky	0.003	<.001	<.001

** The treatment-by-site interaction is significant with a p-value of 0.0713 (less than the cutoff point p-value 0.1). In this case, the by-site analyses were done.
*** The treatment-by-site interaction is significant with a p-value of 0.0322 (less than the cutoff point p-value 0.1). In this case, the by-site analyses were done.

Sponsor's conclusions

Tri-Nasal at doses of 200 or 400 µg per day was efficacious in relieving the symptoms of seasonal allergic rhinitis for the SSI and most of the secondary efficacy endpoints. The NASACORT, as an active control, demonstrated an equal efficacy as did the Tri-Nasal.

Reviewer's analyses

The reviewer analyzed data of 377 patients at 13 trial centers during a two-week treatment period. The data Analyses of variance (ANOVA) and analyses of covariance (ANCOVA) were done on the following endpoint variables, based on the patient-diary data. Additional repeated measures analyses of variance and analysis of covariance were also performed, in which the time effect or dose effect was taken into consideration.

Endpoint	Definition
SSI	Symptom severity index
Sneezing	Sneezing
Rnoses	Rhinorrhea
Ncongs	Nasal congestion
Itchns	Itchy nose/throat/palate
Itches	Itchy/red/watery eyes

For the above 6 variables measured at 3 time points, the reviewer's univariate ANOVA and ANCOVA comprised a total of 18 separate analyses, including one analysis of baseline. Note that the baseline ANOVA was conducted to compare the homogeneity among the 4 treatment groups prior to the treatment period.

In addition to the treatment effect, center effect and interaction between the two were also examined. The following tables summarize the reviewer's univariate analyses and repeated measures analyses. The test results were presented in terms of p-values.

Overall significance of treatment effect

Endpoint	Baseline	Week 1	Week 2
SSI	0.7611	0.0015	0.0001
Sneezing	0.3403	0.0037	0.0001
Rhinorrhea	0.3291	0.0094	0.0032
Nasal Cng	0.7741	0.0017	0.0005
Itchy nose	0.6678	0.0879	0.0008
Itchy eyes	0.2992	0.2641	0.2254
# of significant tests (<.05)	0	4	5

Pairwise comparison

Tri-Nasal 200 µg vs The placebo

Endpoint	Baseline	Week 1	Week 2
SSI	0.6019	0.0258	0.0005
Sneezing	0.6892	0.0356	0.0001
Rhinorrhea	0.6158	0.0996	0.0129
Nasal Cngs	0.7881	0.0102	0.0025
Itchy nose	0.7604	0.0424	0.0017
Itchy eyes	0.1399	0.8685	0.2255
# of significant tests (<.05)	0	4	5

Pairwise comparison

Tri-Nasal 400 µg vs The placebo

Endpoint	Baseline	Week 1	Week 2
SSI	0.4725	0.0022	0.0001
Sneezing	0.5967	0.0036	0.0001
Rhinorrhea	0.0857	0.0082	0.0006
Nasal Cngs	0.5540	0.0046	0.0002
Itchy nose	0.7852	0.0278	0.0002
Itchy eyes	0.6513	0.2435	0.0526
# of significant tests (<.05)	0	5	5

Pairwise comparison

NASACORT vs The placebo

Endpoint	Baseline	Week 1	Week 2
SSI	0.2938	0.0003	0.0001
Sneezing	0.0818	0.0007	0.0001
Rhinorrhea	0.2343	0.0017	0.0036
Nasal Cngs	0.5572	0.0002	0.0006
Itchy nose	0.4246	0.0450	0.0024
Itchy eyes	0.1093	0.1468	0.1021
# of significant tests (<.05)	0	5	5

Pairwise comparison

Tri-Nasal 200 µg vs Tri-Nasal 400 mg

Endpoint	Baseline	Week 1	Week 2
SSI	0.8437	0.4023	0.3440
Sneezing	0.8969	0.4144	0.3080
Rhinorrhea	0.2244	0.3136	0.3462
Nasal Cngs	0.3919	0.7867	0.4664
Itchy nose	0.9746	0.8679	0.5703
Itchy eyes	0.3068	0.1845	0.4677
# of significant tests (<.05)	0	0	0

Pairwise comparison

Tri-Nasal 200 µg vs NASACORT

Endpoint	Baseline	Week 1	Week 2
SSI	0.5948	0.1437	0.4745
Sneezing	0.1800	0.1821	0.2305
Rhinorrhea	0.4899	0.1307	0.6578
Nasal Cngs	0.3957	0.2471	0.6553
Itchy nose	0.2720	0.9890	0.9244
Itchy eyes	0.8885	0.1061	0.6662
# of significant tests (<.05)	0	0	0

Pairwise comparison

Tri-Nasal 400 µg vs NASACORT

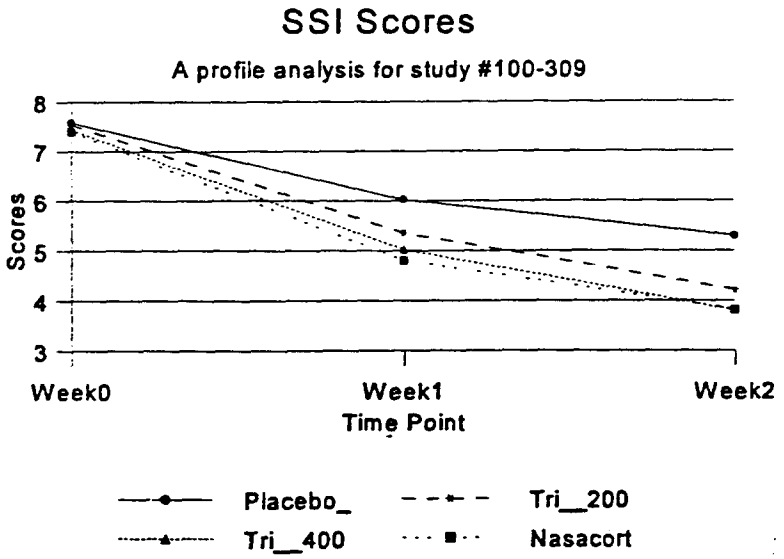
Endpoint	Baseline	Week 1	Week 2
SSI	0.7371	0.5251	0.8201
Sneezing	0.2261	0.5951	0.8496
Rhinorrhea	0.6068	0.6079	0.6179
Nasal Cngs	1.0000	0.3738	0.7799
Itchy nose	0.2869	0.8578	0.5085
Itchy eyes	0.2496	0.7645	0.7700
# of significant tests (<.05)	0	0	0

The above analysis indicates that the effect of Tri-Nasal at doses 200 µg or 400 µg and NASACORT in 440 µg are not significantly different, based on the above individual symptom scores and the SSI score. Tri-Nasal at either dose is as efficacious in relieving most of the selected symptoms as is NASACORT. However, they are not as effective in improving itchy/red/watery eyes.

The reviewer's repeated measures analysis of covariance was based on all 377 patients' data. The results are summarized as follows. Only results on SSI are listed here.

Source of variation	P-value	Source of variation	P-value
Pairwise comparisons		*Main effect*	
Tri200 vs placebo	0.0069	Treatment effect	0.0001
Tri400 vs placebo	0.0001	Time	0.8002
Nasacort vs placebo	0.0001		
Tri200 vs Tri400	0.1798	*Interaction*	
Tri200 vs Nasacort	0.2198	Time*treatment	0.3427
Tri400 vs Nasacort	0.9174	Time*center	0.0055

the treatment effect, known as between subject effect, was strongly significant (p=0.0001). The time effect was not significant with p-values 0.8002. These tests were done based on Wilks' Lambda, Pillai's Trace, Hotelling-Lawley Trace, Roy's Greatest Root statistics. The following graph depicts the mean SSI scores against time (in weeks) by treatment groups.



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Appendix 2 (Study No. 100-204)

NDA 20-120

Objectives of the trial

The purpose of this trial was to compare the safety and topical efficacy of triamcinolone acetonide (TAA) nasal spray solution (Tri-Nasal) at doses of 50 and 400 µg once daily against the placebo and a systemic form of TAA, intramuscularly administered Kenalog-40 at dose 4 µg once weekly and in treating seasonal allergic rhinitis (SAR) secondary to mountain cedar pollen sensitivity.

Emphasis of this statistical review

This statistical review was focused on the efficacy aspect of the drug on the intent-to-treat (ITT) patients. The statistical analyses were based on the total and individual symptom severity scores of the selected rhinitis symptoms recorded by the participating patients.

Study design

This study was conducted at 5 centers for a period of 4 weeks. It was a double-blind, randomized, parallel, placebo-controlled, multicenter study. The baseline observations lasted 4-7 days prior to the randomization.

Participating patients

Two hundred ninety six 296 patients were enrolled in this study. The participating patients consisted of both sexes and were 18-65 years of age.

Treatment Group:

Control Group: Treated with the placebo
Dose Group 1: Treated with 50 µg Tri-Nasal daily
Dose Group 2: Treated with 400 µg Tri-Nasal daily
Active control Group: Treated with 4 µg Kenalog-40 weekly

Patient accountability

	Completed	other	Total
Evaluable			120 (40.5%)
other			176 (59.5%)
Total	269 (91%)	27 (9%)	296 (100%)

Of the 176 non-evaluable patients, 118 (67%) were non-compliant with respect to study medications.

Patients by treatment by center

Center	Placebo	Tri-Nasal 50	Tri-Nasal 400	Kenalog®	Total
1	14	15	15	15	59
2	15	15	15	15	60
3	14	15	15	15	59
4	15	15	15	15	60
5	15	14	15	14	58
Total	73	74	75	74	296

Statistical Procedure

The statistical procedure followed the following order.

Test the significance of baseline-(treatment) group interaction at significance level of $\alpha=0.1$.

- If the baseline-(treatment) group interaction was not significant, then fit an ANCOVA model with baseline as a covariate, treatment, site, and treatment-site interaction.

  Test the significance of treatment-site interaction at $\alpha=0.1$.
  - If the treatment-site interaction was not significant, fit an ANCOVA model with baseline, treatment, and site. Then test baseline at $\alpha=0.1$.
  - If the treatment-site interaction was significant, fit the by-site ANCOVA models with baseline, treatment. Then test baseline at $\alpha=0.1$.

- If the baseline-(treatment) group interaction was significant, then fit an ANOVA model with treatment, site, and treatment-site interaction.

  Test the significance of treatment-site interaction at $\alpha=0.1$.
  - If the treatment-site interaction was not significant, then fit an ANOVA model with treatment, and site.
  - If the treatment-site interaction was significant, then fit the by-site ANOVA models with treatment.

Efficacy variables

- Primary endpoints:
  - Symptom severity index (SSI), which was the sum of the individual scores of sneezing, rhinorrhea, and nasal congestion.
  - Individual rhinitis symptoms
    Sneezing
    Rhinorrhea
    Nasal congestion
    Itchy nose/throat/palate
    Itchy/red/watery eyes
- Secondary endpoints:
  - Physician's (global and individual) evaluations at patients' visits
  - Patient global evaluation of efficacy
  - Use of rescue medication

Sponsor's results and reviewer's comments

Analysis of baseline symptoms

- There was a statistically significant (treatment) group-by-site interactions (p=0.051) at baseline for the SSI score. The significant results from the same test for individual symptoms are listed in the following table.

Treatment-site interaction	p-value
Sneezing	.049
Itchy nose/throat/palate	.072

The baseline scores were significantly different among the treatment groups for the following individual symptoms. For these symptoms, the treatment-center interactions were not significant.

Rhinorrhea	0.0116
Itchy/red/watery eyes	0.042

Analysis of Efficacy

SSI

In the following tables, the figures in parentheses were p-values from the physicians' assessment scores which served as secondary endpoints. For comparison purposes, these number were listed with the p-values based on the patient-diary scores. Only do the significant discrepancies appear in the following tables.

Treatment effect

Significance of treatment effect	Baseline	week 1	week 2	week 3	week 4
	.006 (.962)	.017	<.001	.003	.185 (.023)

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	4 µg Kenalog vs Placebo
Week 1	.733 (.078)	.009	.915
Week 2	.065	<.001	.032
Week 3	.011	<.001	.005
Week 4	.218	.034	.115

Besides, the pairwise comparisons also showed that the differences between Tri-Nasal 50 µg and Kenalog were not statistically significant. However, Tri-Nasal 400 µg and both Kenalog and Tri-Nasal 50 µg dose group were statistically different for the weeks 1 and 2. Tri-Nasal 400 µg was more effective than the others.

Analysis of Individual symptom severity scores

1. Sneezing

Treatment effect

Significance of treatment effect	Baseline	week 1	week 2	week 3	week 4
	.018 (0.928)	.002	.01 (<.001)	.002	.007

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	4 µg Kenalog vs Placebo
Week 1	.337 (.108)	<.001	.652
Week 2	.069	<.001	.101 (.024)
Week 3	.019	<.001	.008
Week 4	.065	<.001	.040

2. Rhinorrhea

Treatment effect

Significance of treatment effect	Baseline	week 1	week 2	week 4	week 3
	0.012 (.471)	0.013	<.001	0.057 (.104)	0.004 (.010)

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	4 µg Kenalog vs Placebo
Week 1	.954	.012	.749
Week 2	.032	<.001	.055
Week 3	.012	<.001	.016
Week 4	.273	.007	.181

3. Nasal congestion

Treatment effect

Significance of treatment effect	Baseline	week 1	week 2	week 3	week 4
	.229 (.167)	.137 (.002)	.001	011 (.054)	.116 (.041)

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	4 µg Kenalog vs Placebo
Week 1	.485	.023	.403 (.046)
Week 2	.094	<.001	.020
Week 3	.021	.006	.003
Week 4	.124	.097	.019

4. Itchy nose/throat/palate

Treatment effect

Significance of treatment effect	Baseline	week 1	week 2	week 3	week 4
	.141	.013 (<.001)	.003	.005 (.010)	.357

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	4 µg Kenalog vs Placebo
Week 1	.360 (.001)	.002	.370 (.001)
Week 2	.035	<.001	.016
Week 3	.016	<.001	.011
Week 4	.153	.098	.242

5. Itchy/red/watery eyes

Treatment effect

Significance of treatment effect	Baseline	week 1	week 2	week 3	week 4
	.042 (.857)	.098 (.005)	.021 (.005)	.055 (.002)	.145 (.008)

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 400 µg vs Placebo	4 µg Kenalog vs Placebo
Week 1	.576	.070	.757 (.032)
Week 2	.945	.020	.032
Week 3	.902 (.045)	.038	.054
Week 4	.621	.206 (.003)	.153 (.007)

Sponsor's conclusions

Tri-Nasal at doses of 400 µg was superior to the placebo in relieving the SAR symptoms. It was also superior to the other two treatment arms, Tri-Nasal 50 µg group ans Kenalog for SSI, sneezing, and rhinorrhea.

Reviewer's analyses

The reviewer analyzed data of 296 patients at 5 trial centers during a four-week treatment period. The data Analyses of variance (ANOVA) and analyses of covariance (ANCOVA) were done on the following endpoint variables. Additional repeated measures analyses were also performed, in which the time effect or dose effect was taken into account.

Endpoint	**Definition**
SSI	Symptom severity index
Sneezing	Sneezing
Rnose	Rhinorrhea
Ncongs	Nasal congestion
Itchns	Itchy nose/throat/palate
Itches	Itchy/red/watery eyes

The endpoint variables for individual symptoms were the mean weekly scores based on the patients' diaries. The SSI score was the sum of the individual scores. In addition to the mean scores at weeks 1-4, the baseline mean scores also were used in the analyses. For the above 6 variables and for the 5 time points, the reviewer's analyses comprised a total of 30 separate univariate analyses, including 1 baseline analysis.

Note that the baseline ANOVA was conducted to compare the homogeneity among the 4 treatment groups prior to the treatment.

This reviewer also applied the repeated measures analysis to evaluate the time effect.

In addition to the treatment effect, the center effect and the interaction between the two were also tested. The following table gives a concise summary of the reviewer's univariate analyses and multivariate repeated measures analyses. The test results were represented by p-values.

Overall significance of treatment effect

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.0061*	0.0164*	0.0018*	0.0031*	0.1980
Sneezing	0.0183*	0.0688	0.0108*	0.0016*	0.0286*
Rhinorrhea	0.0116*	0.0122*	0.0001*	0.0054*	0.1202
Nasal Cng	0.2459	0.1497	0.0110*	0.0502	0.1142
Itchy nose	0.1410	0.0112*	0.0032*	0.0050*	0.4048
Itchy eyes	0.0394*	0.1081	0.0209*	0.0573	0.1572
# of *	4	3	6	4	1

In this and the following tables, the asterisks, "*" mark the total numbers of significant treatment effects using a cutoff point p-value of 0.05. These numbers describe an overall effect of the drug on the selected symptoms and at different time points. The treatment effect appeared to be the strongest during week 2.

Pairwise comparison
Tri-Nasal 50 µg vs The placebo

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.0252*	0.6443	0.0842	0.0125*	0.2108
Sneezing	0.1834	0.0089*	0.0731	0.0200*	0.0918
Rhinorrhea	0.0200*	0.9619	0.0318*	0.0172*	0.2127
Nasal Cng	0.1442	0.4827	0.3963	0.1729	0.1251
Itchy nose	0.0474*	0.3077	0.0376*	0.0137*	0.1663
Itchy eyes	0.0277*	0.5320	0.9581	0.9307	0.7040
# of *		1	2	4	

Tri-Nasal 50 µg was most effective during week 3 in which only the relief of nasal congestion and itchy/red/watery eyes were not significant. This dose level was significantly effective in relieving the remaining individual symptoms and SSI.

Pairwise comparison
Tri-Nasal 400 µg vs The placebo

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.0005*	0.0075*	0.0001*	0.0004*	0.0374*
Sneezing	0.0020*	0.2268	0.0009*	0.0001*	0.8803
Rhinorrhea	0.0014*	0.0107*	0.0001*	0.0005*	0.3477
Nasal	0.1304	0.0257*	0.0502*	0.1658	0.1033
Itchy nose	0.0430*	0.0013*	0.0003*	0.0006*	0.1192
Itchy eyes	0.0068*	0.0871	0.0216*	0.0364*	0.1858
# of *		4	6	5	1

Tri-Nasal 400 µg was significantly effective in relieving most of the symptoms during weeks 1-3.

Pairwise comparison
Kenalog 4 µg vs The placebo

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.0513*	0.9537	0.0600	0.0062*	0.1167
Sneezing	0.0468*	0.2648	0.1138	0.0098*	0.2737
Rhinorrhea	0.0302*	0.7624	0.0692	0.0209*	0.0202*
Nasal Cng	0.9191	0.4332	0.1630	0.8649	0.0177*
Itchy nose	0.2881	0.2632	0.0143*	0.0135*	0.2808
Itchy eyes	0.0617	0.8411	0.0313*	0.0656	0.1421
# of *			2	4	2

Kenalog 4 µg was mostly effective in week 3. However, not all symptoms were significantly relieved during this period. The above three tables indicated that Tri-Nasal 400 µg was superior to both Tri-Nasal 50 µg and Kenalog.

Pairwise comparison
Tri-Nasal 50 µg vs Tri-Nasal 400 mg

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.2084	0.0228*	0.0268*	0.2788	0.4103
Sneezing	0.0747	0.1100	0.1119	0.1162	0.0421*
Rhinorrhea	0.3804	0.0104*	0.0112*	0.2663	0.7515
Nasal Cng	0.9623	0.1213	0.0027*	0.0054*	0.9580
Itchy nose	0.9717	0.0249*	0.1108	0.3333	0.8932
Itchy eyes	0.6105	0.0177*	0.0230*	0.0427*	0.0855
# of *		4	5	2	1

Pairwise comparison
Tri-Nasal 50 µg vs Kenalog 4 mg

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.7694	0.5981	0.8871	0.8106	0.7622
Sneezing	0.5063	0.0852	0.8281	0.7874	0.0029*
Rhinorrhea	0.8715	0.7224	0.7257	0.9363	0.2850
Nasal Cng	0.1725	0.9362	0.0175*	0.1250	0.4166
Itchy nose	0.3335	0.9242	0.7272	0.9959	0.7447
Itchy eyes	0.7355	0.4028	0.0346*	0.0786	0.0652
# of *			2		1

Pairwise comparison
Tri-Nasal 400 µg vs Kenalog 4 mg

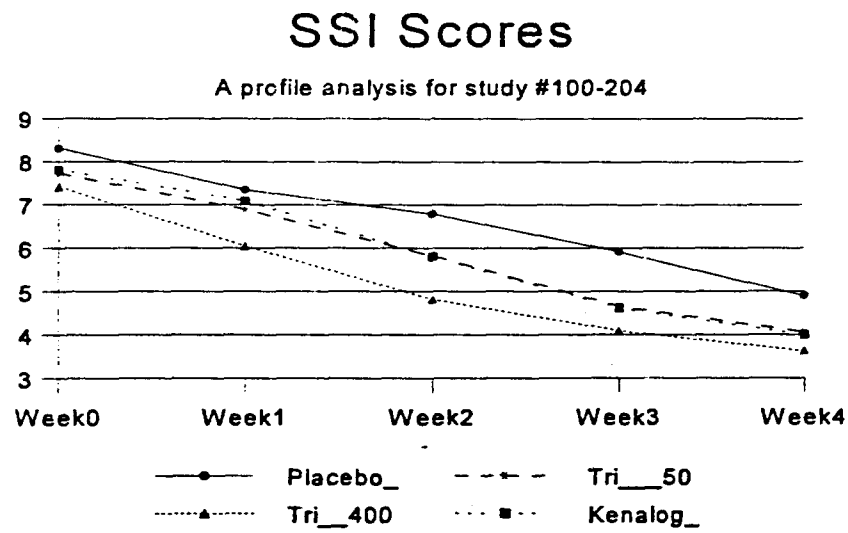
Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.1210	0.0053*	0.0369*	0.4008	0.6020
Sneezing	0.2631	0.9040	0.0682	0.1922	0.2944
Rhinorrhea	0.2987	0.0036*	0.0037*	0.2339	0.1616
Nasal Cng	0.1568	0.1433	0.5782	0.2215	0.4337
Itchy nose	0.3335	0.0320*	0.2092	0.3317	0.6376
Itchy eyes	0.3965	0.1239	0.8648	0.8024	0.8707
# of *		3	2		

The above three tables show comparisons among Tri-Nasal 50 µg, Tri-Nasal 400 µg and Kenalog. For most symptoms for weeks 2 and 3, Tri-Nasal 400 µg were more efficacious than Tri-Nasal 50 µg and Kenalog.

The reviewer's repeated measures analysis of variance was based on all 296 patients' data. The results are summarized as follows. Only results on SSI are listed here.

Source of variation	P-value	Source of variation	P-value
Pairwise comparisons		*Main effect*	
Tri50 vs placebo	0.0581	Treatment effect	0.0048
Tri400 vs placebo	0.0004	Time	0.0880
Kenalog vs placebo	0.1361		
Tri50 vs Tri400	0.0825	*Interaction*	
Tri50 vs Kenalog	0.6849	Time*treatment	0.2383
Tri400 vs Kenalog	0.0320	Time*center	0.0591

the treatment effect, known as between subject effect, was strongly significant (p=0.0048). The time effect was not significant with p-values 0.0880. These tests were done based on Wilks' Lambda, Pillai's Trace, Hotelling-Lawley Trace, Roy's Greatest Root statistics. Only was Tri 400 significantly effective as compared to the placebo. The following graph depicts the mean SSI scores against time (in weeks) by treatment groups.



APPEARS THIS WAY
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Appendix 3 (Study No. 100-305)

NDA 20-120

Objectives of the trial

To compare the efficacy and safety of triamcinolone acetonide (TAA) nasal spray solution (Tri-Nasal) at doses of 50 µg, 200 µg and 400 µg daily against the placebo in the treatment of seasonal allergic rhinitis (SAR) during the grass pollen season.

Emphases of this statistical review

This statistical review was focused on the efficacy aspect of the drug on the intent-to-treat (ITT) patients. The statistical analyses were based on the total and individual symptom severity scores of the selected rhinitis symptoms recorded by the participating patients.

Study design

The study 100-305 was conducted at 6 centers. It was a four-week, double-blind, randomized, parallel, placebo-controlled, multicenter study.

Participating Patients

Two hundred sixty nine (269) patients were enrolled in this study. These patients comprised both sexes and were 18-65 years of age.

Treatment Groups

Control Group:	Treated with the placebo
Dose Group 1:	Treated with 50 µg Tri-Nasal daily
Dose Group 2:	Treated with 200 µg Tri-Nasal daily
Dose Group 3:	Treated with 400 µg Tri-Nasal daily

Patient accountability

	Completed	Other	Total
Evaluable			154 (56.9%)
other			115 (43.1%)
Total	249 (93%)	20 (7%)	269 (100%)

Of the 115 non-evaluable patients, 66 (58%) were non-compliant with respect to study medications and 56 (49%) used restricted medications.

Patients by treatment by center

Center	Placebo	Tri-Nasal 50	Tri-Nasal 200	Tri-Nasal 400	Total
1	12	13	13	13	51
2	12	12	12	12	48
3	13	12	13	12	50
4	9	10	10	10	39
5	9	9	9	8	35
6	11	12	12	11	46
Total	66	68	69	66	269

Statistical analyses

The statistical procedure followed the following order.

Test the significance of baseline-(treatment) group interaction at significance level of α=0.1.

- If the baseline-(treatment) group interaction was not significant, then fit an ANCOVA model with baseline as a covariate, treatment, site, and treatment-site interaction.

  Test the significance of treatment-site interaction at α=0.1.
  - If the treatment-site interaction was not significant, fit an ANCOVA model with baseline, treatment, and site. Then test baseline at α=0.1.
  - If the treatment-site interaction was significant, fit the by-site ANCOVA models with baseline, treatment. Then test baseline at α=0.1.

- If the baseline-(treatment) group interaction was significant, then fit an ANOVA model with treatment, site, and treatment-site interaction.

  Test the significance of treatment-site interaction at α=0.1.
  - If the treatment-site interaction was not significant, then fit an ANOVA model with treatment, and site.
  - If the treatment-site interaction was significant, then fit the by-site ANOVA models with treatment.

Efficacy variables

- Primary endpoints:
  - Symptom severity index (SSI), which is the sum of the individual scores of sneezing, rhinorrhea, and nasal congestion.
  - Individual rhinitis symptoms
    1. Sneezing
    2. Rhinorrhea
    3. Nasal congestion
    4. Itchy nose/throat/palate
    5. Itchy/red/watery eyes
- Secondary endpoints:
  - Physician's (global and individual) evaluations at visits
  - Patient global evaluation of efficacy
  - Nasal examination
  - Use of rescue medication

Sponsor's results and reviewer's comments

The sponsor's results were verified and summarized in the following context. In most cases, the reviewer agreed upon the sponsor's conclusions. Otherwise, the disagreements were noted and discussed.

Analysis of baseline symptoms

There was no statistically significant (treatment) group-by-site interaction at baseline for the SSI score (p=0.51). There were no statistically significant (treatment) group-by-site interactions at baseline for most of the individual symptom severity scores except for the symptom of itchy/red/watery eyes with a p-value of 0.0728 as compared to 0.1.

A statistically significant difference in the SSI scores at baseline was found among the treatment groups. For all the individual symptoms, statistically significant differences were also found among the treatment groups at baseline: for sneezing, .0147; rhinorrhea, .0118; nasal congestion, .0321; itchy nose, .0656; and itchy eye, .0052.

Based on the physicians' evaluations, there were no statistically significant treatment-site interactions at the baseline for either the individual symptom severity scores or the SSI score. Except for the individual symptom, itchy/red/watery eyes, there were no significant differences in either individual or SSI scores among the treatment groups.

Comment: The sponsor's analysis based on the physicians' evaluations was not consistent with the findings based on patients' diaries. The differences are compared in the following table.

	P-values based on patients' diaries	P-values based on physicians' evaluation
SSI	.001	.203
Sneezing	.009	.223
Rhinorrhea	.007	.206
Nasal congestion	.022	.486
Itchy nose/throat/palate	.043	.374
Itchy/red/watery eyes	*	.029

* not computed due to significant treatment-site interaction at 0.1 level

Analysis of Efficacy

The analyses based on physicians' evaluations were quoted in parentheses in the following tables for comparison purposes.

- Analysis of primary endpoints

SSI

Treatment effect

Time point	Baseline	week 1	week 2	week 3	week 4
	0.001 (.203)	0.010 (.075)	0.022 (.486)	0.049 (.107)	0.026 (.058)

Comment: Discrepancies existed between the physicians' evaluations and the patients' self-evaluations.

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo
Week 1	.007 (.863)*	.003 (.089)*	.302 (.032)*
Week 2	.024 (.641)*	.007 (.202)*	.563 (.193)
Week 3	.022 (.319)*	.011 (.023)	.213 (.061)
Week 4	.014 (.146)*	.007 (.019)	.031 (.016)

Comment: The above table showed that about 50% of the time, the p-values based on the physicians' evaluations could lead to opposite conclusions to those based on the patients' self-evaluations. The patients' data indicated that Tri-Nasal 400 µg was not efficacious as compared to Tri-Nasal at doses of 50 µg and 200 µg which were significantly efficacious.

Individual symptom severity scores
1. Sneezing

Treatment effect

Time point	Baseline	week 1	week 2	week 3	week 4
	.009 (.223)	.039 (.110)	.022 (.534)	.023 (.277)	.064 (.131)

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo
Week 1	.041 (.172)	.006 (.591)	.271 (.344)
Week 2	.051 (.711)	.010 (.156)	.880 (.586)
Week 3	.034 (.427)	.004 (.053)	.404 (.256)
Week 4	.072 (.177)	.008 (.049)	.119 (.033)

2. Rhinorrhea

Treatment effect

Time point	Baseline	week 1	week 2	week 3	week 4
	.007 (.206)	.085 (.401)	.220 (.904)	.176 (.243)	.077 (.143)

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo
Week 1	.024 (.624)	.034 (.276)	.309 (.107)
Week 2	.203 (.761)	.055 (.461)	.701 (.797)
Week 3	.059 (.527)	.086 (.053)	.588 (.196)
Week 4	.023 (.228)	.060 (.029)	.032 (.074)

3. Nasal congestion

Treatment effect

Time point	Baseline	week 1	week 2	week 3	week 4
	.022 (.486)	.025 (.046)	.057 (.227)	.124 (.115)	.047 (.266)

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo
Week 1	.009 (.165)	.010 (.020)	.224 (.011)
Week 2	.010 (.426)	.037 (.263)	.191 (.040)
Week 3	.052 (.277)	.043 (.059)	.056 (.025)
Week 4	.022 (.163)	.015 (.080)	.035 (.099)

4. Itchy nose/throat/palate

Treatment effect

Time point	Baseline	week 1	week 2	week 3	week 4
	.043 (.374)	.091 (.222)	.006 (.344)	.010 (.084)	.248 (.584)

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg g vs Placebo
Week 1	.713 (.568)	.052 (.147)	.642 (.726)
Week 2	.085 (.844)	.002 (.103)	.859 (.734)
Week 3	.275 (.249)	.004 (.015)	.967 (.627)
Week 4	.174 (.199)	.068 (.271)	.664 (.377)

5. Itchy/red/watery eyes

Treatment effect

Time point	Baseline	week 1	week 2	week 3	week 4
	.005 (.029)	.344 (.089)	.160 (.289)	.080 (.274)	.082 (.227)

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo
Week 1	.105 (.056)	.907 (.855)	.472 (.155)
Week 2	.452 (.917)	.096 (.502)	.630 (.221)
Week 3	.646 (.958)	.021 (.093)	.837 (.598)
Week 4	.313 (.762)	.011 (.062)	.385 (.791)

Patients global evaluations (Physicians' global evaluations)

Pairwise comparisons

	Tri-Nasal 50 µg vs Placebo	Tri-Nasal 200 µg vs Placebo	Tri-Nasal 400 µg vs Placebo
Week 1	.010 (.012)	.001 (.020)	.063 (.004)
Week 2	.030 (.011)	.003 (.020)	.053 (.017)
Week 3	.221 (.172)	.070 (.012)	.137 (.144)
Week 4	.002 (.011)	.002 (.021)	.012 (.012)

Comment: For the individual symptoms, nasal congestion, rhinorrhea, and itch eyes, the overall treatment effect was not significant. This indicated that the varying doses did not significantly affect these symptoms.

Sponsor's conclusions

Tri-Nasal was superior to the placebo. The SSI scores in the 50 and 200 µg dose groups were significantly lower than those in the placebo. In comparing the SSI scores in the 400 µg dose group against the placebo, fewer statistically significant differences were noted. The sponsor asserted that "these data may have been confounded by low symptom severity scores in the 400 µg groups at baseline."

Comment: The sponsor found that Tri-Nasal at 400 µg dose was not as efficacious as the other two dose groups. This finding contradicted the results in the study 100-309 in which, the Tri-Nasal 400 µg dose was superior to the Tri-Nasal 200 µg dose. Moreover, there were a number of cases in which the patient-diary data and the physician-evaluation data lead to opposite conclusions.

Reviewer's analyses

The reviewer analyzed data of 267 patients at 6 trial centers during a four-week treatment period. The data Analyses of variance (ANOVA) and analyses of covariance (ANCOVA) were done on the following endpoint variables. Additional repeated measures analyses were also performed, in which the time effect was taken into account.

Endpoint	**Definition**
SSI	Symptom severity index
Sneezing	Sneezing
Rnose	Rhinorrhea
Ncongs	Nasal congestion
Itchns	Itchy nose/throat/palate
Itches	Itchy/red/watery eyes

The above endpoint variables for individual symptoms were the mean weekly scores based on the patients' diaries. The SSI score was the sum of the individual scores for sneezing, rhinorrhea and nasal congestion. In addition to the mean scores at weeks 1 through 4, the baseline mean scores also were used in the analyses. For the above 6 variables measured at the 5 time points, the reviewer performed a total of 30 separate univariate analyses.

Note that the baseline ANOVA was conducted to compare the homogeneity among the 4 treatment groups prior to the treatment.

In addition to the treatment effect, the center effect and the interaction between the two were also tested. The following tables summarize the reviewer's univariate analyses and repeated measures analyses. The test results were presented in terms of p-values.

Overall significance of treatment effect

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.0025	0.0101	0.0216	0.0494	0.0260
Sneezing	0.0147	0.0387	0.0215	0.0225	0.0637
Rhinorrhea	0.0118	0.0847	0.2204	0.1761	0.0771
Nasal Cng	0.0321	0.0248	0.0570	0.1235	0.0471
Itchy nose	0.0656	0.0914	0.0060	0.0099	0.2476
Itchy eyes	0.0052	0.1889	0.1599	0.0796	0.0821
# of significant tests (<.05)	5	3	3	3	2

On the last row of the table are the number of p-values that are less than 0.05. These numbers describe an overall effect of the drug on the selected symptoms and the SSI. The treatment effect was equally strongest in the weeks 1-3. Note that during the first two weeks of the treatment, only 50% of all the tests showed significant results.

The overall treatment group differences in the individual and the SSI scores at baseline were statistically significant. To test the significance of the treatment effect at a selected Time point, the analysis of covariance (ANCOVA) was employed to adjust for such differences. The test for interaction between the treatment effect and the baseline effect was done to verify the assumption for the validity of the use of ANCOVA. For the endpoint, itchy/red/watery eye, observed at week 1, the sponsor used the ANOVA method instead. The reviewer found the p-value for treatment-baseline interaction to be 0.1528, which did not appear to be significant. Still using the ANCOVA, the reviewer found that the overall treatment effect was not significant (p=0.1889).

The overall treatment effect was not statistically significant for the symptoms of rhinorrhea and itchy/red/watery eyes. Namely, these symptoms scores were not significantly different among the treatment groups.

Pairwise comparison
Tri-Nasal 50 µg vs The placebo

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.0294	0.0069	0.0237	0.0224	0.0138
Sneezing	0.0683	0.0411	0.0507	0.0338	0.0724
Rhinorrhea	0.3127	0.0238	0.2026	0.0586	0.0229
Nasal Cng	0.0277	0.0088	0.0101	0.0518	0.0220
Itchy nose	0.1223	0.7133	0.0851	0.2746	0.1744
Itchy eyes	0.0049	0.0626	0.4518	0.6464	0.3126
# of significant tests (<.05)	3	4	2	2	3

The Tri-Nasal 50 µg was significantly superior to the placebo for all four weekly observations based on the following endpoints: SSI, sneezing, and nasal congestion. This dose level was least effective in relieving itchy nose/throat/palate and itchy/red/watery eyes.

Pairwise comparison
Tri-Nasal 200 µg vs The placebo

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.0267	0.0034	0.0074	0.0114	0.0068
Sneezing	0.0144	0.0061	0.0099	0.0044	0.0084
Rhinorrhea	0.0575	0.0338	0.0551	0.0855	0.0601
Nasal Cng	0.6743	0.0096	0.0374	0.0433	0.0146
Itchy nose	0.1031	0.0523	0.0020	0.0037	0.0683
Itchy eyes	0.0376	0.8550	0.0962	0.0214	0.0112
# of significant tests (<.05)	3	4	4	5	4

The Tri-Nasal 200 µg dose seemed to be more effective then 50 µg dose. Tri-Nasal at 200 µg dose was significantly efficacious on almost all individual symptoms over the four-week treatment period.

Pairwise comparison
Tri-Nasal 400 vs The placebo

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.3791	0.3022	0.5627	0.2126	0.0305
Sneezing	0.8049	0.2712	0.8801	0.4043	0.1189
Rhinorrhea	0.2026	0.3087	0.7012	0.5880	0.0318
Nasal Cng	0.5329	0.2243	0.1911	0.0561	0.0348
Itchy nose	0.5747	0.6415	0.8590	0.9671	0.6635
Itchy eyes	0.9313	0.4442	0.6302	0.8369	0.3845
# of significant tests (<.05)	0	0	0	0	3

The figures in the above table showed that Tri-Nasal at 400 µg dose was not as efficacious as the Tri-Nasal at 50 or 200 µg. Note that the differences between Tri-nasal 400 µg and the placebo at baseline was not as big as that between the Tri-Nasal 50 µg (or 200 µg) and the placebo. One may think the significant treatment effect for the 50 and 200 µg dose groups might be confound by the difference at baseline, even if the baseline effect was adjusted using the ANCOVA procedure.

The following three tables give comparisons among the three Tri-Nasal dose groups.

Pairwise comparison
Tri-Nasal 50 µg vs Tri-Nasal 200 mg

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.9742	0.8511	0.0848	0.8131	0.8289
Sneezing	0.5265	0.4869	0.5326	0.4625	0.4012
Rhinorrhea	0.3682	0.8712	0.5178	0.8553	0.6723
Nasal Cong	0.0705	0.9206	0.5791	0.9747	0.9376
Itchy nose	0.9353	0.1157	0.1679	0.0672	0.0557
Itchy eyes	0.4460	0.0520	0.3690	0.0659	0.1358
# of significant tests (<.05)	0	0	0	0	0

Pairwise comparison
Tri-Nasal 50 µg vs Tri-Nasal 400 mg

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.0024	0.0992	0.0982	0.2962	0.7490
Sneezing	0.0399	0.3502	0.0756	0.1987	0.7983
Rhinorrhea	0.0228	0.2234	0.3824	0.1806	0.8960
Nasal Cng	0.0051	0.1616	0.2040	0.9555	0.8246
Itchy nose	0.0363	0.4113	0.1271	0.2585	0.3579
Itchy eyes	0.0040	0.2848	0.2236	0.8000	0.8746
# of significant tests (<.05)	6	0	0	0	0

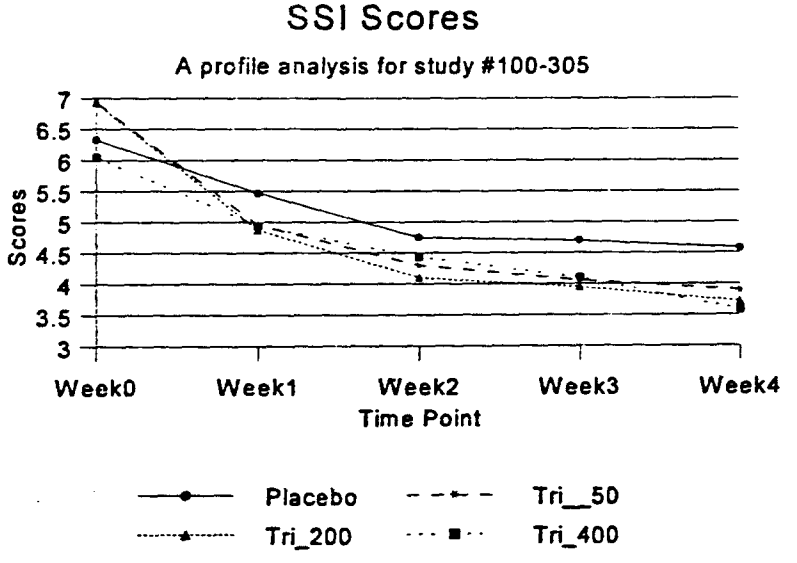
Pairwise comparison
Tri-Nasal 200 µg vs Tri-Nasal 400 mg

Endpoint	Baseline	Week 1	Week 2	Week 3	Week 4
SSI	0.0021	0.0637	0.0395	0.1195	0.5863
Sneezing	0.0075	0.1053	0.0170	0.0451	0.2778
Rhinorrhea	0.0016	0.2867	0.1337	0.2454	0.7759
Nasal Cng	0.2953	0.1802	0.4545	0.9290	0.7577
Itchy nose	0.0294	0.0180	0.0040	0.0034	0.1691
Itchy eyes	0.0317	0.3650	0.0338	0.0372	0.0968
# of significant tests (<.05)	0	5	1	4	3

The reviewer's repeated measures analysis of variance was based on all 269 patients' data. The results are summarized as follows. Only results on SSI are listed here.

Source of variation	P-value	Source of variation	P-value
Pairwise comparisons		*Main effect*	
Tri50 vs placebo	0.0058	Treatment effect	0.0122
Tri200 vs placebo	0.0029	Time	0.2525
Tri400 vs placebo	0.0963		
Tri50 vs Tri200	0.8276	*Interaction*	
Tri50 vs Tri400	0.2722	Time*treatment	0.6866
Tri200 vs Tri400	0.1891	Time*center	0.027

the treatment effect, known as between subject effect, was strongly significant (p=0.0122). The time effect was not significant with p-values 0.2525. These tests were done based on Wilks' Lambda, Pillai's Trace, Hotelling-Lawley Trace, Roy's Greatest Root statistics. Note that Tri 400 was not significant as compared to the placebo with a p-value of 0.0963. This repeated measures analysis was consistent with the univariate ANCOVA. The following graph depicts the mean SSI scores against time (in weeks) by treatment groups.



APPEARS THIS WAY
ON ORIGINAL

Appendix 4 (Study No. 0501)

NDA 20-120

Objectives of the trial

The purpose of this trial was to compare the safety and topical efficacy of triamcinolone acetonide (TAA) nasal spray solution (Tri-Nasal) at doses of 200 µg twice daily against the placebo in the treatment of seasonal allergic rhinitis (SAR) secondary to spring hay fever.

This statistical review

This statistical review was focused on the efficacy study on all patients. The statistical analyses were based on the individual severity scores for selected rhinitis symptoms recorded by the participating patients. The use of concomitant medication was also studied.

Study design

This study was conducted at 5 trial centers for a period of 6 weeks, which included a two-week baseline period. This study was a double-blind, randomized, parallel, placebo-controlled, multicenter study.

Participating patients

One hundred eighteen (118) patients were enrolled in this study. The participating patients comprised both sexes and were 18-65 years of age.

Treatment Groups

- Control Group: Treated with the placebo
- Dose Group: Treated with 200 µg Tri-Nasal twice daily

Patient accountability

	Completed	Discontinued	Total
Placebo group	58	1	59
Dosed group	58	1	59
Total	116	2	118

Patients by treatment by center

Center	Placebo	Tri-Nasal 400 daily	Total
ALBANY	12	13	25
FLORIDA	7	6	13
HARTFORD	13	12	25
VIRGINIA	15	15	30
W SENECA	12	13	25
Total	59	59	118

Statistical Procedure

Analysis of demographics

Type of variable	Variable	Method
Continuous	age, weight, height, etc.	ANOVA
Categorical	sex, race, etc.	Fisher's exact test

Analysis of efficacy

Repeated measures analysis of variance was employed with terms treatment; center; week; and center-treatment and week-treatment interactions. Two-sided t-tests were used to compare the dosed group against the control group, for each week of treatment and for each efficacy variable. Tests of no changes from baseline were done within each treatment group at each week of treatment.

If there an existed treatment-baseline interaction, the baseline was included as a covariate.
Analysis of safety
(not described in this report)

Efficacy variables

- Use of concomitant therapy which was defined as the number of tablets taken during the treatment period. This number indicated the extent to which an additional therapy was needed.

- Scores of severity for individual symptoms listed as follows, based on patients' diaries:

Sneezing
Nasal secretions
Nasal congestion
Itchy nose/throat/palate
Eye symptoms

- Physician's evaluations of individual symptoms at visits
- Physician's evaluations based on nasal examinations
- Physician's evaluations of overall control of symptoms
- Patients' evaluations of overall control of symptoms

Sponsor's results

- Use of concomitant therapy: The difference in numbers of tablets taken between the two treatment groups at baseline was not significant (p=.43). The changes from baseline in both groups were significant (p<0.01). The difference between the two treatment groups over the entire treatment period was significant (p=0.03).

  Analyses of scores of severity for individual symptoms are listed as follows.

- Sneezing: The difference between the two treatment groups at baseline was not statistically significant (p=0.16). The reductions in severity scores from baseline for both treatment groups were significant (p<0.01). The treated group showed a significantly greater decrease in severity scores than the placebo group (p<0.01).

- Nasal secretions (rhinorrhea): The difference between the two treatment groups at baseline was not statistically significant (p=0.43). The reductions in severity scores from baseline for both treatment groups were significant (p<0.01). The treated group showed a significantly greater decrease in severity scores than the placebo group (p=0.01).

- Nasal congestion: The difference between the two treatment groups at baseline **was statistically significant** (p=0.01). The reductions in severity scores from baseline for both treatment groups were significant (p<0.01). The treated group showed a significantly greater decrease in severity scores than the placebo group (p<0.01), after an adjustment for the baseline values.

- Itchy nose/throat/palate: The difference between the two treatment groups at baseline was not statistically significant (p=0.32). The reductions in severity scores from baseline for both treatment groups were significant (p<0.01). The treated group showed a significantly greater decrease in severity scores than the placebo

group (p=0.02).

- Eye symptoms : The difference between the two treatment groups at baseline was not statistically significant (p=0.88). The reductions in severity scores from baseline for both treatment groups were **not significant** (p=0.19). The treated group showed a significantly greater decrease in severity scores than the placebo group (p<0.01).

Physician's evaluations of individual symptoms at visits

- Sneezing: The difference between the two treatment groups at baseline was not statistically significant (p=0.43). The reductions in severity scores from baseline for both treatment groups were significant (p<0.01). The treated group showed a significantly greater decrease in severity scores than the placebo group (p<0.01).

- Nasal secretions: The difference between the two treatment groups at baseline was not statistically significant (p=0.56). The reductions in severity scores from baseline for both treatment groups were significant (p<0.01). The treated group showed a significantly greater decrease in severity scores than the placebo group (p=0.01).

- Nasal congestion: The difference between the two treatment groups at baseline was statistically significant. The reductions in severity scores from baseline for both treatment groups were significant (p<0.01). The treated group showed a significantly greater decrease in severity scores than the placebo group (p=0.05), after an adjustment for the baseline values.

- Itchy nose/throat/palate: The difference between the two treatment groups at baseline was not statistically significant (p=0.51). The reductions in severity scores from baseline for both treatment groups were significant (p<0.01). The treated group showed a significantly greater decrease in severity scores than the placebo group (p=0.02).

- Eye symptoms : The difference between the two treatment groups at baseline was not statistically significant (p=0.55). The reductions in severity scores from baseline for both treatment groups were significant (p<0.01). The treated group did **not** showed a significantly greater decrease in severity scores than the placebo group (p=0.13).

- Physician's evaluations based on nose examinations: (not described by the reviewer in this report)

- Physicians' evaluations of overall control of symptoms: Based on the Physicians assessments, the patients in the treated group showed significantly greater control of symptoms than in the control group at each week of the treatment: p=0.02 for week 1 and p<0.01 for weeks 2, 3, and 4.

- Patients' evaluations of overall control of symptoms: The patients in the treated group showed significantly greater control of symptoms than in the control group at each week of the treatment ($p<0.01$).

Sponsor's conclusions

Tri-Nasal at doses of 200 µg twice daily was more effective than the placebo in controlling the symptoms of allergic rhinitis secondary to spring hay fever. The changes from baseline were statistically significant between the two treatment groups. The sponsor noted that the magnitudes of the mean values of the endpoint variables were not clinically significant.

Reviewer's analyses

The reviewer analyzed data of 118 patients at 5 trial centers during a four-week treatment period. The data Analyses of variance (ANOVA) and analyses of covariance (ANCOVA) were done on the following endpoints variables. The repeated measures analysis was also applied to evaluate the time effect.

Endpoint variables

- Number of tablets of Chlortrimeton as a concomitant therapy taken during the treatment period
- Scores of severity for Individual symptoms based on patients' diaries
  - Sneezing
  - Nasal secretions
  - Nasal congestion
  - Itchy nose/throat/palate
  - Eye symptoms
- Physicians' evaluations of individual symptoms at visits
- Physicians' evaluations of overall control of symptoms
- Patients' evaluations of overall control of symptoms

The reviewer's repeated measures analysis of variance was based on all 118 patients' data. The results are summarized as follows. Results based on individual variables are listed as follows.

Tablets of rescue medication

Source of variation	P-value	Source of variation	P-value
Pairwise comparisons		*Main effect*	
Tri200 twice daily vs placebo	0.0023	Treatment effect	0.0023
		Time	0.3402
		Interaction	
		Time*treatment	0.1310
		Time*center	0.7994

Sneezing

Source of variation	P-value	Source of variation	P-value
Pairwise comparisons		*Main effect*	
Tri200 twice daily vs placebo	0.0001	Treatment effect	0.0001
		Time	0.8366
		Interaction	
		Time*treatment	0.0144
		Time*center	0.4339

Nasal secretion

Source of variation	P-value	Source of variation	P-value
Pairwise comparisons		*Main effect*	
Tri200 twice daily vs placebo	0.0001	Treatment effect	0.0001
		Time	0.6518
		Interaction	
		Time*treatment	0.0018
		Time*center	0.2139

Nasal congestion

Source of variation	P-value	Source of variation	P-value
Pairwise comparisons		*Main effect*	
Tri200 twice daily vs placebo	0.0001	Treatment effect	0.0001
		Time	0.0592
		Interaction	
		Time*treatment	0.0085
		Time*center	0.0486

Itching

Source of variation	P-value	Source of variation	P-value
Pairwise comparisons		*Main effect*	
Tri200 twice daily vs placebo	0.0003	Treatment effect	0.0003
		Time	0.7133
		Interaction	
		Time*treatment	0.0105
		Time*center	0.1304

Eye symptoms

Source of variation	P-value	Source of variation	P-value
Pairwise comparisons		*Main effect*	
Tri200 twice daily vs placebo	0.1353	Treatment effect	0.1353
		Time	0.8719
		Interaction	
		Time*treatment	0.4390
		Time*center	0.0171

the treatment effect, known as between subject effect, was strongly significant with one exception for eye symptoms (p=0.1353). Because the baseline was treated as covariate, the MANCOVA adjusted for the baseline while testing the treatment effect.

The following graphs depicts the symptom scores across time by treatment groups by endpoints.