U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	N20-468/SE05-024
Drug Name:	NASACORT® AQ Nasal Spray
Indication(s):	Treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients aged 2 to 5 years
Applicant:	Sanofi Aventis US
Date(s):	Received 11/19/07; User Fee 09/19/08
Review Priority:	Standard
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Keywords: NDA review, clinical Studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

NASACORT® AQ Nasal Spray (NAQ) has been approved for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients 6 years of age and above. This supplemental submission proposed to extend the indicated population for NASACORT® AQ Nasal Spray 110mcg down to children 2 years of age. One study, Study XRG5029C/3502 (referred to as Study 3502 in this review), was used to support the extension.

Study 3502 was a randomized, double-blind, parallel group, multi-center, and placebo-controlled study. Four hundred and seventy-four pediatric patients 2 to 5 years old with PAR (who might also have SAR) were enrolled to receive treatments of either NAQ 110mcg (238) or placebo (236) for a 4-week period. The results of this study showed that NAQ 110mcg QD had statistically significantly greater reduction in the reflective Total Nasal Symptom Score (rTNSS) in the targeted patient population (p=0.033) compared with placebo. The treatment comparison in the primary efficacy endpoint of instantaneous Total Nasal Symptom Score (iTNSS) did not reach the statistical significance at the level of 0.05 (p=0.095). As the approval of drugs for allergic rhinitis is usually primarily based on the assessment of the rTNSS and supported by results of the iTNSS, Study 3502 has demonstrated that NAQ 110mcg QD is efficacious in treating pediatric patients 2 to 5 years of age with PAR (who might have SAR).

A 4-way cross-over knemometry study, Study RG5029Y-315 (also referred to as Study 315), was conducted to assess NAQ's effect on lower leg growth. The duration of each treatment period was 2 weeks with 2-week washout period in between. Both NAQ 110 and 220mcg doses once daily showed statistically significant reductions in growth velocity compared with placebo. An increasing dose-response trend was observed in the NAQ dose groups.

1.2 Brief Overview of Clinical Studies

NASACORT® AQ Nasal Spray (triamcinolone acetonide) has been approved for the treatment of SAR and PAR in patients 6 years of age and above. This efficacy supplement provides information to support the approval of NASACORT® AQ Nasal Spray in pediatric patients 2-5 years of age. The submission included three efficacy studies. The claim for the efficacy of NAQ 110mcg once daily in pediatric patients 2 to 5 years of age was based on one clinical study (Study 3502) conducted in the United States (US). The other two studies, Studies 312 and 314, were conducted in patients 6-11 years of age and 4-12 years of age, respectively, and were submitted and reviewed in previous submission cycle. In addition, a growth study (Study 315) was submitted. Table 1 presents the study design and brief study results of the four studies.

Table 1. Clinical Trials

Study/Center/ Study Period	Study Design	Key Inclusion Criteria	No. patients by treatment entered/completed	Primary Endpoint	LS Mean (NAQ-PLA) p-value [a] 95% CI
XRG5029/3502 59 centers in US 4/04 – 3/06 4-weeks DB period follow by 6 months open-label period	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 2-5 yrs; 2. at least 1-year history of PAR with/out SAR; 3. positive skin prick test;	NAQ 110mcg: 238/216; Placebo: 236/216; NAQ 110mcg open-label: 410/355;	Mean change from baseline over the 4-weeks in mean daily instantaneous Total Nasal Symptom Score (iTNSS)	iTNSS: 110mcg: Δ=-0.36, p=0.095 (-0.77, 0.06) rTNSS: 110mcg: Δ=-0.44, p=0.033 (-0.84, -0.04)
RG5029Y-312 9 centers in US 5/94 – 7/94 2-week treatment period	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 6-11yrs; 2. at east 1-years history of SAR; 3. positive skin prick test;	NAQ 220mcg: 73/65; NAQ 110mcg: 74/67; Placebo: 76/72;	Mean change from baseline over the 2-weeks in the nasal index (the sum of nasal stuffiness, nasal discharge, sneezing)	Nasal index: 220mcg: Δ=-0.72, p=0.012 110mcg: Δ=-0.84, p=0.004
RG5029Y-314 20 centers in US 4 centers in Canada 10/95 – 3/96 12-week treatment period	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 4-12 yrs; 2. at east 1-years history of PAR; 3. positive skin prick test;	NAQ 220mcg 114/100; NAQ 110mcg: 105/91; Placebo: 100/95;	Mean change from baseline over the 4-weeks in the reflective nasal index (the sum of nasal stuffiness, nasal discharge, sneezing)	Nasal index: 220mcg: Δ=-0.49, p=0.016 110mcg: Δ=-0.51, p=0.020
RG5029Y-315 Investigator: David Skoner, MD 10/98 – 9/99 Short Term Growth 2-weeks treatment period	Randomized 4-waycross-over, with placebo and active comparators	1. Age 4-10 yrs; 2. at east 1-years history of PAR; 3. positive skin prick test; 4. Height was within normal limits.	NAQ 220mcg 59/55; NAQ 110mcg: 59/56; Placebo: 59/55; Flonase 200mcg 59/51:	Growth velocity	220mcg: Δ=-0.17, p=0.036 (-0.33, -0.01) 110mcg: Δ=-0.15, p=0.064 (-0.31, 0.01) Flonase 200mcg: Δ=-0.15, p=0.085 (-0.27, 0.06)

1.3 Statistical Issues and Findings

There was no special statistical issue in this review. My evaluation of the data confirmed the analysis results in the sponsor's study reports

2. INTRODUCTION

2.1 Overview

NASACORT® AQ Nasal Spray (triamcinolone acetonide) was initially introduced to the Division of Pulmonary and Allergy Products via IND 39,306. NASACORT® AQ Nasal Spray was approved for the treatment of SAR and PAR in patients 12 years of age and above and patients 6-11 years of age under NDA 20-468 on May 20, 1996 and September 26, 1997, respectively. Each actuation delivers 55mcg triamcinolone acetonide from the nasal actuator; for adults and children 12 years of age and older the recommended starting and maximum dose is 220mcg per day as two sprays in each nostril once daily. In children 6 to 12 years of age the recommended starting dose is 110mcg per day given as one spray in each nostril once daily, and the maximum recommended dose is 220mcg per day.

The sponsor submitted this application on November 19, 2007 (NDA 20-468/SE5/024) in support of extending the indication for NAQ 110mcg to include the treatment of SAR and PAR in children aged 2 to 5 years. The sponsor's submission included 5 studies: 1 phase III efficacy study (Study 3502); 1 phase II pharmacokinetic study (XRG5029C/1000), 1 short term growth study (Study 315) and 2 phase III studies in pediatric patients 4 to 12 years of age with PAR (Study 314) and in pediatric patients 6 to 11 years of age with SAR (Study 312), respectively. The claim for the efficacy in children aged 2 to 5 years was based on Study 3502 conducted in US. This reviewer focused on only Study 3502 and the growth study as outlined in Table 1 and listed some efficacy results for the two phase III studies (Studies 314 and 312) which had been reviewed in previous submission cycle.

2.2 Data Sources

Documents reviewed were accessed from the CDER document room at: \\...\N20468\SE5_024\

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The main body of my evaluation of efficacy discuses Study 3502 and list the study results for Studies 312 and 314 which had been reviewed in the previous submission and review cycle.

3.1.1 Study 3502

Study Design, Efficacy Endpoints, and Statistical Methodologies

Study 3502 was conducted during the year of 2004 and 2006 to evaluate the efficacy and safety of NAQ 110mcg once daily compared to placebo in children aged 2 to 5 years with PAR with or without SAR. This multi-center, randomized, double-blind, placebo-controlled, and parallel-group study was conducted in 59 centers in U.S. Four hundred and seventy-four patients 2 to 5 years of age with at least 1-year history of PAR were centrally randomized in a 1:1 ratio to NAQ 110mcg or placebo. An attempt was made to enroll approximately equal numbers of patients who were 2, 3, 4, and 5 years of age during the study periods. The study consisted of a screening period of up to 14 days, a randomization visit, and a double-blind treatment period of 4 weeks. This study also included a 6-month open-label treatment period to all patients completing the 4-week double-blind segment of the study or qualifying for continuation into the open-label segment after early withdrawal from the double-blind segment.

The primary efficacy endpoint was the change from baseline over the 4-week double blind treatment period in the mean daily instantaneous Total Nasal Symptom Score (iTNSS).

The secondary efficacy variables included the reflective Total Nasal Symptom Score (rTNSS), weekly instantaneous total nasal symptoms score, weekly reflective total nasal symptoms score, total instantaneous symptom score, total reflective symptom score, physician's global evaluation of efficacy, patient's global evaluation of efficacy, treatment failure after 2 weeks of treatment, number of patients using rescue medication during the double-blind treatment period, and frequency of rescue medication use during double-blind treatment period. The sponsor did not provide any multiplicity adjustment for the secondary variables.

The primary analysis employed an analysis of covariance (ANCOVA) with treatment and pooled site as fixed effects and the corresponding baseline value for the mean daily TNSS (iTNSS and rTNSS).

According to the protocol, analyses and summaries of safety and efficacy data were based on the randomized patients who had a TNSS score recorded on the morning following any dose of double-blind investigational product (ITT).

Based on previous studies, the sponsor determined that a sample of size 400, assuming a pooled standard deviation of 2.0 in iTNSS change from baseline, would be required to detect an effect size of 0.65 (or more) between treatment and placebo with 90% power.

Patient Disposition, Demographic and Baseline Characteristics

Four hundred and seventy-four patients were eligible for entry into the double-blind treatment period and were randomized. As shown in Table 2, 432 patients (91%) completed the double-blind portion of the study. Patients who completed the double-blind treatment were permitted to enter the open-label period. Of the 432 patients who completed double-blind period, 422 patients (97.7%) opted to continue into the open-label period and 10 patients (2.3%) did not.

Table 2. Patients' Accountability N (%), (ITT)

Study 3502 ***Double Blinded Period***	***Placebo (n=238)***	***NAQ 110mcg (n=236)***
Randomized patients	238	236
Completed treatment period	216 (90.8)	216 (91.5)
ITT	233	231
Discontinued	22 (9.2)	20 (8.5)
Reason of early discontinuation during double blind treatment		
Lack of efficacy	3 (13.6)	1 (5.0)
Adverse event	3 (13.6)	4 (20.0)
Not wishing to continue	6 (27.3)	3 (15.0)
Lost to follow-up	7 (31.8)	6 (30.0)
Other	3 (13.6)	6 (30.0)
Open-label Period		
Total no. of patients		428
Completed treatment period		357 (83.4)
ITT		410
Discontinued		71 (16.6)
Reason of early discontinuation in open label phase		
Protocol violation		2 (2.8)
Adverse event		15 (21.1)
Not wishing to continue		23 (32.4)
Lost to follow-up		17 (23.9)
Other		14 (19.7)

Descriptive demographics and baseline characteristics were summarized for the randomized patients who received at lease one dose of double-blind study medication in Table 3. There was no significant difference between the 2 treatment groups for any of the demographic variables. Mean age was 3.5 and 3.6 years for placebo and NAQ groups, respectively. There was no major imbalance between treatment groups with respect to age categories, but placebo group was younger with median age of 3 compared to NAQ group with median age of 4. There were more males than females in the study. The majority of the patients were white (67.4% placebo; 64.1% NAQ), followed by black (12.4% placebo; 16.9% NAQ), and other race (14.6% placebo; 11.7% NAQ). Baseline characteristics were similar across the treatment groups.

Table 3. Patients' Demographic and Baseline Characteristics N (%), (ITT)

Study 3502	Placebo (n=233)	NAQ 110mcg (n=231)	Open-label (n=428)
Age			
Mean (SD)	3.5 (1.04)	3.6 (1.05)	3.6 (1.05)
Median (range)	3 (2-5)	4 (2-5)	4 (2-5)
2 years, n (%)	52 (22.3)	43 (18.6)	85 (19.9)
3 years, n (%)	67 (28.8)	53 (22.9)	110 (25.7)
4 years, n (%)	70 (30.0)	77 (33.3)	136 (31.8)
5 years, n (%)	44 (18.9)	58 (25.1)	97 (22.7)
Sex			
Female	90 (38.6)	108 (46.8)	182 (42.5)
Male	143 (61.4)	123 (53.2)	246 (57.5)
Race			
White	157 (67.4)	148 (64.1)	281 (65.7)
Black	29 (12.4)	39 (16.9)	60 (14.0)
Other	34 (14.6)	27 (11.7)	58 (13.6)
Multiracial	8 (3.4)	10 (4.3)	18 (4.2)
Asian/Oriental	5 (2.1)	7 (3.0)	11 (2.6)
Weight [a] (kg)			
Mean (SD)	17.3 (3.9)	17.6 (4.1)	17.49 (4.0)
Median (range)	16.8 (8.3 – 33.2)	17.3 (10.0 – 34.5)	16.8 (8.3 – 34.5)
Height [a] (cm)			
Mean (SD)	102.1 (9.3)	103.0 (9.7)	102.6 (9.4)
Median (range)	102.0 (81 – 122)	103.7 (77 – 124)	102.8 (77 – 124)
Skin Prick Test, # of patients who tested positive (%)			
Cat	91 (38.2)	111 (47.0)	--
Dog	140 (58.8)	19 (50.4)	--
Molds	81 (34.0)	93 (39.4)	--
Dust mites	46 (19.3)	57 (24.2)	--
Other	56 (23.5)	63 (62.7)	--
Baseline instantaneous Total Nasal Symptom Score (iTNSS)			
Mean (SE)	7.6 (0.15)	7.5 (0.13)	
Median	7.5	7.5	
Range	0 – 12	3.3 – 12	
Baseline reflective Total Nasal Symptom Score (rTNSS)			
Mean (SD)	7.9 (0.14)	8.0 (0.13)	
Median (range)	7.8 (1.8 – 12)	8.0 (3.5 – 12)	

a: Determined at Screening. * Results from reviewer's analysis.

Results and Conclusions

The results of the efficacy analyses are shown in Table 4 and Figure 1. Baseline scores for the iTNSS and rTNSS were comparable between the 2 treatment groups. The adjusted mean change (±SE) from baseline over the double-blind period for the iTNSS was –1.92 (±0.16) for the placebo group and –2.28 (±0.16) for the NAQ treatment group. LS Mean difference between the two groups was -0.36 and it did not reach the statistical significant (p=0.095). Statistical significance was not observed in the completer (p=0.101) or PP population (p=0.119) either. For the key secondary efficacy variable of rTNSS, the adjusted mean change (±SE) from baseline over the double-blind period was –1.87 (±0.15) for the placebo group and –2.31 (±0.15) for the NAQ treatment group in the ITT population. The LS Mean difference between the two groups was -0.44. A statistically significant treatment effect was observed in the ITT population (p=0.033), but was not observed in the completer (p=0.052) or PP population (p=0.079). Weekly

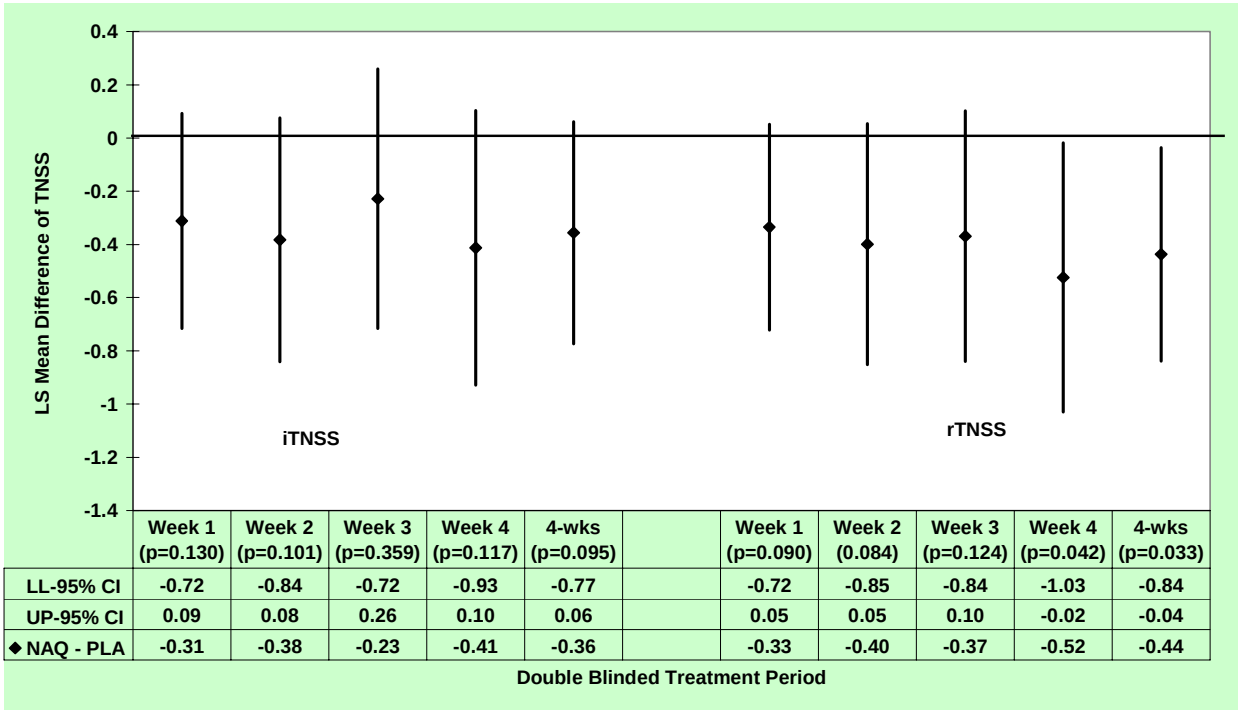
iTNSS and rTNSS were the secondary variables. A statistically significant treatment effect was only observed during Week 4 of the double-blind period in rTNSS (p=0.042).

Table 4. Mean Change from Baseline of Total Nasal Symptom Score, (ITT)

Study 3502	***Placebo (n=233)***	***NAQ 110mcg (n=231)***	***NAQ 110mcg- Placebo***		
Study Drug Duration in Days					
Mean (SD)	*28.3 (5.09)*	*28.3 (4.46)*	--	--	--
Median (range)	*29 (2-42)*	*29 (2-41)*			
iTNSS	***LS Mean (SE)***	***LS Mean (SE)***	***LS Mean (SE)***	***95% CI***	***p-value***
Baseline	7.61 (0.14)	7.51 (0.14)	-0.09 (0.19)	(-0.47, 0.28)	0.619
Change from Baseline of iTNSS					
Week 1	-1.38 (0.15)	-1.69 (0.15)	-0.31 (0.20)	(-0.71, 0.09)	0.130
Week 2	-1.93 (0.17)	-2.31 (0.17)	-0.38 (0.23)	(-0.84, 0.08)	0.101
Week 3	-2.25 (0.18)	-2.48 (0.18)	-0.23 (0.25)	(-0.72, 0.26)	0.359
Week 4	-2.43 (0.20)	-2.84 (0.20)	-0.41 (0.26)	(-0.93, 0.10)	0.117
4 Weeks (ITT)	**-1.92 (0.16)**	**-2.28 (0.16)**	**-0.36 (0.21)**	**(-0.77, 0.06)**	**0.095**
rTNSS	***LS Mean (SE)***	***LS Mean (SE)***	***LS Mean (SE)***	***95% CI***	***p-value***
Baseline	7.87 (0.14)	7.96 (0.14)	-0.09 (0.18)	(-0.28, 0.45)	0.641
Change from Baseline of rTNSS					
Week 1	-1.33 (0.15)	-1.66 (0.15)	-0.33 (0.20)	(-0.72, 0.05)	0.090
Week 2	-1.92 (0.17)	-2.32 (0.17)	-0.40 (0.23)	(-0.85, 0.05)	0.084
Week 3	-2.18 (0.18)	-2.55 (0.18)	-0.37 (0.24)	(-0.84, 0.10)	0.124
Week 4	-2.36 (0.19)	-2.89 (0.19)	-0.52 (0.26)	(-1.03, -0.02)	0.042
4 Weeks (ITT)	**-1.87 (0.15)**	**-2.31 (0.15)**	**-0.44 (0.20)**	**(-0.84, -0.04)**	**0.033**

a: LS Means are obtained from the two-way ANOVA model with treatment, baseline value, and pooled center effects.
Note: Results from reviewer analysis.

Figure 1. Mean Change from Baseline of Total Nasal Symptom Score (ITT)



	Week 1 (p=0.130)	Week 2 (p=0.101)	Week 3 (p=0.359)	Week 4 (p=0.117)	4-wks (p=0.095)		Week 1 (p=0.090)	Week 2 (0.084)	Week 3 (p=0.124)	Week 4 (p=0.042)	4-wks (p=0.033)
LL-95% CI	-0.72	-0.84	-0.72	-0.93	-0.77		-0.72	-0.85	-0.84	-1.03	-0.84
UP-95% CI	0.09	0.08	0.26	0.10	0.06		0.05	0.05	0.10	-0.02	-0.04
◆ NAQ - PLA	-0.31	-0.38	-0.23	-0.41	-0.36		-0.33	-0.40	-0.37	-0.52	-0.44

Other Secondary variables -

The total symptom score, physician's and patients' global evaluation of efficacy at end of double-blind treatment period were the other secondary variables. I was able to replicate the sponsor's results and Table 5 displays the treatment differences and nominal p-value for other secondary efficacy variables.

Table 5. Other Pulmonary Function Endpoint – Change from Baseline, (ITT, LOCF)

Study 3502	***Placebo (n=238)***	***NAQ 110mcg (n=236)***	***NAQ 110mcg- Placebo***		
	LS Mean (SE)	***LS Mean (SE)***	***LS Mean (SE)***	***95% CI***	***p-value***
Total symptom score – instantaneous (iTSS)[1]					
Baseline	9.10 (0.18)	8.94 (0.18)	-0.15 (0.25)	(-0.64, 0.33)	0.529
Change from Baseline	-2.27 (0.19)	-2.66 (0.19)	-0.38 (0.26)	(-0.89, 0.12)	0.138
Total symptom score – reflective (rTSS)[1]					
Baseline	9.44 (0.18)	9.45 (0.18)	-0.01 (0.24)	(-0.47, 0.49)	0.970
Change from Baseline	-2.24 (0.18)	-2.71 (0.18)	-0.47 (0.25)	(-0.96, 0.01)	0.057
Physician's global evaluation of efficacy at the end of double-blind treatment period					
Score	n (%)	n (%)			0.004[2]
0	47 (21.1)	28 (12.5)			
1	69 (30.9)	60 (26.8)			
2	54 (24.2)	73 (32.6)			
3	40 (17.9)	48 (21.4)			
4	13 (5.8)	15 (6.7)			
Patient's global evaluation of efficacy at the end of double-blind treatment period					
Score	n (%)	n (%)			0.060[2]
0	41 (18.4)	30 (13.4)			
1	66 (29.6)	55 (24.6)			
2	56 (25.1)	74 (33.0)			
3	51 (22.9)	49 (21.9)			
4	9 (4.0)	16 (7.1)			

1: LS Means are obtained from the two-way ANOVA model with treatment, baseline value, and pooled center effects.
2: p value based on Cochran-Mantel-Haenszel test (CMH) with modified RIDIT score controlled for pooled sites.
Note: Results from reviewer analysis.

Conclusion -

Overall, the results of the analyses of the efficacy variables support the efficacy of NAQ compared to placebo in pediatric patients 2 to 5 years of age with a diagnosis of PAR.

- Based on the primary efficacy endpoint, mean change from baseline in iTNSS over the double-blind treatment period in the ITT population, treatment with NAQ showed an improvement of 0.36 scale of TNSS over treatment with placebo, which was not statistically significant at the level of 0.05 for a 2-sided p-value (p=0.095, 95%CI: -0.77, 0.06).
- The key secondary efficacy variable, rTNSS, over the double-blind treatment period demonstrated a statistically significantly greater improvement of 0.44 in favor of NAQ (p=0.033, 95%CI: -0.84, -0.04) compared with placebo. The analyses of the rTNSS and rTNSS by week showed numerically larger improvements favoring NAQ than placebo for each week. Treatment differences tended to increase over time, particularly for the rTNSS, where it reached statistical significance at Week 4.
- For the other efficacy variables, only the physician's global evaluation of treatment efficacy support the efficacy.

3.1.2 Study 312 and Study 314

During the year of 1994 and 1996, the sponsor conducted Studies 312 (in patients 6 to 11 years of age with SAR) and 314 (in patients 4 to 12 years of age with PAR) to evaluate the efficacy and safety of NAQ Nasal Spray. Both studies were conducted in the US and had previously been reviewed under supplement submission S-002 under NDA 20-468 for the approval in pediatric patients 6 to 11 years of age with SAR and PAR. The sponsor submitted the study reports for the two studies in this submission.

Both studies were randomized, double-blind, placebo-controlled, parallel group studies to compare the efficacy and safety of once daily administration of 110mcg and 220mcg of NAQ with placebo. Study 312 was a 2-week study in children ages 6 to 11 years with SAR and Study 314 was a 12-week study in children ages 4 to 12 years with PAR.

Primary efficacy variables for both studies were the mean changes from baseline in nasal symptoms including nasal stuffiness, nasal discharge, and sneezing recorded daily, and the nasal index (the sum of the three aforementioned variables) averaged over the 2-week (SAR) and the first 4-week (PAR) period.

The sponsor's analyses results are displayed in Table 6. The result of Study 312 demonstrated that110mcg and 220mcg groups had statistically significantly larger mean reductions in overall nasal stuffiness and nasal index from baseline compared to placebo. NAQ 110mcg and 220mcg were effective in relieving most of the symptoms of SAR. The result of Study 314 demonstrated that the NAQ groups had statistically significantly larger mean reductions from baseline in nasal discharge and nasal index compared to the placebo group.

Table 6. Primary Efficacy Endpoint for Both Studies

SAR Study 312	***Placebo***	***NAQ 110 mcg***	***NAQ 220 mcg***	***NAQ 110 mcg vs. Placebo***	***NAQ 220 mcg vs. Placebo***
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	p-value	p-value
Change from Baseline over 2-week					
N	76	74	73	--	--
Nasal Stuffiness	-0.57 (0.08)	-0.87 (0.08)	-0.85 (0.08)	0.007*	0.010*
Nasal Discharge	-0.60 (0.09)	-0.92 (0.09)	-0.80 (0.09)	0.009*	0.100
Sneezing	-0.61 (0.08)	-0.83 (0.08)	-0.84 (0.08)	0.052	0.040
Nasal Index	-1.78 (0.20)	-2.62 (0.21)	-2.50 (0.21)	0.004*	0.012*

PAR Study 314	***Placebo***	***NAQ 110 mcg***	***NAQ 220 mcg***	***NAQ 110 mcg vs. Placebo***	***NAQ 220 mcg vs. Placebo***
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	p-value	p-value
Change from Baseline over 4-week					
N	100	102	113	--	--
Nasal Stuffiness	-0.50 (0.06)	-0.67 (0.06)	-0.64 (0.05)	0.037	0.082
Nasal Discharge	-0.44 (0.06)	-0.64 (0.06)	-0.63 (0.06)	0.015*	0.021*
Sneezing	-0.47 (0.05)	-0.62 (0.05)	-0.66 (0.05)	0.057	0.013*
Nasal Index	-1.42 (0.15)	-1.93 (0.15)	-1.91 (0.14)	0.016*	0.020*

a: Results from the sponsor's table 5 of study reports of 312 and 314.
*: indicate the significant at 0.025 α level (α=0.05 for 2-sided test, Bonferroni adjusted for two comparisons).

3.2 Evaluation of Safety

The routine evaluation of the safety data was conducted by Dr. Durmowicz. The reader is referred to Dr. Durmowicz's review for information regarding the adverse event profile. In this review, the safety evaluation is focused on the evaluation of the knemometry growth study.

3.2.1 Study 315- Short Term Growth Study

Study Design, Efficacy Endpoints, and Statistical Methodologies

During the year of 1998 and 1999, the sponsor conducted Study 315 to determine short term effect of NAQ 110 and 220mcg and Flonase Nasal Spray (FP) 200mcg on lower leg growth compared to placebo in children aged 4 to 10 years with AR. This randomized, four-way crossover, placebo-controlled study was conducted in a single center (Dr. David Skoner) in the U.S. Fifty-nine patients received four treatments (NAQ 110mcg, NAQ 220mcg, Flonase 200mcg, and placebo) in a randomized sequence. As shown in Table 7, the study consisted of a screening period of up to 60 days (1 visit), four 2-week treatment periods (3 visits), three 2-week washout periods (1 visit) and a 1-week follow-up period (1 visit). For each treatment period, the three visits were scheduled at the start of the treatment, one week after the start of the treatment period, and at the end of the treatment period.

Table 7. Study Flowchart

Study Period	Duration	Visits
Baseline	Variable	1
Treatment A	2 Weeks	2,3,4
Washout	2 Weeks	5
Treatment B	2 Weeks	6,7,8
Washout	2 Weeks	9
Treatment C	2 Weeks	10,11,12
Washout	2 Weeks	13
Treatment D	2 Weeks	14,15
Final	-	16
Follow-up	1 Week	17

The primary variable was growth velocity. At each visit, four knemometry measurements were recorded. The value utilized for analysis was the mean of the three values closest in range. The primary variable is the growth velocity which was estimated in two ways:

- Slope: the slope obtained by fitting a regression line to the three knemometry values for each patient during a given treatment period.

- Two time points: the actual growth (last visit - first visit) during the period divided by the length of the treatment period

As only three time points were available for each patient during each treatment period and the middle time point plays no role in slope estimation, the slope approach is same to the method using only two time points. Because two approaches were the same, we only present the analysis results based on the two time point's estimate in this review.

For each analysis, analysis of variance was performed including effects for patient, period, and treatment. The primary treatment comparisons were between the two NAQ dosage regimens and placebo. Secondary comparisons were between each NAQ dose and FP Nasal Spray, and between FP Nasal Spray and placebo.

Three study populations were defined: 1. all randomized; 2. ITT - patients who completed at least two treatment periods; 3. evaluable - patients who were in ITT population with no major protocol violation. The ITT population was used in the after mentioned analyses. An additional analysis was performed on data from patients who completed the entire trial.

The primary objective of the study was to determine whether a given dose of triamcinolone acetonide reduced growth velocity (mm/week) by 50% or more as measured by knemometry. Sample size calculation was based on detecting a 50% reduction in growth rate. A sample size of 48 patients in this crossover study would provide at least 90% power for the comparison of each Nasacort dose versus placebo, assuming a detectable difference of 0.20 mm per week.

Patient Disposition, Demographic and Baseline Characteristics

Fifty-nine patients were randomized into the study in one of 15 treatment sequences as shown in Table 8, where A=placebo, B=NAQ 110mcg, C=NAQ 220mcg, and D=FP. Ten patients withdrew prior to completing all four treatment periods.

Table 8 . Patients' Disposition by Treatment Group, All Patients

Treatment Sequence	Patients Randomized	Patients Received Treatment In Period 1	2	3	4	Completed Periods 1-4
	n	n	n	n	n	
ABCD	6	6	6	6	5	4
ACBD	5	5	5	5	5	5
ACDB	4	4	3	2	2	2
ADBC	4	4	4	4	4	4
BACD	5	5	4	4	4	4
BADC	3	3	3	3	3	3
BCAD	5	5	4	4	4	4
BDCA	3	3	2	2	2	2
CABD	5	5	5	5	4	4
CBAD	5	5	5	5	5	4
CBDA	2	2	1	1	1	1
CDAB	3	3	3	3	3	3
DACB	3	3	3	3	3	3
DBAC	2	2	2	2	2	2
DCBA	4	4	4	4	4	4
TOTAL	59	59	54	53	51	49

Source: Table 4 on page 27 in study report 315.pdf and this reviewer confirmed it.

Demographic data are summarized for all randomized patients, all patients included in the Intent-to-treat analysis and all patients included in the evaluable analysis. As shown in Table 9, there were 59 randomized patients; 42 (71%) male and 17 (29%) female, 25 (42%) Caucasian and 34 (58%) Black. The mean age was 7.2 years with a range of 4 to 10. The mean patient height at baseline as measured by stadiometry was 126.3 cm and mean lower leg length as measured by knemometry was 394.2 mm.

Table 9. Patients' Demographic and Baseline Characteristics N (%)

	All randomized patients	All ITT patients	All evaluable patients
Number of Patients	59	53	51
Sex			
Male	42 (71.2%)	38 (71.7%)	37 (72.5%)
Female	17 (28.8%)	15 (28.3%)	14 (27.5%)
Race			
Caucasian	25 (42.4%)	23 (43.4%)	23 (45.1%)
Black	34 (57.6%)	30 (56.6%)	28 (54.9%)
Age (Years)			
Mean	7.17	7.15	7.08
S.D.	1.65	1.70	1.68
Range	(4 - 10)	(4 - 10)	(4 - 10)
Baseline Stadiometry (cm)			
Mean	126.31	126.37	125.91
S.D.	10.43	10.40	10.24
Range	104.13 - 145.03	104.13 - 145.03	104.13 - 141.83
Baseline Knemometry (mm)			
Mean	394.15	393.89	391.98
S.D.	39.87	38.93	38.06
Range	(315.7 - 472.0)	(315.7 - 469.4)	(315.7 - 455.1)
Weight (kg)			
Mean	29.28	29.14	28.77
S.D.	8.63	8.24	8.07
Range	(16.8 - 50.9)	(16.8 - 49.3)	(16.8 - 49.3)

Source: Table 10 on page 33 in study report 315.pdf and this reviewer confirmed it.

Results and Conclusions

Table 10 displays the raw mean of growth velocity (mm/wk). The growth velocities varied significantly by period in the placebo treatment periods. However, the overall period effect was not statistically significant (p=0.5238).

Table 10. Raw Mean of Growth Velocity (mm/wk) by Period (Mean, (n)), (ITT)

Period	*Placebo*	*NAQ 110µg*	*NAQ 220µg*	*FP Nasal Spray 200µg*
1	0.473 (17)	0.345 (13)	0.468 (14)	0.485 (9)
2	0.474 (15)	0.325 (14)	0.287 (15)	0.350 (9)
3	0.607 (14)	0.428 (18)	0.295 (15)	0.372 (6)
4	0.714 (7)	0.448 (8)	0.489 (9)	0.421 (28)

Table 11 presents the results of the analyses of the growth velocity rates estimated by total growth divided by the number of weeks for both ITT (53) and completer (49, who completed all four treatment periods) populations. For the ITT population, the growth velocity rates was 0.51 mm/week during the placebo period compared to 0.34 mm/week during treatment with NAQ 220mcg and 0.36 mm/week during the NAQ 110mcg and FP Nasal Spray 200mcg period. The lower bounds of the 2-sided 95% CI for the difference between the treated periods and the placebo periods in growth velocity were -0.31 and -0.33 mm/week for NAQ 110mcg - placebo and NAQ 200mcg – placebo, respectively. The difference between NAQ 220mcg and placebo was statistically significant (p=0.036) at the level of 0.05. The difference between NAQ 110mcg and placebo was marginally significant (p=0.064) at the level of 0.05.

Table 11. Analysis of Growth Velocity (mm/wk) (ITT and Completer)

ITT (n=53)	***Placebo***	***NAQ 110mcg***	***NAQ 220mcg***	***FP Nasal Spray 200mcg***
LS Mean (SE)	0.51 (0.06)	0.36 (0.06)	0.34 (0.06)	0.36 (0.06)
LS Mean of treatment differences Active vs. Placebo (SE)		-0.15 (0.08)	-0.17 (0.08)	-0.15 (0.08)
95%CI		(-0.31, 0.01)	(-0.33, -0.01)	(-0.31, 0.02)
p-value		p=0.064	p=0.036	p=0.085
Treatment effect compared to placebo[b]		-29.4%	-33.3%	-29.4%
Completer (n=49)				
LS Mean (SE)	0.47 (0.06)	0.36 (0.06)	0.32 (0.06)	0.36 (0.06)
LS Mean of treatment differences Active vs. Placebo (SE)		-0.11 (0.08)	-0.15 (0.08)	-0.10 (0.08)
95%CI		(-0.27, 0.05)	(-0.31, 0.01)	(-0.27, 0.06)
p-value		p=0.186	p=0.066	p=0.222
Treatment effect compared to placebo[b]		-23.4%	-31.9%	-21.3%

a: LS Means are obtained from the repeated model with treatment and period as fix effect, patient nested within sequence as random effect.
b: LS mean of treatment difference of active group/growth velocity estimated of placebo group.
Note: Results from reviewer analysis.

Conclusion -
Both NAQ 110 and 220mcg doses once daily showed statistically significant reductions in growth velocity compared with placebo. An increasing dose-response trend was observed in the NAQ dose groups.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age

The sponsor performed the subgroup analyses based on gender and race for the iTNSS for Study 3502. Table 12 and Figure 2 summarize subgroup analysis results of mean change from baseline of rTNSS by gender, race, and age subgroups. This reviewer used ANCOVA models with treatment as fixed effects and baseline value of rTNSS as covariate. There was no statistically

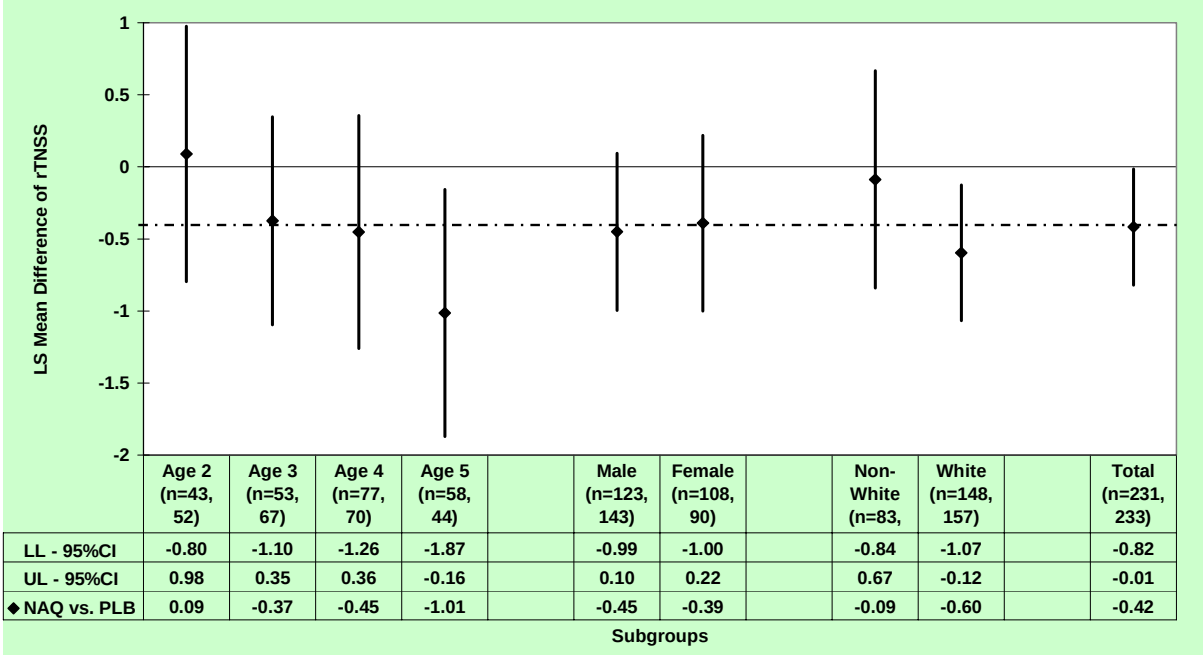
significant treatment by gender, treatment by race interaction, or treatment by age. However, the older age subgroups showed numerically higher treatment differences than the younger subgroup.

Table 12. Mean Change from Baseline of rTNSS, (Study 3502, ITT)

	NAQ 110mcg (n=231)			Placebo (n=233)		
Subgroup (p-Value)†	**N**	**LS Mean**	**SE**	**N**	**LS Mean**	**SE**
Gender (p=0.8785)						
Male	123	-2.38	0.20	143	-1.93	0.19
Female	108	-2.20	0.21	90	-1.81	0.23
Race Group (p=0.2605)						
White	148	-2.43	0.17	157	-1.83	0.17
Non-White	83	-2.09	0.26	76	-1.99	0.28
Age Group (p=0.3829)						
2	43	-2.26	0.33	52	-2.35	0.30
3	53	-2.26	0.27	67	-1.89	0.24
4	77	-2.34	0.28	70	-1.88	0.29
5	58	-2.33	0.28	44	-1.32	0.32

† p-Value for treatment-by-subgroup.

Figure 2. Mean Change from Baseline of rTNSS (Study 3502, ITT)



	Age 2 (n=43, 52)	Age 3 (n=53, 67)	Age 4 (n=77, 70)	Age 5 (n=58, 44)		Male (n=123, 143)	Female (n=108, 90)		Non-White (n=83,	White (n=148, 157)		Total (n=231, 233)
LL - 95%CI	-0.80	-1.10	-1.26	-1.87		-0.99	-1.00		-0.84	-1.07		-0.82
UL - 95%CI	0.98	0.35	0.36	-0.16		0.10	0.22		0.67	-0.12		-0.01
◆ NAQ vs. PLB	0.09	-0.37	-0.45	-1.01		-0.45	-0.39		-0.09	-0.60		-0.42

5. LABEL REVIEW

5.1 The Sponsor Proposed Labeling

(b) (4)

[redacted]

5.2 The Recommended Label Change

14. Clinical Studies

(b) (4)

[redacted]

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