CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-746

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL

Date: SEP 7 1997

NDA#:20-746

Applicant:	Astra USA
Name of Drug:	Rhinocort® Aqua Nasal Spray (budesonide)
Indication:	Treatment of seasonal allergic rhinitis
Documents Reviewed:	• Study #05-3038: Vol. 116-123 • Study #05-3039: Vol. 147-158 • Sponsor cover letter of 7/29/1996 • Amendment to FDA's IR on 3/6/97
Statistical Reviewer:	Ted (Jiyang) Guo, DOB II/OEB, HFD-715
Medical Input:	Raymond Anthracite, ODE II, HFD-570

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Introduction

The sponsor proposed that Rhinocort® (budesonide) Aqua Nasal Spray[1] is indicated for treating symptoms of seasonal and perennial allergic rhinitis for children (6-17 years of age) and adults (18+ years of age). A starting daily dose of 256 µg is proposed as the market dose.

To support the efficacy of the drug in treating seasonal rhinitis, the sponsor presented evidence from seven randomized placebo-controlled studies. These studies, identified in this NDA, are listed in Table 1.

Table 1. List of Efficacy Studies

Allergic Symptom	Study #	Location	# Volumes in NDA	Type of study
Seasonal	05-3038	USA	8	Placebo controlled
Seasonal	05-3006	Foreign	4	Placebo controlled
Seasonal	05-3011	Foreign	3	Placebo controlled
Seasonal	05-3030	Foreign	11	Placebo controlled
Perennial	05-3039	USA	12	Placebo controlled
Perennial	05-3012	Foreign	6	Placebo controlled
Perennial	05-3024	Foreign	5	Placebo controlled

Study **05-3038** was conducted from August through October 1994. Four hundred and five (405) patients with seasonal allergic rhinitis from two geographic regions (Northeast and Midwest), who met the inclusion criteria, were enrolled in the study. Based on the first-dose date and last-dose date provided in the patient-diary-data file, Table 2 describes patient accountability. The numbers in the numerators are the numbers of patients staying on study for at least 25 days of the four-week trial. The denominators represent the total number of patients.

Table 2. Patient Accountability: Patients on Study for At Least 25 Days (05-3038: 4-week Study)

Treatment Group	No. Patients/Total No. Patients	Percent
Placebo	79/83	95%
32 µg	71/78	91%
64 µg	75/79	95%
128 µg	79/83	95%
256 µg	76/82	93%

Study **05-3039** was conducted from December 1994 through April 1995. Four hundred seventy three (473) patients with perennial allergic rhinitis who met the inclusion criteria were enrolled in the study. Based on the first-dose date and last-dose date provided in the patient-diary-data file, Table 3 describes patient accountability. The numbers in the numerators are the numbers of patients staying on study for at least 39 days of the six-week trial. The denominators represent the total number of patients.

[1] Rhinocort Nasal Inhaler (NDA 20-233), approved for marketing 2/14/94, is delivered as a pressurized aerosol metered dose inhaler (pMDI). In this NDA, Rhinocort® Aqua Nasal Spray as an extended formula of Rhinocort Nasal Inhaler is developed for the US market. This formula is currently marketed in Europe.

Table 3. Patient Accountability: Patients on Study for At Least 39 Days (05-3039: 6-week Study)

Treatment Group	No. Patients/Total No: Patients	Percent
Placebo	88/96	92%
32 µg	86/97	89%
64 µg	86/91	95%
128 µg	82/92	89%
256 µg	93/97	96%

Both studies were randomized, double blind, placebo controlled trials. The trial-dosage regimens were 32, 64, 128, and 256 µg daily for the treated patients. The drug was delivered as a nasal spray.

The primary efficacy variable (or outcome measurement) was the nasal index score (NIS), defined as the sum of selected individual symptom scores: nasal congestion, runny nose, and sneezing. Other efficacy variables included individual nasal symptoms (congestion, runny nose, sneezing and nasal itching) and eye complex symptoms (itching, redness, and tearing). In addition, the sponsor analyzed the patient overall assessment of efficacy, the number of patients requiring breakthrough medication, and discontinuations from the study.

During the trial, when the symptoms became intolerable, patients were allowed to take *Chlor-Trimeton* in tablet or liquid formulation as rescue medication.

The efficacy variable used in the primary statistical analysis was the average change in NIS from baseline. Note that in the sponsor's analysis changes in NIS were calculated by subtracting the baseline scores from treatment NIS. Changes were calculated as the averages over the entire treatment period. No weekly means were considered in the sponsor's protocol.

The changes in NIS from baseline were analyzed using the analysis of variance (ANOVA) model including the baseline as the covariate whenever applicable [ANCOVA]. This statistical model included the following terms as the independent variables: treatment, center, and interaction between the two. When the interaction was not significant at the 0.1 level, it was excluded from the model.

The sponsor also analyzed dose-response trends. The lowest active dose was compared against the highest one. Then, a regression line was fit for the outcome variable against doses. In the original submission, the placebo was part of the dose groups. The placebo was removed in a later amendment dated 3/6/97.

Studies 05-3038 and 05-3039 were similar, except for the following major differences:

- Patients enrolled in Study 05-3038 had seasonal allergic rhinitis, and those in Study 05-3039 had perennial allergic rhinitis.
- Study 05-3038 continued four weeks and Study 05-3039 was a six-week trial.
- There were more centers in Study 05-3039 than in Study 05-3038: Fourteen centers in two geographic regions in Study 05-3038 and twenty centers in Study 05-3039. In Study 05-3038, the two geographic regions (Northeast and Midwest) were analyzed separately, due to the significant variation in pollen counts between the two regions. These analyses were pre-specified in the sponsor's protocol. Geographic regions were not identified in study 05-3039.
- Age group analyses for patients, 6-17 and 18+ years of age were performed in Study 05-3039. The efficacy difference between age groups was not a concern in Study 05-3038.

This reviewer's efficacy evaluation is based on these studies. The safety assessment is focused on the cortisol-level analysis based on study 05-3038.

Sponsor's Results: Efficacy

Study 05-3038

The sponsor concluded, "In the overall analysis with both regions combined, significantly greater decrease in NIS from baseline were observed in all active treatment groups compared to placebo ($p \leq 0.003$) (page 25, vol. 116)."

For the Northeast, "all active treatments had greater decreases in NIS compared to the placebo, with significance being obtained for the 32 µg and the 256 µg groups." For the Midwest, "all active treatments had greater decreases in NIS compared to the placebo, with significance being obtained for the 64 µg, 128 µg, and the 256 µg treatment groups, but not for the 32 µg treatment group." To determine the minimum effective dose (MED), the sponsor used a step-down procedure as follows: The highest dose was compared to the placebo. If the comparison was significant, then the next highest dose was compared to the placebo. This process continued until a non-significant comparison was reached. The last significant dose was determined to be the MED (Page 37, vol. 113). Based on this approach, the sponsor decided that the MED was 256 µg daily.

The dose-response trend was not significant. The sponsor pointed out that the lack of dose-response might be due in part to the low pollen counts observed in the Northeast region (page 25, vol. 116).

In conclusion, the sponsor proposed a starting daily dose of 256 µg to treat seasonal allergic rhinitis (Page 27 vol. 116).

Study 05-3039

The sponsor concluded, "In the overall analysis, nasal index scores decreased significantly from baseline for active treatments 32 µg, 64 µg, and 256 µg compared to placebo." For the dose 128 µg, "the difference in mean change in NIS from baseline between 128 µg and placebo marginally failed to reach significance." (Page 6 and page 78, vol. 147)

For the adult patient group, the "decrease in NIS from baseline for all active treatments compared to placebo were significantly greater." However, for the pediatric patient group, "the differences in mean change in NIS from baseline between active treatments and placebo were not significant." (Page 6, vol.147)

For the dose-response relationship, "No significant differences could be demonstrated between 256 µg and 32 µg in terms of change in NIS from baseline overall or within each age group." (Page 6 and page 78, vol. 147)

In conclusion, the sponsor proposed a starting daily dose of 256 µg to treat seasonal allergic rhinitis. (Page 8. Vol. 147)

Reviewer's Evaluation: Efficacy

Study 05-3038—Seasonal Allergic Rhinitis

Patient Profile

This study included 405 patients in both geographic regions (the Northeast and the Midwest). Table 4 describes the number of patients by region and by treatment group. Table 5 shows the number of patients who completed and who discontinued the trial. Among the 405 patients, there were 10 discontinued patients. For the regions combined, 97.5% of the patients completed the study. Therefore, the completeness of the data is no a concern to this reviewer in the statistical evaluation.

Table 4. Patients by Treatment Groups by Region (Study 05-3038)

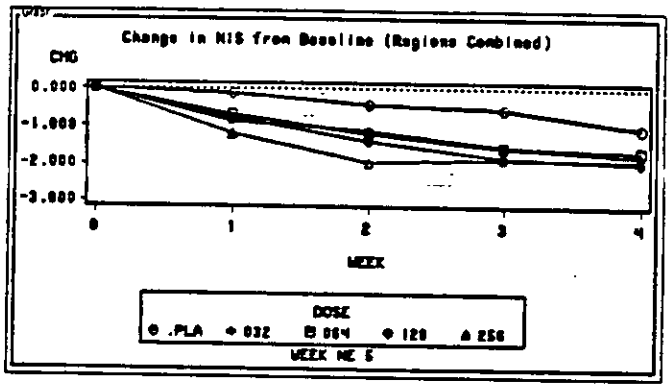
	DOSE					
	.PLA	032	064	128	256	Total
REGION						
MIDWEST	41	42	39	42	41	205
NORTHEAST	42	36	40	41	41	200
Total	83	78	79	83	82	405

Table 5. Patient Accountability (Study 05-3038)

	Patient Termination				
	N		Y		
	Gender		Gender		
	FEMALE	MALE	FEMALE	MALE	ALL
Region					
(1)NORTHEAST	97	95	2	6	200
(2)MIDWEST	81	122	1	1	205
ALL	178	217	3	7	405

Patient distributions by other categories can be found in Appendix 1. Figure 1 depicts the changes in NIS from baseline, by treatment group, for the regions combined. In general, the treated groups demonstrated more improvement in NIS than did the placebo control group. There was a greater reduction in NIS in the 256 µg group than in the other groups, especially for the first two weeks of the study.

Figure 1. NIS Changes by Treatment Group (Study 05-3038)



To explore and visualize the variations in NIS changes from baseline across the centers and over time, the following figures show the NIS changes across the trial centers. Figures 2-5 depicts the NIS changes from baseline by center and treatment. The horizontal axis describes center by treatment. Each of these graphs represents the NIS changes for a specific week of the study.

Figure 2. Week 1 NIS Changes by Center, Treatment (Study 05-3038)

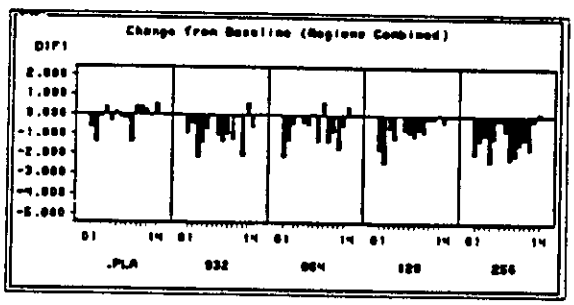


Figure 3. Week 2 NIS Changes by Center, Treatment (Study 05-3038)

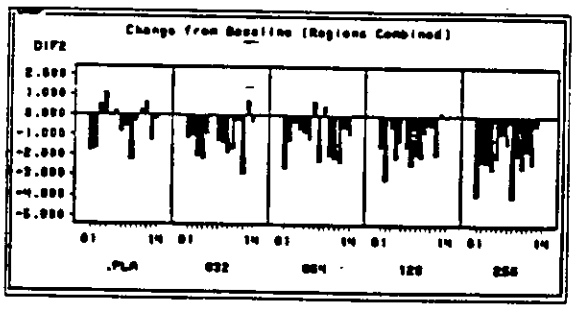


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Figure 4. Week 3 NIS Changes by Center, Treatment (Study 05-3038)

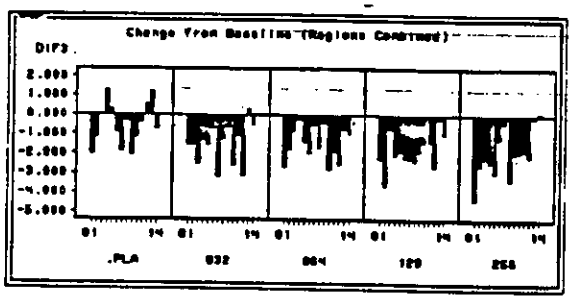
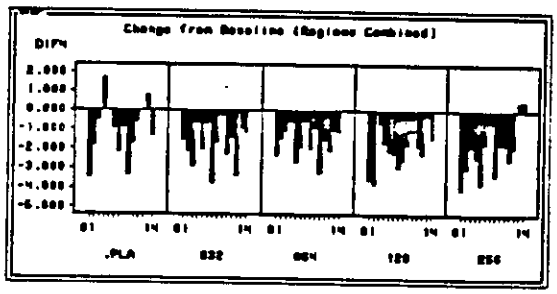


Figure 5. Week 4 NIS Changes by Center, Treatment (Study 05-3038)

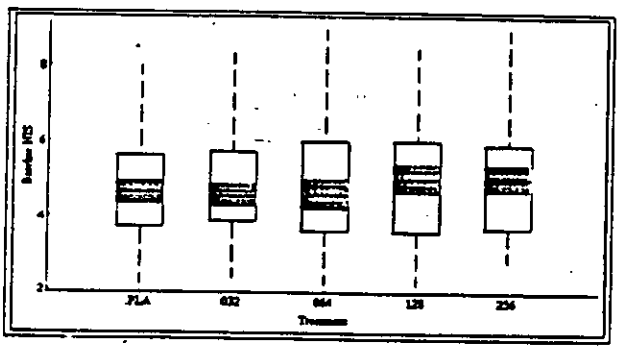


By inspection of the above Figures 1-5, the following points are noted:

- In general, greater improvements in NIS were shown in the active treatment groups, compared to the placebo.
- The improvement in NIS increased with time (week).
- The differences in NIS changes among the active treatment groups appeared to be smaller than that between these groups and the placebo.
- The clear variations among the centers suggested a possibly significant center effect.

The box plot in Figure 6 describes the baseline values by treatment group. The middle lines inside the boxes represent the medians of the baseline values. The bottom and top of the rectangle represent the first and third quartiles, respectively. There did not appear to be any large differences in baseline NIS among the treatment groups.

Figure 6. Distribution of Baseline NIS (Study 05-3038)



Analysis of Baseline

The analysis of baseline comprised the following tests: (1) A test of (treatment) group-baseline interaction, which is the test of validity for the use of the analysis of covariance model (ANCOVA), (2) A test of baseline-value homogeneity across the groups.

The group-baseline interaction was not significant. This reviewer, however, did find that the baseline difference among the treatment groups was significant ($p<0.05$). For these reasons, the use of the analysis of covariance (ANCOVA) model was justified. As in the sponsor's analysis, the baseline was included in the model as a covariate.

Analysis of treatment-Center Interaction

Because of the noticeable across-center differences in NIS (Figures 2-5), the reviewer tested the significance of the treatment-center interaction. The results were obtained based on the 4-week mean NIS changes from baseline for each region and the regions combined. The tests found no significant treatment-center interactions.

Based on the above analyses, the terms of treatment and center were included in the final ANCOVA model in which the baseline NIS served as the covariate.

Analysis of Treatment Effect (NIS)

In Table 6, the week identified as "1-4" represent test based on the 4-week averages compared to the by-week analyses. The analyses shown in Table 6 found that the treatment effect was significant. So was the center effect, based on either the by-week analyses or the all-week analysis (average of 4-week NIS). The center variations in NIS change can be observed in Figures 2-5 above. In this table, p-values less than 0.05 are in bold face.

The analysis of week-2 NIS showed that the treatment and center effects are significant for both regions. The same conclusion held based on the 4-week averages. For other weeks, the results differed between the regions. It should be pointed out that the week-4 analysis did not show a significant treatment effect, which can be observed from Figures 1 and 5 above. In addition, for week 4, neither treatment nor center effect was significant. Overall, Rhinocort reached its maximum strength during the weeks 2 and 3.

Table 6. Analysis of Treatment and Center Effect (Study 05-3038)

Region	Treatment	Center	Week
Northeast	**0.0044**	**0.0315**	1-4
Midwest	**0.0045**	**0.0060**	
All	**0.0014**	**0.0021**	
Northeast	0.0020	0.0742	1
Midwest	0.0511	**0.0016**	
All	**0.0045**	**0.0036**	
Northeast	0.0014	**0.0378**	2
Midwest	**0.0065**	**0.0067**	
All	**0.0002**	**0.0040**	
Northeast	**0.0129**	0.0774	3
Midwest	**0.0015**	**0.0147**	
All	**0.0006**	**0.0058**	
Northeast	0.0867	0.0821	4
Midwest	**0.0422**	**0.0226**	
All	0.1268	**0.0079**	

To compare all of the active treatments with the placebo, a test due to Dunnett was used (Table 7). This test holds the maximum experimentwise error to a level not exceeding the significance level (0.05). The symbol, "✔" indicates that the corresponding dose level is superior to the placebo. The test indicated that Rhinocort at daily doses of 128 and 256 µg is superior to the placebo based on the weekly mean NIS. The doses of 32 and 64 µg, however, did not always demonstrate superiority. Note that the Dunnett's Tests here and the sponsor's results based on all-week averages are consistent. The sponsor did not report by-week studies. Overall, Rhinocort demonstrated statistical superiority to placebo.

Table 7. Analyses of Active Treatments vs. Placebo (Study 05-3038)

Week	Dose vs. Placebo	Simultaneous Lower Limit	Difference Between Mean	Simultaneous Upper Limit	Significance (Dunnett's)
1-4	32 µg	-1.44	-0.79	-0.13	✔
	64 µg	-1.39	-0.74	-0.08	✔
	128 µg	-1.6	-0.96	-0.31	✔
	256 µg	-1.83	-1.19	-0.54	✔
1	32 µg	-1.26	-0.64	-0.02	✔
	64 µg	-1.2	-0.57	0.058	
	128 µg	-1.38	-0.75	-0.11	✔
	256 µg	-1.68	-1.06	-0.43	✔
2	32 µg	-1.44	-0.68	0.068	
	64 µg	-1.50	-0.75	-0.003	✔
	128 µg	-1.71	-0.97	-0.23	✔
	256 µg	-2.28	-1.54	-0.70	✔
3	32 µg	-1.74	-0.99	-0.23	✔
	64 µg	-1.76	-1.00	-0.25	✔
	128 µg	-2.04	-1.29	-0.55	✔
	256 µg	-2.05	-1.30	-0.56	✔
4	32 µg	-1.56	-0.74	0.08	
	64 µg	-1.44	-0.62	0.19	
	128 µg	-1.65	-0.84	-0.03	✔
	256 µg	-1.72	-0.92	-0.11	✔

Symbol "✔" represents a significant test result using Dunnett's Test. This test holds the maximum experimentwise error to a level not exceeding the significance level (0.05). The presence of this symbol indicates that Rhinocort at the indicated dose level is superior to the placebo.

Analysis of Dose-Response Trend

The test for dose-response trend was conducted to evaluate the sponsor's proposal to market a daily dose of 256 µg. The reviewer's statistical method is described in detail in ***The Design and Analysis of Clinical Experiments***, by Joseph L. Fleiss[ii]. Since four treatment arms were involved, the trend test was done by following these steps:

1. Test the hypothesis that the dose-response relationship is no more complicated than a quadratic.
2. If this hypothesis is rejected, then fit higher-degree equations or makes some transformation on the dependent variable.
3. If the dose effect is at most quadratic, then test the hypothesis that the quadratic effect is not significant (hence a linear relationship is considered).

4. If the above hypothesis is not rejected, then test the hypothesis that the linear effect is not significant (test that the slope is zero).

It is convenient to analyze $Z=\log_2(dose/32)$ rather than the raw dose values as an independent variable, because each active dose is twice the preceding one (refer to Fleiss's book). The Z values (0-3) on the horizontal axis represent doses: 32, 64, 128 and 256 (μg), respectively. The response variable (on the vertical axis) represents the NIS change from baseline.

The following scatter-plot (Figure 7) and box-plot (Figure 8) depict the NIS changes (from baseline) among the active doses. Neither increasing nor decreasing trend is demonstrated by these figures.

Figure 7. Scatter Plot of Dose-Response Relationship (Study 05-3038)

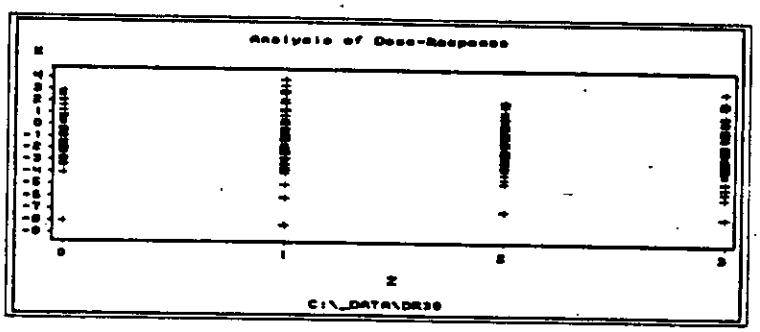
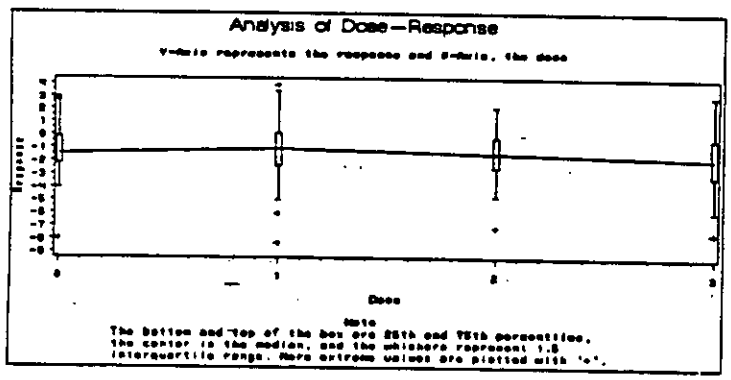


Figure 8. Box Plot of Dose-Response Relationship (Study 05-3038)



First, the dose-response relationship was no more complicated than a quadratic (based on the F-Statistic, 0.007<5.79, the critical value). Second, knowing that the dose effect was no more than quadratic, the second test showed that the quadratic effect was not significant (based on |T|=0.841<2.407, the critical value). The above tests indicated that the dose effect might be linear. A t-test was applied to determine whether the slope of the regression line was zero. This test found that the slope was no significantly different from zero (based on |T|=1.76 < 2.252, the critical value).

In conclusion, there was not a statistically significant dose-response trend. That is, there was not an indication of further improvement in NIS with an increase in dose.

Analysis of Individual Symptoms

This reviewer analyzed the following individual nasal and eye symptom scores: sneezing, runny nose, nasal congestion, nasal itchy, eye itchy, eye redness, and tearing. Significant tests results ($p<0.05$) are labeled as a dot ("•") in Table 8. The following points are worth noting:

- Rhinocort provided greater relief for symptoms, sneezing and nasal congestion than other symptoms;
- For the combined regions and for weeks 1 through 3, a daily dose of 256 µg is consistently superior to the placebo.

Table 8. Analyses of NIS and Individual Symptoms

		Weeks 1-4			Week 1			Week 2			Week 3			Week 4		
		Nor	Mid	All	Nor	Mid	All	Nor	Mid	All	Nor	Mid	All	Nor	Mid	All
NIS	32	•		•	•		•	•		•	•		•	•		•
	64		•	•		•	•		•	•		•	•			
	128		•	•			•	•		•	•	•	•		•	•
	256	•	•	•	•	•	•	•	•	•	•	•	•		•	•
Sneezing	32	•		•	•			•			•		•			
	64		•	•						•		•	•			
	128												•			
	256	•	•	•	•		•	•	•	•		•	•			
Runny Nose	32	•			•			•			•			•		
	64												•			
	128											•	•			
	256							•		•						
Nasal Congestion	32	•		•	•		•	•		•	•		•	•		
	64		•									•	•			
	128		•	•						•		•	•			
	256		•	•		•	•		•	•		•	•		•	
Nasal Itchy	32	•			•			•			•			•		
	64															
	128															
	256							•		•				•		
Eye Itchy	32	•			•			•	•		•					
	64															
	128															
	256										•					
Eye Redness	32							•			•					
	64															
	128															
	256							•								
Tearing	32	•		•	•		•	•			•		•			
	64															
	128								•							
	256	•			•		•	•								

Overall, Rhinocort at the proposed daily dose of 256 µg provided relief for some nasal symptoms, such as sneezing and nasal congestion. However, it did not show the same effect for other nasal and eye symptoms.

Additional Analysis of NIS for Selected Age Groups

Because of the clear differences in NIS improvement between the pediatric patients (6-17 years of age) and adult patients (18+ years of age) found in Study 05-3039, the medical reviewer requested an additional analysis on pediatric patients by grouping ages into 6-12 and 13-17 years. The purpose was to explore the possibly significant difference between the two age groups.

The following tables and figures describe patients using the above age breakdown. Adult patients (eighteen years of age and older) are also included for comparison purposes.

Table 9 describes patient distribution by treatment group and the selected age breakdown. Children 6-12 and 13-17 years of age are evenly distributed. These two groups account for about half of the patients in this study.

Table 9. Number of Patients by Treatment by Selected Age Breakdown

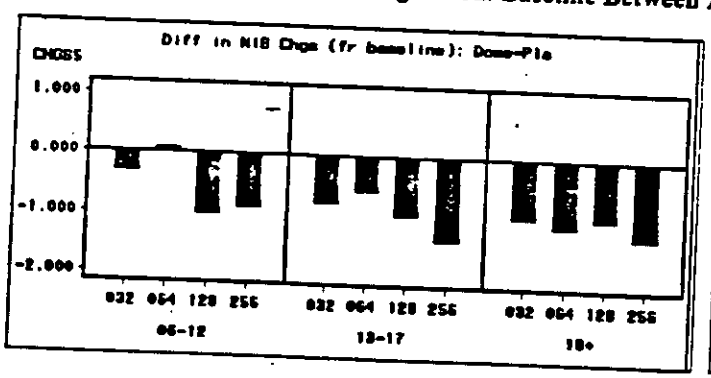
		DOSE					
		.PLA	032	064	128	256	Total
AGE_GP							
06-12	N	21	17	19	20	19	96
	%	25.3	21.8	22.8	24.1	22.8	23.2
13-17	N	14	16	14	18	19	81
	%	16.9	20.5	17.7	21.7	23.2	20.0
18+	N	48	45	47	45	45	230
	%	57.8	57.7	59.5	54.2	54.9	56.8
Total	N	83	78	79	83	82	405
	%	100.0	100.0	100.0	100.0	100.0	100.0

Figure 9 depicts the differences observed in NIS changes from baseline between active doses and the placebo. Overall, these differences were greater among children, 13-17 than those among children, 6-12.

Figures 10 through 13 describe the same quantities as shown in Figure 9 for weeks 1 to 4. The reviewer's observations are summarized in the following points:

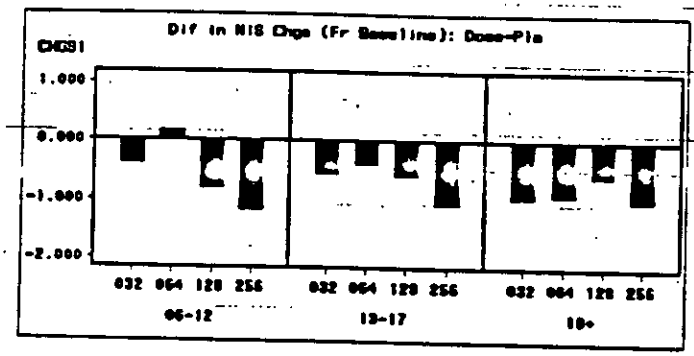
- In general, the differences in NIS changes from baseline between the active doses and the placebo are greater among children, 13-17 years of age than those among the younger children (6-12 years of age).
- Children receiving higher dose (128 or 256 μg) generally had greater improvement in NIS compared to those receiving lower doses.

Figure 9. Differences in NIS Changes from Baseline Between Active Doses and Placebo: 4-Weeks



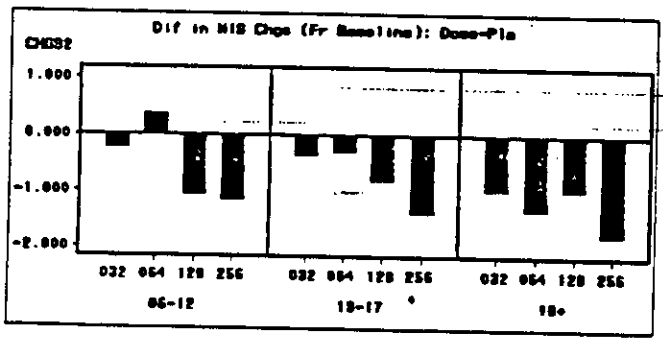
Age Group	Dose	Diff in NIS-Chgs
06-12	032	-0.339
	064	0.075
	128	-1.005
	256	-0.971
13-17	032	-0.786
	064	-0.570
	128	-0.864
	256	-1.370
18+	032	-0.870
	064	-1.036
	128	-0.955
	256	-1.260

Figure 10. Differences in NIS Changes from Baseline Between Active Doses and Placebo: Week-1



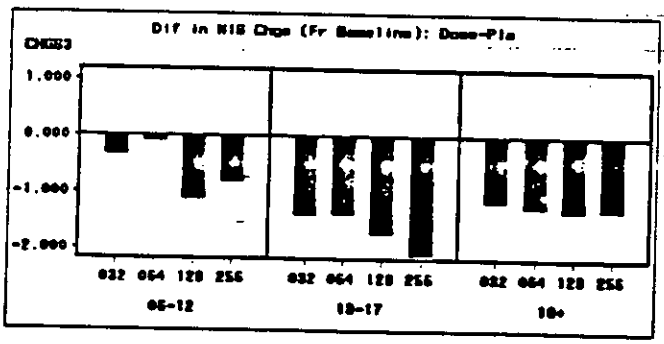
Age Group	Dose	CHGS1
06-12	032	-0.392
	064	0.151
	128	-0.808
	256	-1.174
13-17	032	-0.551
	064	-0.998
	128	-0.583
	256	-1.063
18+	032	-0.932
	064	-0.892
	128	-0.581
	256	-0.984

Figure 11. Differences in NIS Changes from Baseline Between Active Doses and Placebo: Week-2



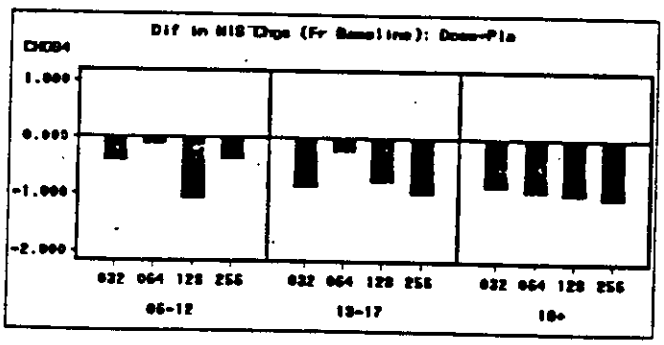
Age Group	Dose	CHGS2
06-12	032	-0.219
	064	0.354
	128	-1.064
	256	-1.145
13-17	032	-0.351
	064	-0.300
	128	-0.808
	256	-1.367
18+	032	-0.970
	064	-1.312
	128	-0.970
	256	-1.750

Figure 12. Differences in NIS Changes from Baseline Between Active Doses and Placebo: Week-3



Age Group	Dose	CHGS3
06-12	032	-0.339
	064	-0.089
	128	-1.093
	256	-0.801
13-17	032	-1.392
	064	-1.362
	128	-1.713
	256	-2.081
18+	032	-1.134
	064	-1.251
	128	-1.303
	256	-1.280

Figure 13. Differences in NIS Changes from Baseline Between Active Doses and Placebo: Week-4



Age Group	Dose	CHGS4
06-12	032	-0.406
	064	-0.117
	128	-1.058
	256	-0.364
13-17	032	-0.850
	064	-0.220
	128	-0.751
	256	-0.969
18+	032	-0.842
	064	-0.929
	128	-0.968
	256	-1.025

Study 05-3039—Perennial Allergic Rhinitis

Patient Profile

Verified by this reviewer, 473 patients were included in the analyses, and these patients had at least one double-blind observation. The patients comprised adults, 18 years of age and older, and children, 6-17 years of age. Table 10 describes the patients by age group. Table 11 describes the number of patients by accountability. Among the 473 patients, 27 did not complete the study. The remaining 94.3% of the patients completed the study. This reviewer does not consider the missing values to be a concern in the analysis.

Note that the sponsor reported that there were 478 patients randomized into the study and 447 completed the study (page 59, vol. 147). In fact, 473 patients had a baseline observation and had at least one double-blind observation. Five patients who were randomized did not receive treatment.

Table 10. Treatment Groups (05-3039)

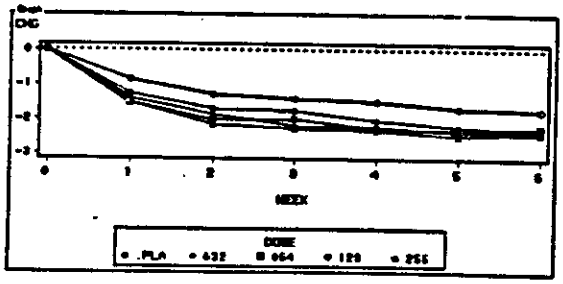
	DOSE					
	.PLA	032	064	128	256	Total
AGE						
18+	52	53	48	47	54	254
6-17	44	44	43	45	43	219
Total	96	97	91	92	97	473

Table 11. Patient Accountability (Study 05-3039)

	DOSE					
	.PLA	032	064	128	256	Total
DISCONTINUE						
N	91	88	89	83	95	446
Y	5	9	2	9	2	27
Total	96	97	91	92	97	473

Patient distribution by other categories can be found in Appendix 2. The following Figure 14 depicts the changes in NIS from baseline, by treatment group. For the age groups combined, the treated groups demonstrated more improvement in NIS than did the placebo group over time. There is no clear difference among the active treatment groups.

Figure 14. NIS Changes by Treatment Group (Study 05-3039)



The following Figures 15 and 16 depict the same NIS change for the pediatric patients and the adult patients. respectively. Figure 10, demonstrated that the differences in NIS change from baseline among the treatment groups were small for the pediatric patients. However, Figure 11 shows a much clearer difference among the treatment groups for adult patients.

Figure 15. NIS Changes: Pediatric (Study 05-3039)

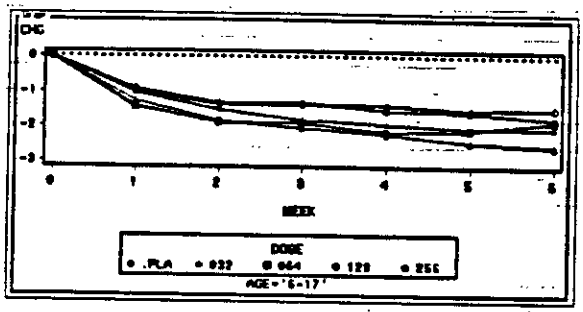


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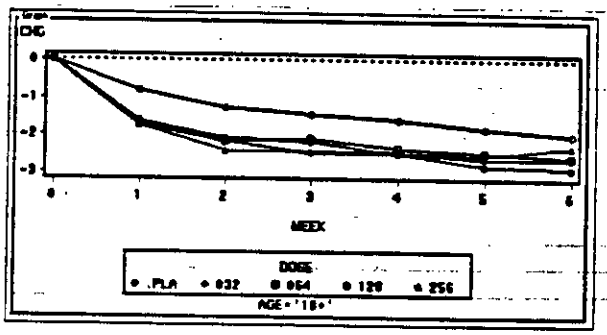
Figure 16. NIS Changes: Adults (Study 05-3039)



The following by-week analyses show the changes in NIS from baseline by treatment group and by center. Figures 17-22 depict the NIS changes from baseline varying with time (week) and center. These figures show that the improvements in NIS were greater for the active treatment groups than for the placebo group. In addition, the drug appeared to be more effective during weeks 2-4 than other time

Figure 17. Week 1 NIS Changes by Center, Treatment (Study 05-3039)

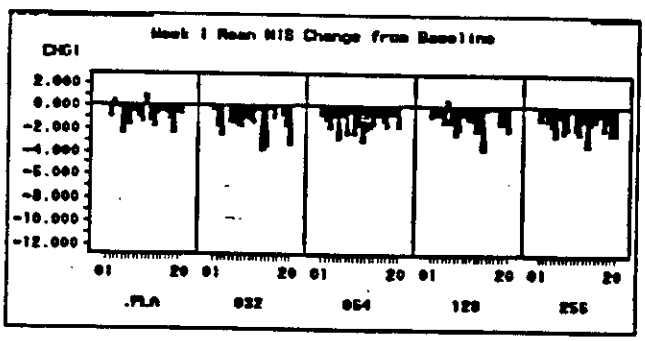


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Figure 18. Week 2 NIS Changes by Center, Treatment (Study 05-3039)

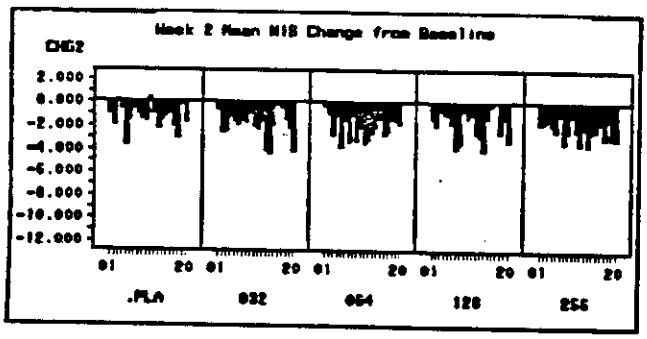


Figure 19. Week 3 NIS Changes by Center, Treatment (Study 05-3039)

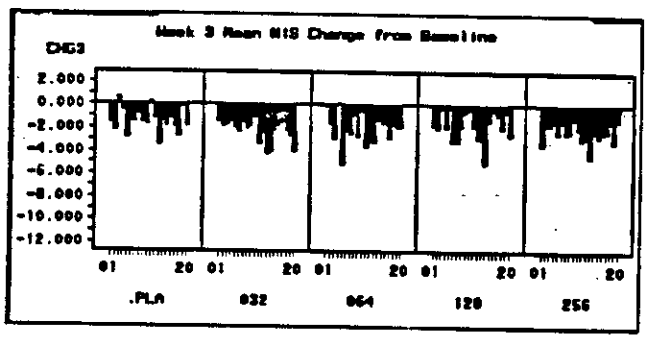


Figure 20. Week 4 NIS Changes by Center, Treatment (Study 05-3039)

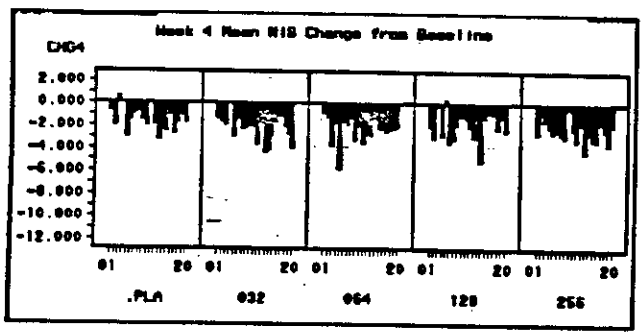


Figure 21. Week 5 NIS Changes by Center, Treatment (Study 05-3039)

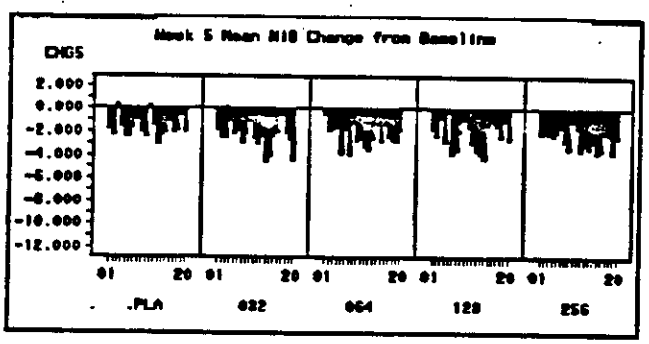
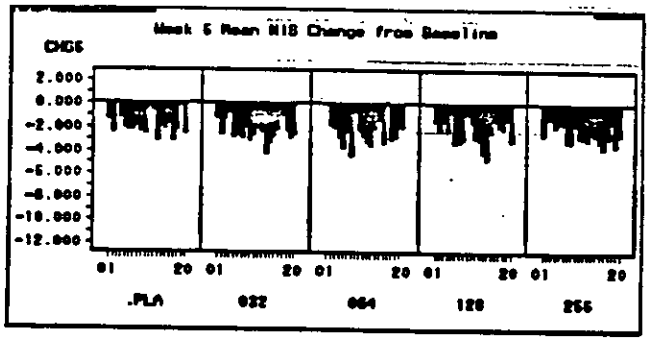


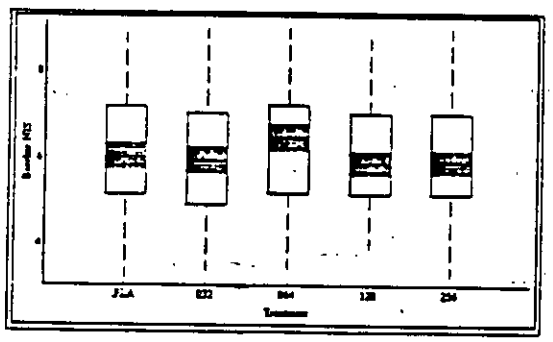
Figure 22. Week 6 NIS Changes by Center, Treatment (Study 05-3039)



Analysis of Baseline

The purpose of the analysis of baseline is to examine the validity of the use of the ANCOVA model. In addition, this analysis examines the homogeneity among the groups prior to the treatment. When the group-baseline interaction is not significant, baseline values are included in the model as the covariate. This way, the pre-dosing variations among the groups are adjusted. Figure 23 depicts the distribution of the baseline NIS by treatment group. The middle lines in the boxes represent the medians of the baseline values. The bottom and top of the box are the first and third quartiles, respectively. There did not appear to be any large differences in baseline NIS among the treatment groups.

Figure 23. Distribution of Baseline NIS (Study 05-3039)



The reviewer found that the (treatment) group-baseline interaction was not significant ($p>0.1$). Thus the use of an ANCOVA model was justified. The baseline NIS was included as the covariate in the following efficacy analysis.

Analysis of Treatment-Center Interaction

This reviewer found that the treatment-center interaction was not significant ($p>0.1$). The center effect was also found insignificant ($p>0.05$). Therefore, the term of center was not included in the final analysis.

Analysis of Treatment Effect (NIS)

Table 12 describes the test results for the treatment effects. Age was significant for weeks 1, 2, 5 and 6. The treatment effect was statistically significant among the adult patients for weeks 1, 2, 3, and 5. However, for the pediatric patients, the treatment was not significant. For the patients as a whole, the treatment effect was significant, except for week 6. These results can be observed from Figures 14-16.

Table 12. Analysis of Treatment and Age Effects (05-3039)

Age Group	Treatment	Age effect	Mean
6-17	0.3605		6-week
18+	0.0106		
All	0.0094	0.0151	
6-17	0.8197		week 1
18+	0.0058		
All	0.0326	0.0401	
6-17	0.7525		week 2
18+	0.0106		
All	0.0312	0.0425	
6-17	0.4575		week 3
18+	0.0137		
All	0.0131	0.0524	
6-17	0.3493		week 4
18+	0.0662		
All	0.0304	0.0789	
6-17	0.2677		week 5
18+	0.0309		
All	0.0267	0.0183	
6-17	0.2609		week 6
18+	0.1469		
All	0.1177	0.0198	

The following analyses (Table 13) using Dunnett's test compare the active treatments against the placebo. The daily dose of 256 µg is consistently superior to the placebo all time except for week 6. The 128 µg was not significantly different from the placebo. The 32 and 64 µg were found superior to the placebo based on the six-week averages if NIS, but this result was not consistently seen in the analyses of weekly NIS.

In the subgroup (age) analyses, Rhinocort appeared to be more effective among the adult patients (18+) than among the pediatric patients (6-17).

Table 13. Analyses of Active Treatments vs. Placebo (05-3039)

Week	Dose vs. Placebo	Simultaneous Lower Limit	Difference Between Mean	Simultaneous Upper Limit	Significance (Dunnett's)
1-6	32 µg	-1.25	-0.66	-0.06	✔
	64 µg	-1.25	-0.65	-0.04	✔
	128 µg	-1.07	-0.46	0.14	
	256 µg	-1.38	-0.78	-0.19	✔
1	32 µg	-1.13	-0.55	0.04	
	64 µg	-1.25	-0.66	-0.07	✔
	128 µg	-0.99	-0.40	0.19	
	256 µg	-1.23	-0.65	-0.07	✔
2	32 µg	-1.24	-0.55	0.14	
	64 µg	-1.43	-0.73	-0.03	✔
	128 µg	-1.09	-0.39	0.31	
	256 µg	-1.53	-0.55	-0.16	✔
3	32 µg	-1.47	-0.77	-0.06	✔
	64 µg	-1.31	-0.59	0.12	
	128 µg	-1.05	-0.34	0.38	
	256 µg	-1.56	-0.86	-0.16	✔
4	32 µg	-1.46	-0.73	0.007	
	64 µg	-1.52	-0.78	-0.03	✔
	128 µg	-1.28	-0.54	0.21	
	256 µg	-1.58	-0.85	-0.11	✔
5	32 µg	-1.42	-0.71	-0.006	✔
	64 µg	-1.35	-0.63	0.09	
	128 µg	-1.26	-0.54	0.17	
	256 µg	-1.54	-0.83	-0.13	✔
6	32 µg	-1.40	-0.64	0.13	
	64 µg	-1.27	-0.49	0.29	
	128 µg	-1.36	-0.58	0.19	
	256 µg	-1.43	-0.67	0.10	

Symbol "✔" represents a significant test result using Dunnett's Test. This test holds the maximum experimentwise error to a level not exceeding the significance level (0.05). The presence of this symbol indicates that Rhinocort at the indicated dose level is superior to the placebo.

In conclusion, Rhinocort Aqua is significantly superior to the placebo. The adult patients had greater improvement in NIS than did the pediatric patients. Because the subgroup analysis may be under powered, it is not certain whether this drug was effective on the pediatric patients. The daily dose of 32 µg performed nearly as well as the daily dose of 256 µg.

Analysis of Dose-Response Trend

The dose-response analysis was performed to determine the existence of significant dose-response trend. The reviewer used transformed dose, $Z=\log_2(\text{dose}/32)$ for convenience. The response variable was the NIS change from baseline, represented on the vertical axis in the following graphs. Figures 24 and 25 are scatter plot and box plot of NIS changes from baseline. The Z values (0-3) on the horizontal axis represent doses: 32, 64, 128 and 256 (µg). The response variable (on the vertical axis) represents the NIS change from baseline.

Figure 24. Scatter Plot of Dose-Response Relationship (Study 05-3039)

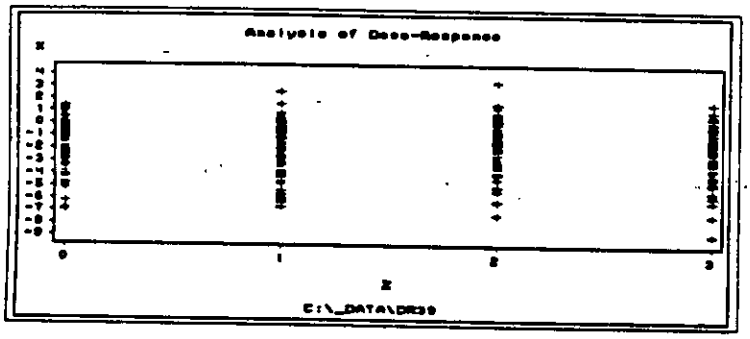
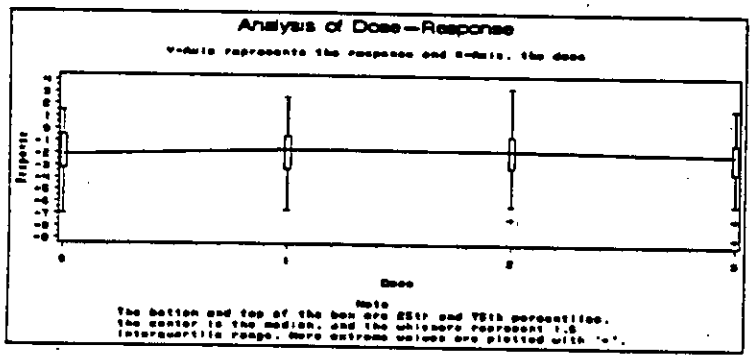


Figure 25. Box Plot of Dose-Response Relationship (Study 05-3039)



The F-test was used to test the hypothesis that the dose-response relationship was no more complicated than a quadratic. The F-test failed to reject the hypothesis, meaning that the dose-response relationship was no more complicated than a quadratic ($F=0.912 < 5.783$, the critical value).

Since the dose effect was no more than quadratic, then the following test challenged the hypothesis that the quadratic effect was not significant. This test was based on a T-statistic. The test showed that the quadratic effect was not significant ($|T|=0.883 < 2.405$, the critical value). The following test was run to determine whether the slope of the regression line was zero. The test based on a T-statistic did not reject this hypothesis ($|T|=0.246 < 2.25$). In conclusion, the linear dose-response trend was not statistically significant.

Analysis of Individual Symptoms

This reviewer analyzed the following individual nasal and eye symptom scores: sneezing, runny nose, nasal congestion, nasal itchy, eye itchy, eye redness, and tearing. Significant tests results ($p<0.05$) are labeled as a dot ("•") in Table 14, Rhinocort at daily doses of 32 and 256 µg provided a significant relief for sneezing. The effectiveness of Rhinocort was not clearly demonstrated for other nasal and eye symptoms.

Table 14. Analyses of NIS and Individual Symptoms (Study 05-3039)

		Week						
		1-6 Average	1	2	3	4	5	6
NIS	32	•	•	•	•	•	•	•
	64	•	•	•		•		
	128	•				•	•	•
	256	•	•	•	•	•	•	•
Sneezing	32	•	•	•	•	•	•	•
	64	•		•		•		
	128							
	256	•	•	•	•	•	•	•
Nasal congestion	32				•			
	64		•					
	128							
	256	•		•	•			
Runny Nose	32							
	64		•					
	128							
	256							
Nasal Itchy	32							
	64							
	128							
	256							
Eye Itchy	32							
	64							
	128							
	256							
Eye Redness	32	•					•	
	64							
	128							
	256							
Tearing	32	•					•	•
	64							
	128							
	256							

Note that, in study 05-3038, Rhinocort at daily doses of 32 and 256 µg provided significant relief for sneezing and nasal congestion over time. As a conclusion drawn from study 05-3038 and this study, 05-3039, Rhinocort provided a significant relief for sneezing, but did not show a strong effect for other nasal and eye symptoms.

Additional Analysis of NIS for Selected Age Groups

Note that the differences in NIS improvement between the pediatric patients (6-17 years of age) and adult patients (18+ years of age) were found in Study 05-3039. The following is an additional analysis on pediatric patients by age groups: 6-12 and 13-17 years of age.

The following tables and figures describe patients using the above age breakdown. Adult patients (18 years of age and older) are also included for comparison purposes.

The following Table 15 describes patient distribution by treatment group and the selected age breakdown. Children, 6-12 and children, 13-17 account for 28% and 18% of all patients, respectively. The two groups combined comprise nearly half of the patients in this study.

Table 15. Number of Patients by Treatment by Selected Age Breakdown

		DOSE					
		.PLA	032	064	128	256	Total
AGE_GP							
06-12	N	91	84	92	89	87	123
	%	32	25	24	32	28	29
13-17	N	13	20	21	15	15	85
	%	14	21	23	17	15	18
18+	N	52	53	48	47	54	254
	%	54	55	53	51	56	54
Total	N	95	97	91	92	97	472
	%	100	100	100	100	100	100

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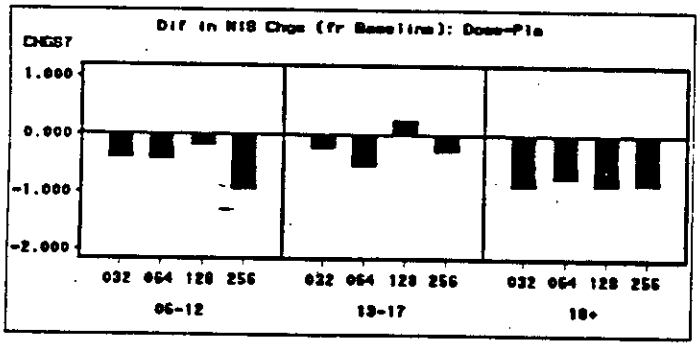
Figure 26 describes the differences observed in NIS changes from baseline between active doses and the placebo. The differences were generally greater among children, 6-12 years of age than those among children, 13-17. This age-group comparison demonstrated an opposite trend to that in Study 05-3038, where the differences were generally greater among the older children (13-17).

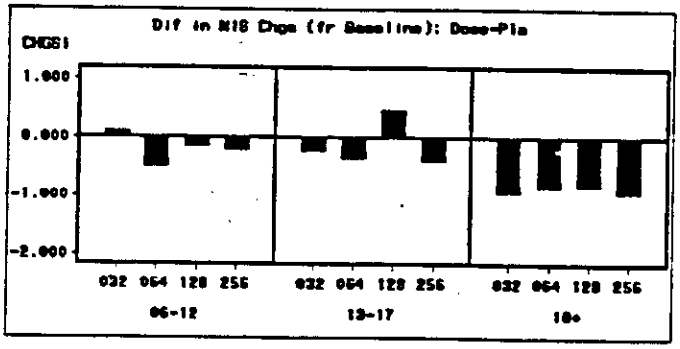
Figures 27-32 describe the same quantities as shown in Figure 26, for weeks 1 through 6. The differences between the two children-age groups varied. In general, the differences appeared to be greater among the younger children (6-12).

Figure 26. Differences in NIS Changes from Baseline Between Active Doses and Placebo: 6-Weeks



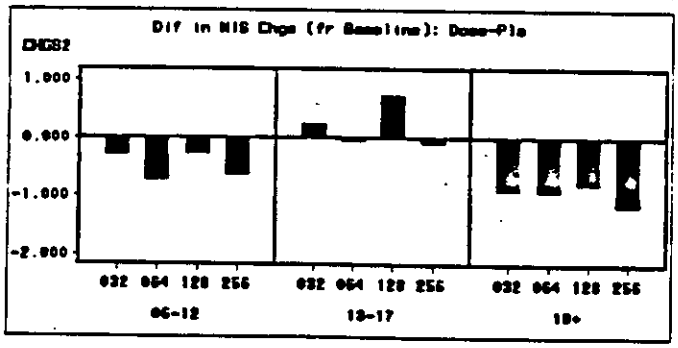
Age Group	Dose	CHGS7
06-12	032	-0.417
	064	-0.426
	128	-0.194
	256	-0.943
13-17	032	-0.225
	064	-0.534
	128	0.250
	256	-0.267
18+	032	-0.884
	064	-0.745
	128	-0.864
	256	-0.835

Figure 27. Differences in NIS Changes from Baseline Between Active Doses and Placebo: Week-1



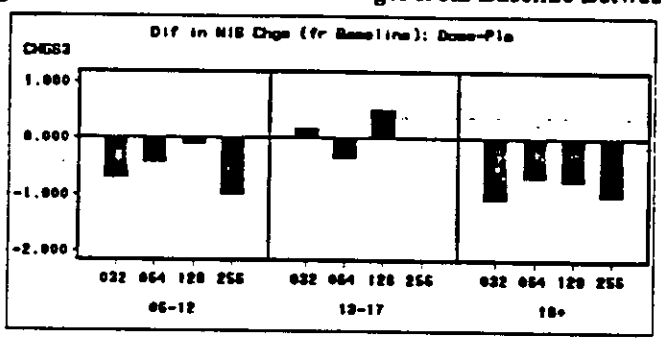
Age Group	Dose	CHGS1
06-12	032	0.100
	064	-0.494
	128	-0.149
	256	-0.216
13-17	032	-0.227
	064	-0.350
	128	0.457
	256	-0.387
18+	032	-0.934
	064	-0.837
	128	-0.820
	256	-0.942

Figure 28. Differences in NIS Changes from Baseline Between Active Doses and Placebo: Week-2



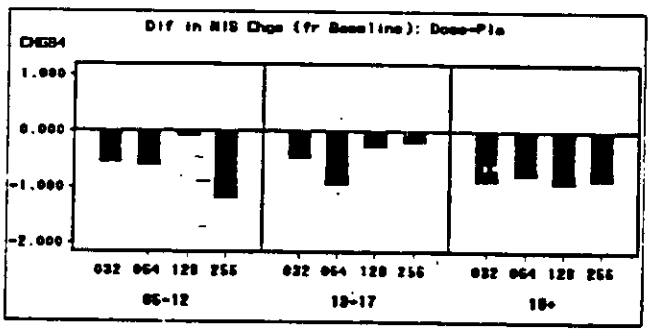
Age Group	Dose	CHGS2
06-12	032	-0.282
	064	-0.742
	128	-0.279
	256	-0.629
13-17	032	0.234
	064	-0.041
	128	0.734
	256	-0.083
18+	032	-0.890
	064	-0.921
	128	-0.801
	256	-1.146

Figure 29. Differences in NIS Changes from Baseline Between Active Doses and Placebo: Week-3



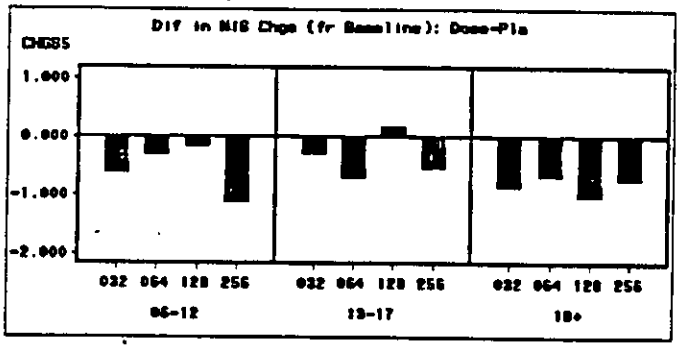
Age Group	Dose	CHGS3
06-12	032	-0.699
	064	-0.423
	128	-0.105
	256	-0.987
13-17	032	0.151
	064	-0.345
	128	0.494
	256	-0.004
18+	032	-1.059
	064	-0.667
	128	-0.731
	256	-1.010

Figure 30. Differences in NIS Changes from Baseline Between Active Doses and Placebo: Week-4



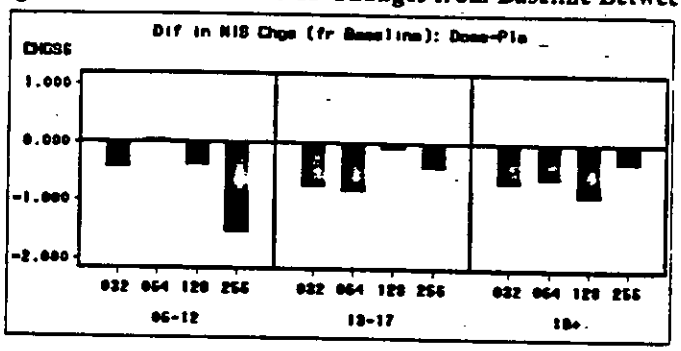
Age Group	Dose	CHGS4
06-12	032	-0.562
	064	-0.618
	128	-0.078
	256	-1.186
13-17	032	-0.477
	064	-0.940
	128	-0.271
	256	-0.189
18+	032	-0.888
	064	-0.771
	128	-0.922
	256	-0.863

Figure 31. Differences in NIS Changes from Baseline Between Active Doses and Placebo: Week-5



Age Group	Dose	CHGS5
06-12	032	-0.616
	064	-0.310
	128	-0.161
	256	-1.118
13-17	032	-0.295
	064	-0.706
	128	0.176
	256	-0.537
18+	032	-0.858
	064	-0.681
	128	-1.018
	256	-0.746

Figure 32. Differences in NIS Changes from Baseline Between Active Doses and Placebo: Week-6



Age Group	Dose	CHGS6
06-12	032	-0.441
	064	0.032
	128	-0.392
	256	-1.521
13-17	032	-0.735
	064	-0.823
	128	-0.092
	256	-0.402
18+	032	-0.672
	064	-0.591
	128	-0.893
	256	-0.302

Sponsor's Results: Cortisol-Level Analysis (Safety)

(Study 05-3038)

The sponsor analyzed differences among treatment groups with respect to the response of cortisol to ACTH-stimulation (Protocol. Page 316, vol. 116). The sponsor concluded, "an assessment comparing adrenal function at baseline and visit #4 indicated no treatment differences in terms of shifts from normal adrenal function at baseline to abnormal at visit #4 (page 27, vol.116)."

Reviewer's Evaluation: Cortisol-Level Analysis (Safety)

(Study 05-3038)

This analysis was requested by the reviewing medical officer because of an interest in assessing the dose effect on the change from basal cortisol level to ACTH-stimulated cortisol level.

The sponsor's analysis and conclusion were described in section 5.5.4.1 Plasma Cortisol Level (Page 103, vol. 116). The statistical results were summarized in Table 43 (Page 229, vol. 116). The selected 10 centers with 300 patients were used in the sponsor's analysis. According to the sponsor, "changes in cortisol levels were also assessed by comparing active treatment to placebo in terms of changes in ACTH-stimulated cortisol levels from baseline (visit 1) to visit 4." The sponsor concluded that there were no significant differences in mean changes in ACTH-stimulated cortisol levels from baseline (page 103, vol. 116).

The statistical results shown in Table 43 (page 229, vol. 116) of the NDA submission, the sponsor used the change in ACTH-stimulated cortisol level as the outcome variable in the analysis. Suggested by the reviewing medical officer, this reviewer adopted a different outcome measure: the difference in ΔCB between visit 1 as the baseline and visit 4, where the quantity ΔCB is defined as

$$\Delta CB = (\text{ACTH-stimulated cortisol level}) - (\text{Basal cortisol level}).$$

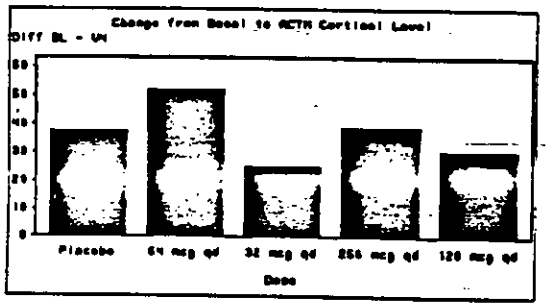
To distinguish ΔCB measured at baseline (visit 1) and visit 4, let ΔCB_1 indicate the cortisol level change at visit 1, and ΔCB_4 for visit 4. The outcome measure is then defined as

$$\delta CB = \Delta CB_1 - \Delta CB_4.$$

This reviewer evaluated whether there was a significant difference in δCB between a selected active dose and the placebo. Note that the sponsor analyzed the ACTH-stimulated cortisol alone and, therefore, the sponsor's analysis did not take the basal cortisol level into account.

The reviewer's analysis of δCB concluded that there was not a statistically significant difference ($p=0.9611$) in δCB among the treatment groups including the placebo control. Figure 23 depicts the δCB by treatment group. No important differences are found among the treatment groups.

Figure 33. Change from Basal to ACTH Cortisol Level (Compared at Visit 4)



This reviewer concludes that there is not a significant difference in cortisol-level changes resulted from ACTH-stimulation between the active drug dose and the placebo.

Conclusions

Two clinical trials, 05-3038 and 05-3039 of Rhinocort Aqua enrolled a total of 878 (405+473) patients with seasonal and perennial allergic rhinitis in 34 study sites in the U.S. The outcome measurements of concern were selected nasal and eye symptom scores and an composite nasal index score, NIS. This reviewer reanalyzed NIS and selected individual nasal-symptom scores based on the U.S. studies. The conclusions from a statistical point of view are:

- Study 05-3038 (a four-week study conducted in the U.S.) showed that Rhinocort, at daily doses of 32, 128 and 256 μg, was consistently superior to the placebo. This conclusion holds for each and every of the four weeks for the patients with seasonal rhinitis.
- Study 05-3039 (a six-week study conducted in the U.S.) showed that Rhinocort, at daily doses of 32 and 256 μg, is consistently superior to the placebo for each and every of the six weeks for the patients with perennial rhinitis.
- The above studies showed that there is not a statistically significant dose-response.
- The safety analysis (Study 05-3038) based on plasma cortisol level showed that there is not a significant difference in cortisol-level changes resulted from ACTH-stimulation among the active treatments and the placebo.
- The analysis of individual symptoms based on the both studies showed that Rhinocort significantly improved sneezing, and to some extent, nasal congestion. However, it did not demonstrate the same effectiveness for other individual nasal and eye symptoms.
- For both studies (05-3038 and 05-3039), the adult patients appeared to have a greater improvement in NIS than did the pediatric patients. For study 05-3038, the improvements in NIS were numerically greater among pediatric patients older than 12 years of age than among those under 13. However, for study 05-3039, such a difference between the two age groups was not demonstrated.

The sponsor in this NDA provided sufficient statistical evidence showing that Rhinocort Aqua Nasal Spray, at the proposed daily dose of 256 μg, is superior to the placebo for treating seasonal and perennial allergic rhinitis; and that it maintains cortisol level under ACTH-stimulation.

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

Concur: Steve Wilson, Ph.D. /S/ 9/4/97
S. Edward Nevius, Ph.D /S/ 9/7/97

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CC:
Archival NDA 20-746

HFD-570/Division file
HFD-570/RAnthracite
HFD-570/GTrout
HFD-715/Division file
HFD-715/SWilson
HFD-715/TGuo

Appendix 1: U.S. Study 05-3038

Rhinocort is indicated for treating seasonal allergic rhinitis (SAR). This section highlights the sponsor's study design, statistical methods and conclusions for this study. It details the reviewer's efficacy and safety evaluations of the drug. The reviewer's analyses are based on the sponsor-submitted data.

Focus of the Statistical Review

This study was conducted by the sponsor to assess the effectiveness and safety of Rhinocort for patients with seasonal allergic rhinitis (based on changes in ACTH-stimulated cortisol level).

The reviewer's efficacy evaluation was based on patients with seasonal allergic rhinitis (SAR) who met the inclusion criteria and had at least one double blind observation. The dose-response trend was also examined. For safety concern, the reviewer analyzed cortisol-level changes due to ACTH-stimulation.

Study Design

The characteristics of the study design are summarized in the following points.

Design	Randomized, double blind, placebo controlled trial
Dosage regimen	Rhinocort (32, 64, 128, or 256 µg daily) and the placebo
Duration	Seven days baseline period followed by 4 weeks of treatment; 08/94-10/94
Rescue medication	When the symptoms became intolerable, patients were allowed to take Chlor-Trimeton as rescue medication.
Centers	Fourteen (14) centers in 2 geographic regions (Northeast and Midwest).
Primary endpoint	The primary endpoint (outcome variable) was the nasal index score (NIS) defined as the sum of scores of selected individual symptoms: nasal congestion, runny nose, and sneezing. The average NIS values recorded by the patients during the 4-week study were used as the response measurements. The baseline NIS was the average NIS during a one-week pretreatment-observation period.

Other endpoints

The secondary endpoints included individual nasal symptoms (congestion, runny nose, sneezing and nasal itching) and eye complex symptoms (itching, redness, and tearing). In addition, there were other endpoints used in the sponsor's analyses: patient overall assessment of treatment efficacy, the number of patients requiring breakthrough (rescue) medication, and the number of patients who did not complete the study.

Symptom scores

The severity of the symptoms was scored 0-3 (none to the most severe) for individual symptoms; and 0-4 (for aggravated symptom to total control) for patients' overall assessment of efficacy.

Reviewer's Comments

Because the sponsor's analyses were based on average symptom scores over the four-week trial period, it would be difficult to find out (1) when the drug started to show its effectiveness, (2) when it reached its maximum strength, and (3) whether or not there were observed declines in treatment effect. Therefore, this reviewer performed additional efficacy analyses on weekly averages. The all-week average was also analyzed for comparison purposes.

Statistical Method

Sponsor's Method

The analysis variable was change in NIS from baseline. It was computed by subtracting the baseline value from the treatment NIS.

The change from baseline was analyzed using the ANOVA model that included the baseline as a covariate whenever it was considered to be appropriate. This model included the following terms: treatment effect, center effect, and the interaction between the two. When the interaction was found not to be significant at the 0.1 level, this term was excluded.

The sponsor also analyzed the dose-response trend. First, the lowest active dose was compared against the highest active dose. Then a regression line was fit for the outcome variable against dose. In the original submission, the placebo group was

included. It was removed later in an amendment dated 3/6/97.

Sample size

It was estimated that 32 patients per group provided 90% power (α=0.05, two-sided) to detect a treatment difference of 1.0 in NIS for a standard error of 1.2. The sponsor's calculation for the sample size was considered to be sufficient.

Missing values

For patients who were lost to follow-up, averages were calculated and were carried to the end of the study. This reviewer adopted this method.

Reviewer's Comments

The sponsor's statistical method for efficacy analysis is valid. As far as the dose-response trend test, this reviewer reanalyzed the dose-response trend using a procedure described by Joseph L. Fleiss (1986).

Descriptions of Patients

A total of 405 patients were included in the analysis. Tables A-1 through A-7 describe the number of patients by treatment, region, sex, etc. Among the 405 patients, 10 did not complete the study. The remaining 97.5% of the participants completed the study.

Table A-1. Patients by Region by Treatment

	DOSE					
	.PLA	032	064	128	256	Total
REGION						
MIDWEST	41	42	38	42	41	205
NORTHEAST	42	36	40	41	41	200
Total	83	78	78	83	82	405

Table A-2. Patients by Region, Sex, & Treatment

		DOSE					
		.PLA	032	064	128	256	Total
REGION	SEX						
MIDWEST	F	11	22	16	15	18	82
	M	30	20	23	27	23	123
NORTHEAST	F	23	18	16	21	21	99
	M	19	18	24	20	20	101
Total		83	78	79	83	82	405

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Table A-3. Patient Accountability

	Patient Termination				
	N		Y		
	Gender		Gender		
	FEMALE	MALE	FEMALE	MALE	ALL
Region					
(1)NORTHEAST	97	95	2	6	200
(2)MIDWEST	81	122	1	1	205
ALL	178	217	3	7	405

Table A-4. Patients by Region, Age Group and Treatment

		DOSE					
		PLA	032	064	128	256	Total
REGION	AGE						
MIDWEST	18+	23	24	23	22	25	117
	6-17	18	18	16	20	16	88
NORTHEAST	18+	25	21	24	23	20	113
	6-17	17	15	16	18	21	87
Total		83	78	79	83	82	405

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Table A-5. Patients by Center within Region (1)

		(1)PLACEBO	(2)32 MCG BD	(3)64 MCG BD	(4)128 MCG BD	(5)256 MCG BD	Total
Region	Ctrm						
(1)NORTH-EAST	03	6	6	6	6	6	30
	05	4	5	4	5	5	23
	07	6	4	5	6	6	27
	09	6	2	6	5	4	22
	10	8	7	8	8	8	39
	12	6	6	6	6	6	29
	14	6	6	6	6	6	30
	Total	42	36	40	41	41	200

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Table A-6. Patients by Center within Region (2)

		(1)PLACEBO	(2)32 MCG BD	(3)64 MCG BD	(4)128 MCG BD	(5)256 MCG BD	Total
Region	Ctrm						
(2)MIDWEST	01	4	4	4	4	3	19
	02	6	6	6	6	6	30
	04	5	5	4	6	6	27
	06	8	8	8	8	8	40
	08	6	8	8	6	6	33
	11	6	6	5	6	6	29
	13	6	5	6	6	6	33
	Total	41	42	39	42	41	205

Table A-7. Patients by Sex by Race

	Race				
	BLACK	CAUCA-SIAN	HISPA-NIC	OTHER	ALL
Gender					
FEMALE	21	152	8	.	181
MALE	14	200	4	6	224
ALL	35	352	12	6	405

Statistical Analyses

Analysis of Treatment-Region Interaction

In the protocol, the sponsor analyzed the NIS for each geographic region (Northeast and Midwest) separately. This was based on the observation that, unlike the Midwest, the pollen counts in the Northeast region were much more variable and lower than the previous pollen season[2]. This reviewer thinks that these by-region analyses are useful in the efficacy evaluation. This reviewer also performed analyses for the regions combined.

Figures (A-1 to A-3) describe the NIS changes from baseline with time (in weeks), by treatment group. According to the definition of the NIS, a negative change indicates an improvement in NIS. In Figure A-1, the vertical axis labeled "CHG" represents the NIS changes from baseline. For the combined region, all the active treatment groups demonstrated a greater improvement than did placebo. The daily dose of 256 µg for the first two weeks appeared to be more efficacious than other groups.

Figure A-1. NIS Changes (Regions Combined)

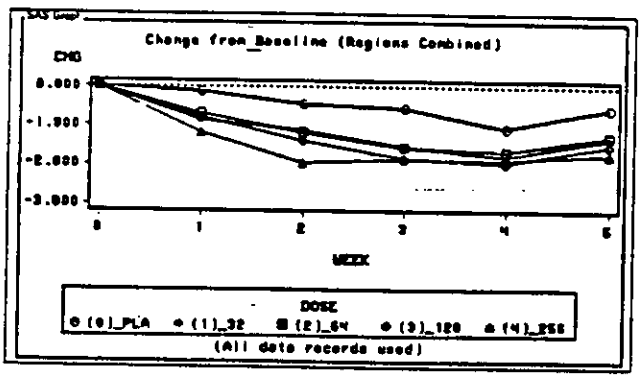


Figure A-2 shows that for the Northeast region the active treatment groups exhibited greater improvements in NIS than did the placebo group. The 32 and 256 µg dose group performed better in the first two weeks of the treatment than other groups.

[2] The sponsor displayed daily mean pollen counts (m^3) for the Midwest and Northeast regions in Figures A and B, respectively, for the study period (pages 78-79, vol. 116).

Figure A-2. NIS Changes (Northeast)

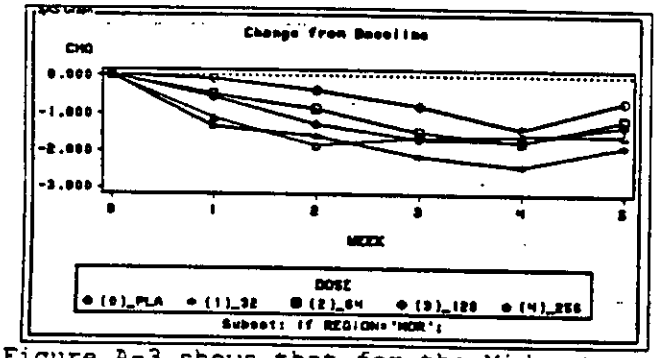


Figure A-3 shows that for the Midwest region the active treatment groups exhibited greater improvements in NIS than did the placebo group. The 32 µg dose group performed better than the placebo group, but worse than other active treatment group. Comparing Figures A-2 with A-3, there was a noticeable difference in efficacy between the two regions.

Figure A-3. NIS Changes (Midwest)

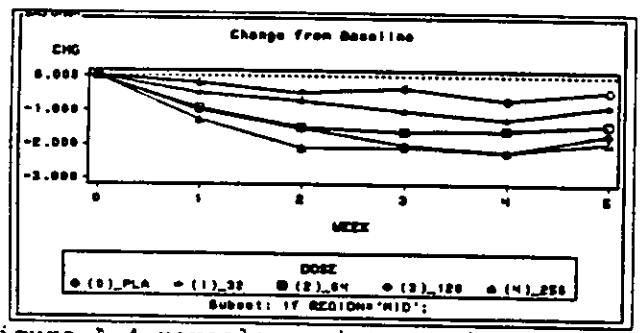
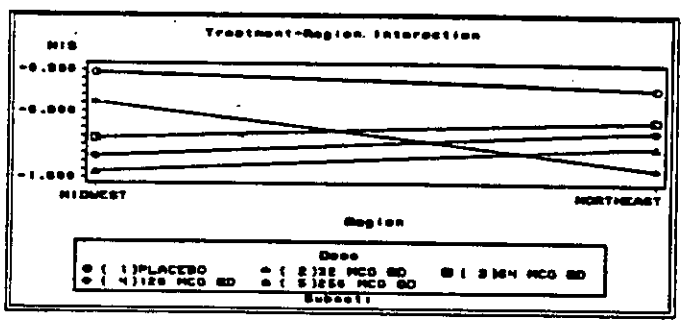


Figure A-4 reveals an interaction between treatment and region. The vertical axis in Figure A-4 represents the 4-week averages of NIS changes from baseline. The treatment-region interaction can be observed from these non-parallel lines. The daily dose of 32 µg appears to be responsible for such an interaction.

Figure A-4. Treatment-Region Interaction



The same descriptions for the **weekly** NIS changes are not shown in this report. Table A-8 summarizes all the tests of treatment-region

interaction with and without the 32 µg dose group. Without the 32 µg dose group, the treatment-region interaction became not significant.

Table A-8. Treatment-Region Interaction

Model fit	Week 1-4	week 4	week 3	week 2	week 1
32 µg Excluded	0.8256	0.5221	0.7762	0.6779	0.7578
32 µg Included	0.0265	0.0463	0.0450	0.0716	0.0337

Analysis of Baseline

The analysis of baseline comprised (1) a test for (treatment) group-baseline interaction, which is the test of validity for the use of the analysis of covariance model (ANCOVA) and (2) a test of baseline-value homogeneity across the groups. Figure A-15 depicts the distribution of baseline NIS values by treatment group.

Figure A-5. Baseline NIS Values

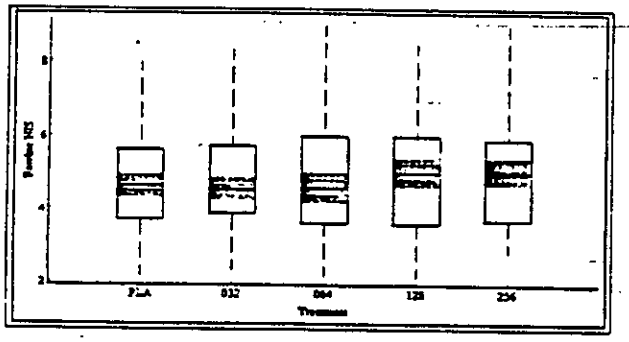


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Table A-9 summarizes the analysis of baseline. There was no significant group-baseline interaction and the baseline-value differences among the groups were significant. Therefore, the use of ANCOVA model was justified.

Table A-9. Analysis of Baseline

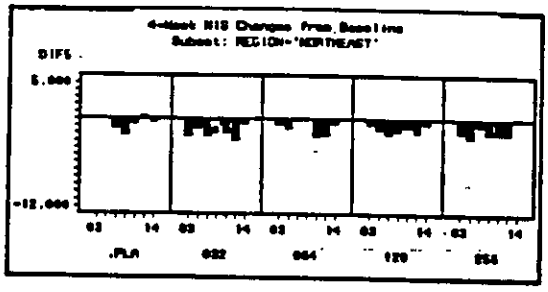
Region	group-baseline interaction
Northeast	0.1349
Midwest	0.2479
All	0.1949

Analysis of Center Effect

To explore the variation in NIS changes across the study centers, the following graphs depict these changes by other variables, such as region, week.

For the **Northeast** region (Figure A-6), the daily dose of 64 µg appeared to perform worse (especially at one center) than other doses. There were noticeable variations among the centers. In general, the treated groups were better off than the placebo group. Note that the NIS changes from baseline shown here are based on the 4-week averages.

Figure A-6. 4-Week NIS Changes (Northeast)



A similar pattern can be observed in Figures A-7 to A-10, in which the NIS changes are based on the weekly averages.

Figure A-7. Week-1 NIS Changes (Northeast)

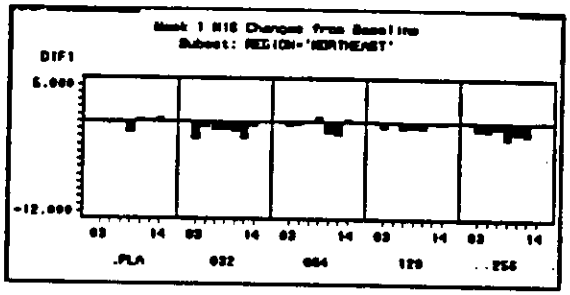


Figure A-8. Week-2 NIS Changes (Northeast)

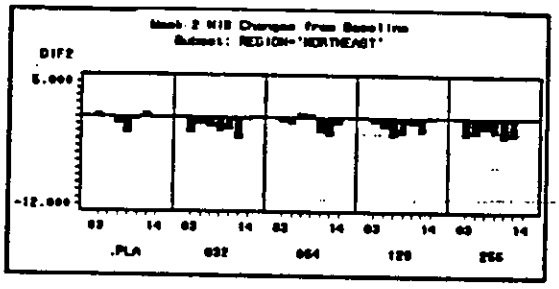


Figure A-9. Week-3 NIS Changes (Northeast)

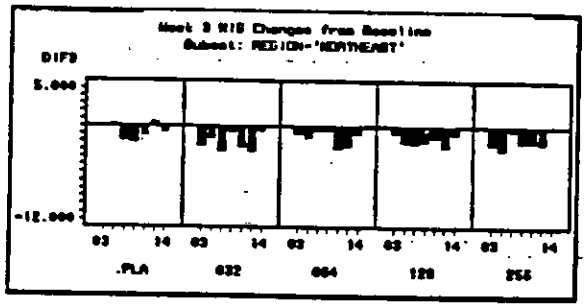
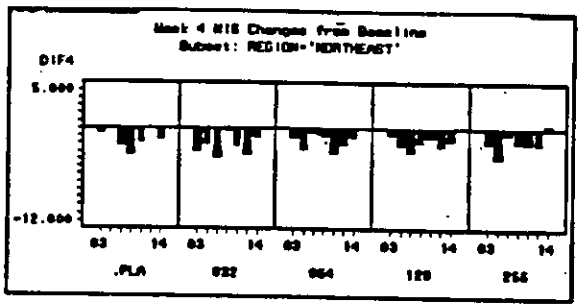


Figure A-10. Week-4 NIS Changes (Northeast)



Similarly, the following graphs depict the NIS changes with center, for the Midwest region, by patient age, and by treatment group. The four-week average and the weekly averages (in NIS change) are described separately.

Figure A-11. 4-Week NIS Changes (Midwest)

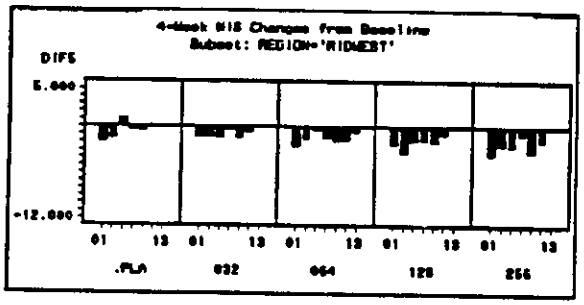


Figure A-12. Week-1 NIS Changes (Midwest)

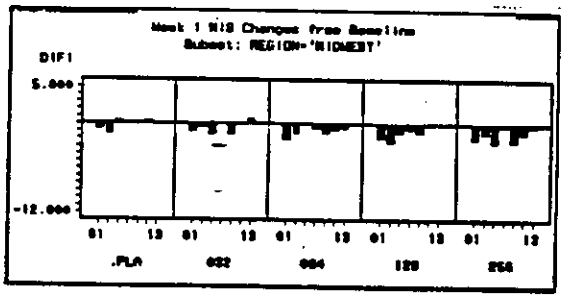


Figure A-13. Week-2 NIS Changes (Midwest)

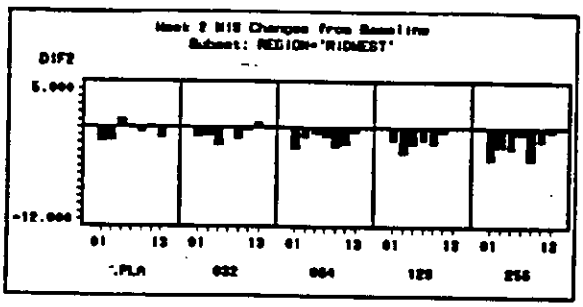


Figure A-14. Week-3 NIS Changes (Midwest)

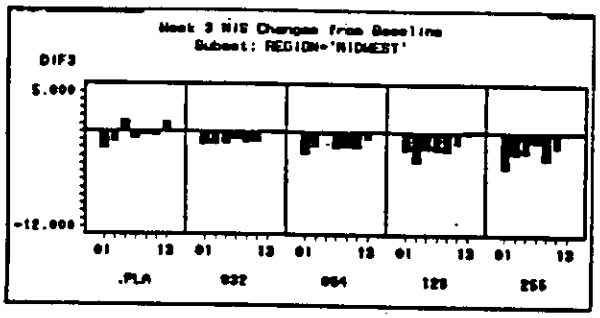
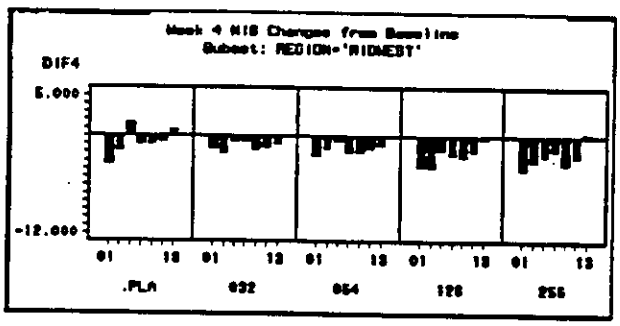


Figure A-15. Week-4 NIS Changes (Midwest)



The tests for treatment-center interactions are shown in Table A-10. The p-values are the results based on the 4-week mean NIS. The tests did not show significant treatment-center interactions. The same tests were done using the weekly data, and no tests showed significant treatment-center interactions.

Table A-10. Treat-Center Interaction

Region	Treatment-center interaction
Northeast	0.5032
Midwest	0.6173
All	0.2907

Efficacy Evaluation: NIS

Based on the above analyses of region, baseline and center, the reviewer decided to include the following terms in the ANCOVA model: baseline (as the covariate), center effect and treatment effect.

The analysis in Table A-11 showed the significance of the treatment effect and the center effect. Except for week 4, for the regions combined, the treatment effect was significant. The center effect was significant.

Table A-11. Analysis of Treatment and Center Effect, by Region

Region	Treatment	center	Week
Northeast	0.0044	0.0315	1-4
Midwest	0.0045	0.0060	
All	0.0014	0.0021	
Northeast	0.0867	0.0821	4
Midwest	0.0422	0.0226	
All	0.1268	0.0079	
Northeast	0.0129	0.0774	3
Midwest	0.0015	0.0147	
All	0.0006	0.0058	
Northeast	0.0014	0.0378	2
Midwest	0.0065	0.0067	
All	0.0002	0.0040	
Northeast	0.0020	0.0742	1
Midwest	0.0511	0.0016	
All	0.0045	0.0036	

To further determine the effectiveness of the active treatments, comparisons between the selected doses and the placebo were made based on both the weekly means and the all-week mean.

The comparisons between selected active treatments and the placebo are reported in Table A-12. To answer whether any active treatment is significantly different from the control, the significant test results from Dunnett's test (based on simultaneous confidence intervals) are indicated with asterisk, "*".

Table A-12. Analyses of Treated Groups vs. the Placebo

Region	32 µg	64 µg	128 µg	256 µg	Week
Northeast	0.0002*	0.1999	0.0912	0.0126	1-4
Midwest	0.4437	0.0097*	0.0093*	0.0014*	
All	0.0032*	0.0067*	0.0029*	0.0001*	
Northeast	0.0081	0.4538	0.5366	0.6469	4
Midwest	0.4176	0.0659	0.0122*	0.0110*	
All	0.0243	0.0690	0.0300*	0.0388*	
Northeast	0.0005*	0.1113	0.0457	0.0394	3
Midwest	0.2279	0.0028*	0.0014*	0.0008*	
All	0.0014*	0.0014*	0.0003*	0.0002*	
Northeast	0.0012*	0.2589	0.0366	0.0003*	2
Midwest	0.8351	0.0215	0.0710	0.0022*	
All	0.0252	0.0153*	0.0068*	0.0001*	
Northeast	0.0003*	0.3095	0.2156	0.0047*	1
Midwest	0.6277	0.0295	0.0927	0.0127*	
All	0.0042*	0.0290	0.0460*	0.0002*	

Based on the 4-week mean NIS changes, for the Northeast region, daily doses of 32 and 256 µg showed significant improvements; for the Midwest region, daily doses of 64, 128 and 256 µg demonstrated significant results. Overall, all the active treatments showed significant results

as compared with the placebo. These results were consistent with the sponsor's report (page 25, vol. 116).

Other Efficacy Evaluations

Efficacy analyses were also performed to evaluate the effectiveness of Rhinocort based on NIS change from baseline, among selected patient groups. This reviewer analyzed the effects due to age and sex differences for each geographic region and two regions combined.

The analysis of NIS by patient age groups (6-17 and 18+ years of age) showed that age differences in NIS were not significant for the first two weeks. Significant age effect was found for other weeks: Particularly, for the Northeast region and the last two weeks of the study (Table 15).

Table A-13. Analysis of Age Effect

	Week 1	week 2	week 3	week 4	week 1-4
Northeast	0.8939	0.2367	0.0031	0.0018	0.0274
Midwest	0.8699	0.8482	0.6268	0.9944	0.9627
All	0.9937	0.4883	0.0127	0.0255	0.1075

Figures A-16 and A-17 demonstrate the difference due to age for weeks 3 and 4 for the Northeast region. Greater improvements in NIS can be observed among adults than among children.

Figure A-16. NIS Changes: Adults and Children Compared (Week 3)

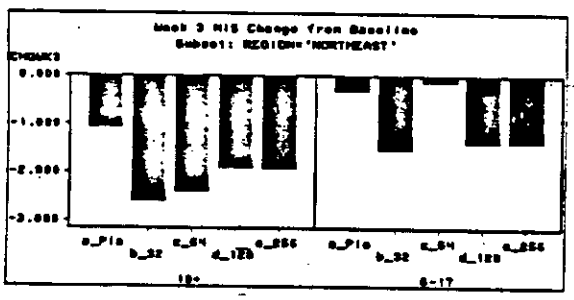


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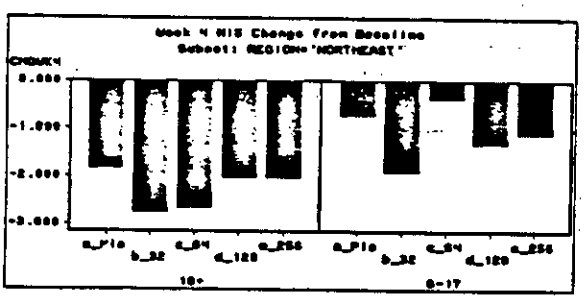
Figure A-17. NIS Changes: Adults and Children Compared (Week 4)



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Efficacy Evaluation: Individual Symptoms

The analyses of individual-symptom scores were performed. The active doses were compared against the placebo using the Dunnett's test. The

results are reported in Table A-14. The significant effects ($p<0.05$) are indicated with dots ("•").

Table A-14. Efficacy Comparisons: Active Doses vs. the Placebo

		Weeks 1-4			Week 1			Week 2			Week 3			Week 4		
		Nor	Mid	All	Nor	Mid	All	Nor	Mid	All	Nor	Mid	All	Nor	Mid	All
Sneezing	32	•		•	•			•			•		•			
	64		•	•						•		•	•			
	128												•			
	256	•	•	•	•		•	•	•	•		•	•			
Runny Nose	32	•			•			•			•			•		
	64												•			
	128											•	•			
	256							•		•						
Nasal Congest	32	•		•	•		•	•		•	•		•	•		
	64		•									•	•			
	128		•	•						•		•	•			
	256		•	•		•	•		•	•		•	•		•	
Nasal Itchy	32	•			•			•			•			•		
	64															
	128															
	256							•		•				•		
Eye Itchy	32	•			•			•	•		•					
	64															
	128															
	256										•					
Eye Redness	32							•			•					
	64															
	128															
	256							•								
Tearing	32	•		•	•		•	•			•		•			
	64															
	128								•							
	256	•			•		•	•								

For the two regions combined, this drug achieved its maximum effect at week 3 in relieving three major symptoms, sneezing, runny nose, and nasal congestion. The doses, 32 and 256 µg made greater improvement for these symptoms than other doses. No dose-response trend was demonstrated for the above symptoms.

Analysis of Cortisol-Level (Safety)

This analysis was requested by the reviewing medical officer because of an interest in assessing the dose effect on the change from basal cortisol level to ACTH-stimulated cortisol level.

The relevant information was found in the sponsor's data submission. The selected 10 centers with 300 patients were used in the sponsor's analysis. According to the sponsor, "changes in cortisol levels were also assessed by comparing active treatment to placebo in terms of

changes in ACTH-stimulated cortisol levels from baseline (visit 1) to visit 4." The sponsor concluded that there were no significant differences in mean changes in ACTH-stimulated cortisol levels from baseline (page 103, vol. 116).

For statistical results shown in Table 43 (page 229, vol. 116) of the NDA submission, the sponsor used change in ACTH-stimulated cortisol level as the outcome variable in the analysis. As recommended by the reviewing medical officer, this reviewer adopted a different outcome measure: the difference in ΔCB between visit 1 as the baseline and visit 4, where the quantity ΔCB is defined as

$$\Delta CB = (\text{ACTH-stimulated cortisol level}) - (\text{Basal cortisol level}).$$

To distinguish ΔCB measured at baseline (visit 1) and visit 4, let ΔCB_1 indicate the cortisol level change at visit 1, and ΔCB_4 for visit 4. The outcome measure is then defined as

$$\delta CB = \Delta CB_1 - \Delta CB_4.$$

This reviewer wanted to determine whether there exists a significant difference in δCB between a selected active dose and the placebo. Note that the sponsor analyzed the ACTH-stimulated cortisol alone. That method did not take the basal cortisol level into account.

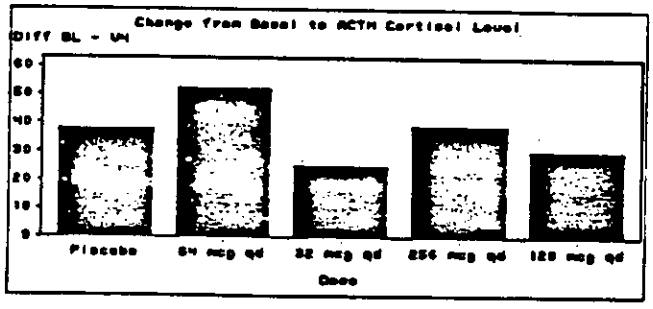
The reviewer's analysis on δCB are summarized in the following Table A-15. There were no statistically significant differences in δCB among the treatment groups.

Table A-15. Treatment and Center Effect

Treatment	Center
0.9611	0.1787

The following Figure A-18 depicts the δCB by treatment group. No important differences are seen among the treatment groups.

Figure A-18. Change from Basal to ACTH Cortisol Level (Compared at Last Visit)



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This reviewer concludes that there is not a significant difference in cortisol-level changes resulting from ACTH-stimulation between the active drug dose and the placebo.

Other Efficacy Analyses

Patient Overall Evaluation of Efficacy

The sponsor asked the patients to give overall efficacy evaluations for Rhinocort at visits 3 and 4. Visits 3 and 4 took place at the end of second and fourth weeks of treatment. The evaluations were scored 0-4. Zero indicated that the symptoms were aggravated, and 4 represented a total control of the symptoms. The sponsor analyzed the average scores over visits 3-4 and concluded:

1. For all four nasal symptoms (nasal congestion, sneezing, runny nose, and nasal itching), Rhinocort demonstrated significant controls of the symptoms compared with the placebo.
2. Pairwise comparisons between the active treatments and the placebo showed that all the active treatments (32-256 µg) provided a significant relief for all four nasal symptoms ($p<0.05$).

This reviewer recognizes that the overall evaluation was specified in the protocol and has no objections to the sponsor's method. The reviewer did not perform confirmatory statistical analyses for the patient overall evaluation.

Patients Taking Rescue Medication

The number of patients taking rescue medication (Chlor-Trimeton) was reported in the section "other therapy" (page 85, vol. 116). The sponsor stated that more patients took the rescue medication in the placebo group than in the active treatment groups. No further analysis was reported on rescue medication. The following table shows the number of patients taking the rescue medication.

Table A-16. Patients Taking Rescue Medication (Chlor-Trimeton)

Treatment	No. Patients taking CT	Pct. Patients taking CT	Total Patients
Placebo	64	77%	83
32 µg	51	65%	78
64µg	41	52%	79
128 µg	52	63%	83
256 µg	47	57%	82

The sponsor collected data on the amount of Chlor-Trimeton taken. Note that Chlor-Trimeton has tablet or liquid form and its formulations cannot be identified in the sponsor's data. Therefore, this reviewer did not perform any statistical analysis in this respect.

Appendix 2: U.S. Study 05-3039

This section details the reviewer's efficacy evaluation of Rhinocort. The reviewer's analyses were based on the sponsor's analysis data.

Focus of the Statistical Review

This clinical trial was conducted to evaluate the effectiveness and safety (based on adverse events) of Rhinocort for the treatment of patients with perennial allergic rhinitis.

This statistical review was focused on the efficacy of the drug for patients with perennial allergic rhinitis who fulfilled the entrance inclusion criteria and who had at least one double-blind observation. The safety of the drug was not evaluated in this report.

Study Design

Listed below is a brief summary of the characteristics of the design.

Design	Randomized, double blind, placebo controlled trial
Dosage regimen	Rhinocort (32, 64, 128, or 256 µg daily) and the placebo
Duration	Seven days baseline period followed by six weeks of treatment, 12/94-04/95
Centers	Twenty (20) centers in the U.S.
Primary endpoint	The primary endpoint was the nasal index score (NIS) which was defined as the sum of scores of three selected individual symptoms: nasal congestion, runny nose, and sneezing. The baseline NIS was defined as the average NIS during the seven-day observation period before the treatment phase started.
Other endpoints	The secondary outcome variables included individual nasal symptoms (congestion, runny nose, sneezing and nasal itching) and eye complex symptoms (itching, redness, and tearing). Other secondary outcome variables were patient overall assessment of treatment efficacy, quality of life, nasal cytology, and discontinuations from the study.

Symptom scores — 0-3 (from none to most severe) for the individual symptoms; 0-4 (from aggravated symptom to total control over symptoms) for the patients' overall assessment of the efficacy

Statistical Method

Sponsor's Method — The outcome variable the sponsor used in the efficacy analysis was the change in NIS from baseline. In the sponsor's analysis, it was calculated by subtracting the baseline score from the treatment NIS. Changes were the averages over the 6-week treatment period. No analyses based on weekly data were reported.

The change from baseline was analyzed using the ANOVA model including the baseline as a covariate whenever it was appropriate. This statistical model included treatment effect, center effect and interaction between the two. When the interaction was not significant at 0.1 level, this term was excluded.

Reviewer Comments — This reviewer argues that the use of the 6-week average alone does not tell when the drug is more effective than other times and when the drug reaches its best result during the study. An alternative measurement of the outcome is the weekly average. This reviewer evaluated efficacy based on the weekly NIS. The all-week average was also analyzed for comparison purposes.

Sample size — It was estimated that 78 patients per group would provide 90% power (α=0.05, two-sided) to detect a treatment difference of 0.7 in NIS based on a standard error of 1.35. With an estimated 15% dropout rate, about 450 patients were needed for randomization. The sponsor's calculation for the sample size was confirmed to be sufficient.

Missing values — For patients who were lost to follow-up, the non-missing averages were calculated and carried over. This reviewer also used this method.

Descriptions of Patients

Verified by this reviewer, 473 patients met the inclusion criteria and had at least one double-blind observation. The patients comprised adults, 18 years of age and older, and children, 6-17 years of age. The following tables, B-1 to B-7, describe the number of patients by various categories. Among the 473 patients, there were 27 discontinued patients. In other words, 94.3% of the patients completed the study.

Note that the sponsor reported that there were 478 patients randomized into the study and 447 completed the study (page 59, vol. 147). These numbers were not accurate. In fact, 473 patients had baseline observations and had at least one double-blind observation. Five patients who entered the randomization did not continue. This minor discrepancy did not change the conclusions of the analyses, therefore, did not cause a concern to this reviewer.

Table B-1. Patient Accountability

	NTERM		Total
	N	Y	
SEX			
FEMALE	219	13	232
MALE	227	14	241
Total	446	27	473

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Table B-2. Patients by Age Group

	DOSE					Total
	PLA	032	064	128	256	
AGE						
18+	52	53	48	47	54	254
6-17	44	44	43	45	43	219
Total	96	97	91	92	97	473

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Table B-3 Patients by Sex

	DOSE					Total
	PLA	032	064	128	256	
SEX						
FEMALE	52	49	48	43	40	232
MALE	44	48	43	49	57	241
Total	96	97	91	92	97	473

APPEARS THIS WAY ON ORIGINAL

Table B-4 Patients by Sex and Race

	Race				
	BLACK	CAUCA-SIAN	HISPA-NIC	ORIEN-TAL	Total
SEX					
FEMALE	9	212	10	1	232
MALE	8	217	13	3	241
Total	17	429	23	4	473

Table B-5 Patients by Center (1)

	DOSE					
	.PLA	032	064	128	256	Total
Investigator						
01	5	7	6	6	6	28
02	7	7	7	6	7	34
03	5	5	4	5	5	24
04	4	4	3	6	6	21
05	4	4	4	2	4	18
06	5	5	5	4	5	24
07	4	4	5	3	4	20
08	5	5	5	5	5	25

Table B-6 Patients by Center (2)

	DOSE					
	.PLA	032	064	128	256	Total
Investigator						
09	5	5	6	7	5	28
10	5	5	4	4	5	23
11	4	4	3	4	4	19
12	5	5	6	6	5	25
13	4	5	4	6	5	23
14	5	4	5	5	5	24
15	5	5	5	5	4	24

Table B-7 Patients by Center (3)

	DOSE					
	.PLA	032	064	128	256	Total
Investigator						
16	5	5	4	5	5	24
17	5	5	4	5	5	24
18	5	5	5	4	5	24
19	5	5	4	5	5	24
20	4	3	3	3	3	16
Total	96	97	91	92	97	473

Statistical Analyses

Analysis of Baseline

The analysis of baseline included (1) a test of (treatment) group-baseline interaction, which is the test of validity for the use of the

analysis of covariance model (ANCOVA), and (2) A test of baseline-value homogeneity across the groups. The following Table B-8 summarizes these tests. Note that the test based on week-1 NIS showed that the group-baseline interaction was significant (<0.1). For other weeks, the test results were not significant. Therefore, with minor violation of assumption, the use of ANCOVA model was justified. Because the baseline-value variation among the treatment groups was significant, the baseline was included in the ANCOVA model as a covariate. Figure B-1 depicts the distributions of baseline values by treatment groups.

Figure B-1. Baseline NIS Values

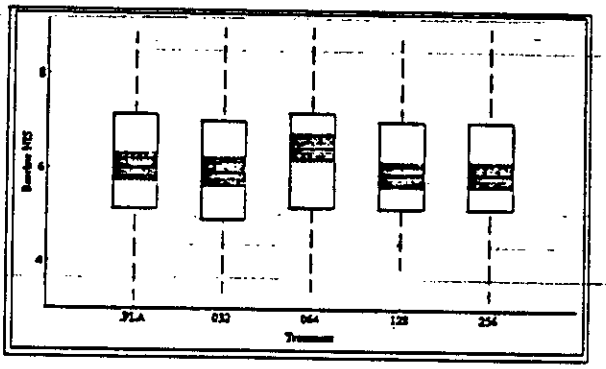


Table B-8. Analysis of Baseline

Average NIS based on	group-baseline interaction
6-Week Mean	0.1278
Week 1 Mean	0.0086
Week 2 Mean	0.1141
Week 3 Mean	0.6562
Week 4 Mean	0.3304
Week 5 Mean	0.1730
Week 6 Mean	0.2671

Analysis of Center Effect

To explore the variation in NIS changes from baseline across the study centers, Figures B-2 through B-8 depict the NIS changes with center, by treatment group and by patient age group. The all-week average and weekly averages in NIS changes are described separately in each graph.

The possible interaction between the treatment and center was checked. This reviewer did not find a significant treatment-center interaction. The center effect was not significant as well. Therefore, this reviewer excluded center effect from the model.

Figure B-2. All-Week NIS Changes from Baseline

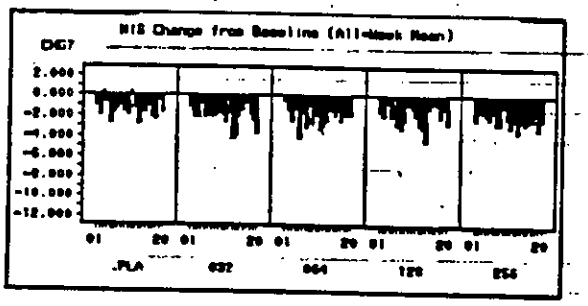


Figure B-3. Week-1 NIS Changes from Baseline

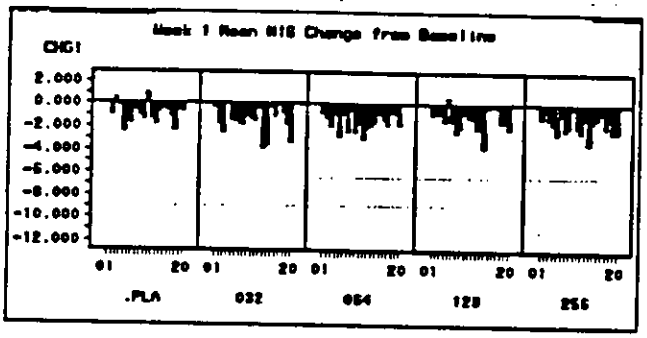


Figure B-4. Week-2 NIS Changes from Baseline

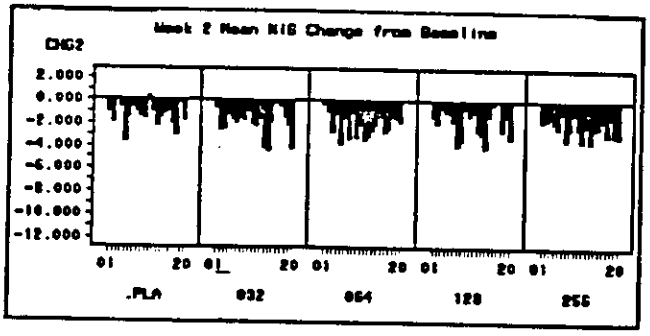


Figure B-5. Week-3 NIS Changes from Baseline

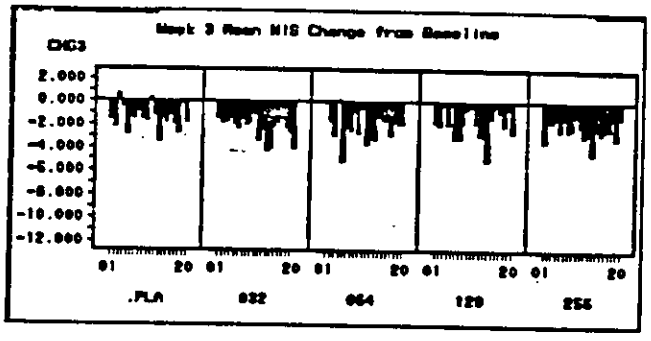


Figure B-6. Week-4 NIS Changes from Baseline

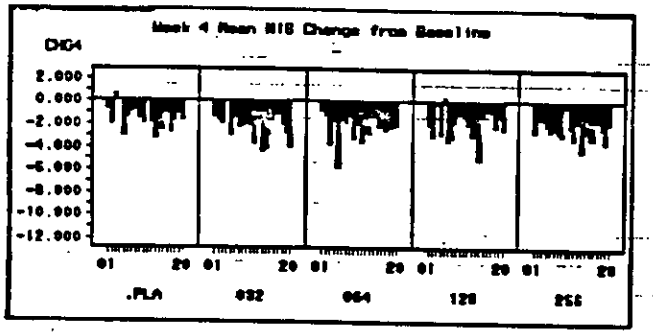


Figure B-7. Week-5 NIS Changes from Baseline

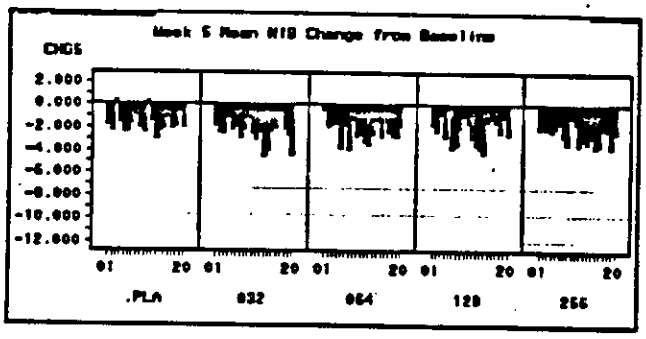
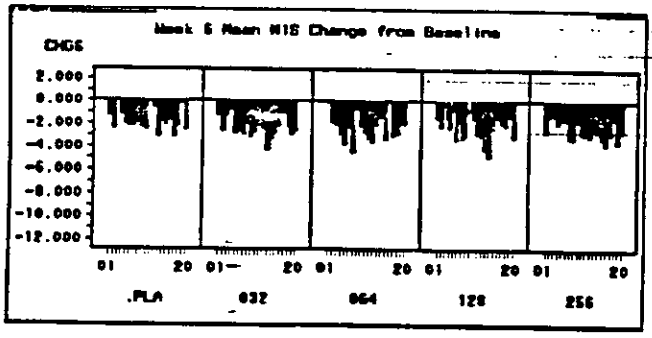


Figure B-8. Week-6 NIS Changes from Baseline



Figures B-2 to B-8 demonstrated that patients in the active treatment groups had greater improvements than those in the placebo group. The drug appeared to be more efficacious during weeks 2 through 4. The differences among the active treatment groups were small.

Efficacy Evaluation: NIS

Because of observable age differences, this reviewer included the baseline (as a covariate), treatment, and age group in the ANCOVA model.

Figures B-9 through B-15 depict the NIS changes from baseline by treatment and age. The patients in the active treatment groups had greater improvements than in the placebo group. The daily doses of 32 and 256 µg appeared to perform better than other doses.

Figure B-9. 6-Week NIS Changes by Age

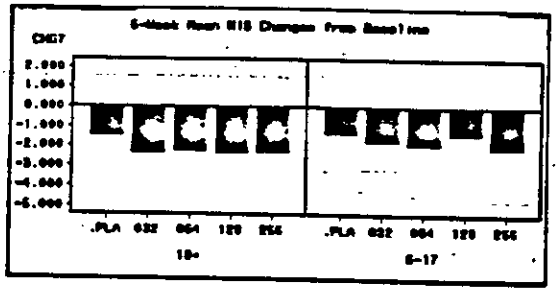


Figure B-10. Week-1 NIS Changes by Age

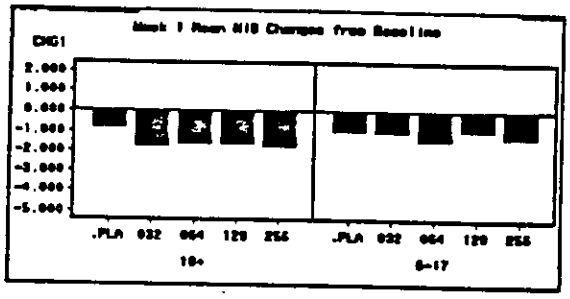


Figure B-11. Week-2 NIS Changes by Age

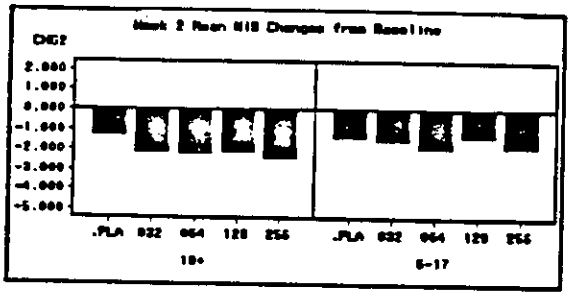


Figure B-12. Week-3 NIS Changes by Age

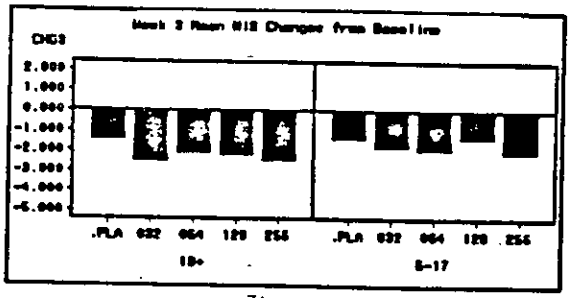


Figure B-13. Week-4 NIS Changes by Age

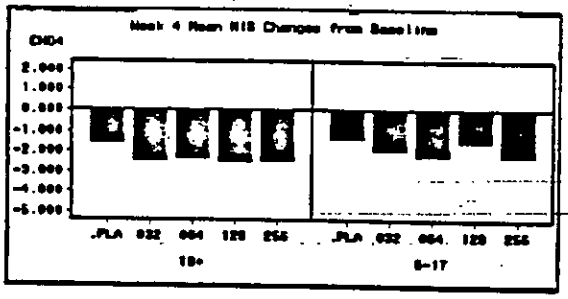


Figure B-14. Week-5 NIS Changes by Age

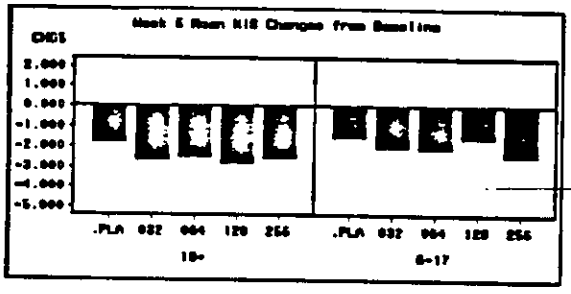


Figure B-15. Week-6 NIS Changes by Age

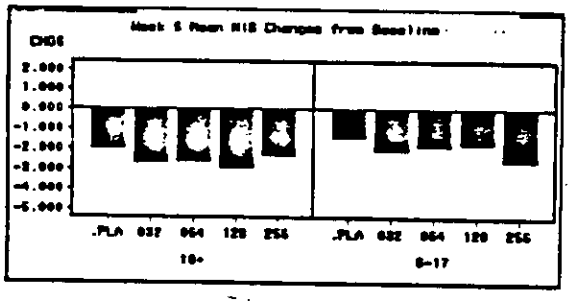


Figure B-16 depicts the NIS changes with time by treatment group. Patients in the active treatment groups had greater improvements than those in the placebo group. The differences among the active treatment were not clear.

Figure B-16. NIS Changes (All Ages)

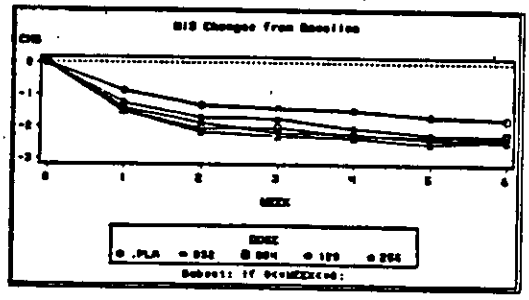
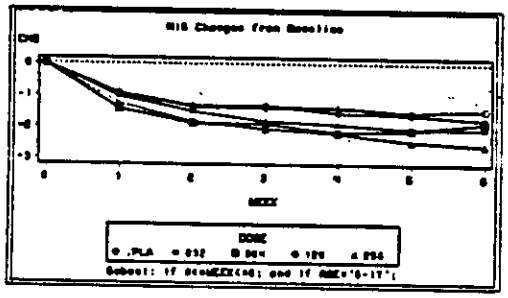


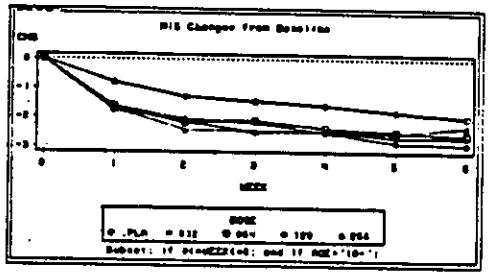
Figure B-17 describes the NIS changes from baseline for the pediatric patients. No clear improvements can be seen. This might indicate that the drug is not effective for the pediatric patients.

Figure B-17. NIS Changes (Age 6-17)



In contrast to the above figure, Figure B-18 demonstrates that the drug was efficacious among the adult patients.

Figure B-18. NIS Changes (Age 18+)



In Table B-9, the dose group of 64 and 256 µg for the pediatric patients had the smallest sample size (=43). Based on the same sample-size calculation used by the sponsor, to detect a treatment difference of 0.7 in NIS for a hypothetical standard deviation of 1.35, the statistical power for the pediatric age subgroups would be about 60% (the type one error is protected at the 0.05 level). Therefore, an attempted subgroup (age) analysis may be under powered.

Table B-9. Number of Patients by Treatment by Age

	AGE				Total	
	18+		6-17			
	Count	Percent	Count	Percent	Count	Percent
DOSE						
.PLA	52	20.5	44	20.1	96	20.3
032	53	20.9	44	20.1	97	20.5
064	48	18.9	43	19.6	91	19.2
128	47	18.5	45	20.6	92	19.5
256	54	21.3	43	19.6	97	20.5
Total	254	100.0	219	100.0	473	100.0

The final analysis is shown in the following tables. The p-values less than 0.05 are highlighted. Because of the clear difference between the age groups, the subgroup analyses based on age are still. In Table B-10, are the tests for the treatment effect. Age was a significant factor most of the weeks. The treatment was statistically significant among the adults for weeks 1-5. For patients with all ages, the treatment was also significant.

Table B-10. Test of Overall Treatment and Age Effect

Group	Treatment	Age effect	Mean of
6-17	0.3605		6-week
18+	0.0106		
All	0.0094	0.0151	
6-17	0.8197		week 1
18+	0.0058		
All	0.0326	0.0401	
6-17	0.7525		week 2
18+	0.0106		
All	0.0312	0.0425	
6-17	0.4575		week 3
18+	0.0137		
All	0.0131	0.0524	
6-17	0.3493		week 4
18+	0.0662		
All	0.0304	0.0789	
6-17	0.2677		week 5
18+	0.0309		
All	0.0267	0.0183	
6-17	0.2609		week 6
18+	0.1469		
All	0.1177	0.0198	

To further determine the efficacy for a specific active dose compared to the placebo, pairwise comparisons between the doses were also made based on the weekly means as well as the 6-week mean. Only the comparisons between the active doses and the placebo are reported in the following Table B-11. To find the p-values for the multiple comparisons, contrasts were constructed. The p-values with asterisk, "*" indicate a significance test using the method due to Dunnett. This method adjusts the comparisons of all active treatments with the placebo for multiplicity.

Over all patients, The drug was superior to the placebo at the dose level of 256 µg over time. The drug at 32 and 64 µg, for some weeks, was more effective than the placebo. The drug did not demonstrate statistically significant effect among the pediatric patients. In addition, the drug at 128 µg was not much different from the placebo.

Table B-11. Comparisons between Active Doses and the Placebo, by Age Group

Age Group	32 µg	64 µg	128 µg	256 µg	Week
All	0.0023*	0.0235*	0.0300	0.0010*	1-6
	0.0084	0.0156*	0.0548	0.0048*	1
	0.0242	0.0232*	0.1071	0.0022*	2
	0.0029*	0.0877	0.1572	0.0023*	3
	0.0066	0.0253*	0.0449	0.0040*	4
	0.0055*	0.0648	0.0346	0.0033*	5
	0.0216	0.1948	0.0393	0.0287	6
6-17	0.2286	0.2785	0.9205	0.0920	1-6
	0.7013	0.3767	0.8270	0.5891	1
	0.6522	0.3732	0.8780	0.3746	2
	0.2746	0.4103	0.8334	0.1932	3
	0.1735	0.1496	0.7652	0.1031	4
	0.1787	0.3280	0.9163	0.0615	5
	0.1871	0.5922	0.5722	0.0376	6
18+	0.0025	0.0381	0.0037	0.0033	1-6
	0.0014	0.0155	0.0054	0.0011	1
	0.0073	0.0225	0.0164	0.0007	2
	0.0022*	0.1178	0.0291	0.0027*	3
	0.0159	0.0906	0.0148	0.0162	4
	0.0103	0.1045	0.0037*	0.0198	5
	0.0535	0.1875	0.0158	0.2846	6

In conclusion, Rhinocort Aqua is significantly superior to the placebo--for some, but not all the dose levels. It improves NIS more among the adult patients than among the pediatric patients. For the patients as a whole, the dose of 256 µg is more effective than other doses. No clear dose-response trend is seen in this study.

Efficacy Evaluation: Individual-Symptoms

The analyses of individual-symptom scores were performed. The active doses were compared against the placebo using a method proposed by Dunnett. The results are included in the following Table B-12, in which the significant test results ($p<0.05$) are marked as a dot, "•."

Table B-12. Efficacy Comparisons: Active doses vs. Placebo

			Week						
			1-6 Average	1	2	3	4	5	6
Composite	NIS	32	•	•	•	•	•	•	•
		64	•	•	•		•		
		128	•				•	•	•
		256	•	•	•	•	•	•	•
Individual	Sneezing	32	•	•	•	•	•	•	•
		64	•		•		•		
		128							
		256	•	•	•	•	•	•	•
	Nasal congestion	32				•			
		64		•					
		128							
		256	•		•	•			
	Runny Nose	32							
		64		•					
		128							
		256							
	Nasal Itchy	32							
		64							
		128							
		256							
	Eye Itchy	32							
		64							
		128							
		256							
	Eye Redness	32	•					•	
		64							
		128							
		256							
	Tearing	32	•					•	•
		64							
		128							
		256							

This drug improved the symptom of sneezing more than other symptoms. The doses, 32 and 256 µg improved these symptoms better than other doses. No clear dose-response trend was demonstrated in the above table.

Other Efficacy Analyses

Patient Overall Evaluation of Efficacy

The sponsor asked the patients to give overall efficacy evaluations for Rhinocort at visits 3, 4 and 5. The evaluations were scored 0-4. Zero indicated that the symptoms were aggravated, and 4 represented a total control of the symptoms. The sponsor analyzed the average scores over visits 3-5 and concluded the following: The comparisons between the active treatments and the placebo showed that all the active treatments (32-256 µg) provided a significant relief for all four nasal symptoms ($p<0.05$).

This reviewer recognizes that the overall evaluation was specified in the protocol and has no objections to the sponsor's method. The reviewer did not perform confirmatory statistical analyses for the patient overall evaluation.

Safety Evaluation

The sponsor's safety analysis was focused on adverse events. The sponsor concluded that the majority of the reported adverse events were mild or moderate in intensity (page 69, vol. 147). The cortisol-level analysis was not intended in this study.

References

[i] Dunnett, C.W. (1955). *A Multiple Comparisons Procedure for Comparing Several Treatments with a Placebo*. JASA, 50, 1096-1121.

[ii] Fleiss, Joseph L. (1986). *The Design and Analysis of Clinical Experiments*. New York: Wiley.