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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	202813/S007
Drug Name:	QNASL™ (beclomethasone dipropionate) Nasal Aerosol
Indication(s):	Treatment of Nasal Symptoms of Seasonal and Perennial Allergic Rhinitis in Patients 4 Years of Age and Older
Applicant:	Teva Branded Pharmaceutical Products R&D, Inc.
Date(s):	Receipt date: February 27, 2014
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Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
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Keywords: NDA review, clinical studies

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

Teva Branded Pharmaceutical Products R&D (Teva) submitted an efficacy supplement to satisfy all PREA requirements following the approval of Qnasl® (beclomethasone dipropionate) Nasal Aerosol, herein after referred to as Qnasl, which was approved on March 23, 2012. Based on this submission, Teva proposes to lower the indicated minimum age from 12 years of age to 4 years of age for the currently approved product for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis (SAR and PAR). The applicant conducted two studies, BDP-AR-305 (referred to as 305) and BDP-AR-306 (referred to as 306) to evaluate the efficacy and safety of Qnasl 80 mcg/day in subjects with nasal symptoms due to SAR (study 305) or PAR (study 306).

Both studies 305 and 306 demonstrated statistically significant effects on the primary endpoint, reflective Total Nasal Symptom Score (rTNSS) and the secondary endpoints, instantaneous Total Nasal Symptom Score (iTNSS) (study 305), iTNSS over the first 6 weeks of treatment for subjects 6 to 11 years of age (study 306), rTNSS over the first 6 weeks of treatment for subjects 4 to 11 years of age (study 306), and iTNSS over the first 6 weeks of treatment for subjects 4 to 11 years of age (study 306) for Qnasl 80 mcg relative to placebo. There were no missing data imputations stated in the protocol. The applicant did state that missing data was predicted to be low and thus assumed that the behavior of the post-withdrawal data would be predicted from the observed variables. The overall completion rates were approximately 97% and 90% in studies 305 and 306, respectively.

The statistical review of the two clinical studies supports the claim of the treatment of nasal symptoms of SAR and PAR in patients 4 years of age and older.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Teva is currently marketing Qnasl 320 mcg per day for the treatment of nasal symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older, Qnasl is an anti-inflammatory corticosteroid. Qnasl was approved in the United States in March 2012. Based on the results from the current submission, the applicant is proposing to lower the indicated minimum age from 12 years to 4 years for the currently approved Qnasl product.

2.1.2 History of Drug Development

The pediatric program for Qnasl was conducted under IND 101,639. Teva had several interactions with the Division of Pulmonary, Allergy, and Rheumatology Products regarding their pediatric program. A pre-NDA meeting was held on November 5, 2013. No statistical issues were discussed or identified.

2.1.3 Specific Studies Reviewed

This review will focus on the results from two efficacy studies, 305 and 306.

2.2 Data Sources

The submission of NDA 202-813 was submitted on February 27, 2014. The study reports including protocols, statistical analysis plan, and all referenced literature were submitted by the applicant to the Agency. The data and final study report for the electronic submission were archived under the following network path location: \\cdsesub1\evsprod\NDA202813\0048

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the electronic data submitted by the applicant were of sufficient quality to allow a thorough review of the data. I was able to reproduce the analyses of the primary and secondary efficacy endpoints for each clinical study submitted. I was able to verify the randomization of the treatment assignments.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The summary of the study designs and endpoints for the two key efficacy studies are given in Table 1. Both studies were phase 3, randomized, double-blind, placebo-controlled, parallel-group, multi-center, outpatient studies that enrolled male and female pediatric subjects (6 to 11 years of age in study 305 and 4 to 11 years of age in study 306). Study 305 was a dose ranging study that was 2 weeks in duration and evaluated subjects with SAR; Study 306 was 12 weeks in duration in subjects with PAR. The design and efficacy endpoints are explained in detail in the following paragraphs.

Table 1. Summary of Study Design

Study ID	Indication	Length of the Study	Treatment Arms (Per Nostril, Q.D.)	Number of Patients	Primary Efficacy Endpoints
305	SAR	RI: 7-21 days TP: 2 weeks	Qnasl 80 mcg/day Qnasl 160 mcg/day Placebo	239 242 234	Change from baseline in the average AM and PM daily rTNSS
306	PAR	RI: 7-21 days TP: 12 weeks	Qnasl 80 mcg/day Placebo	362 185	Change from baseline in the average AM and PM daily rTNSS

RI: Run-in period, TP: Treatment period rTNSS: Reflective Total Nasal Symptom Score
iTNSS: Instantaneous Total Nasal Symptom Score
Source: Reviewer

Studies 305 and 306 were similar in design. Both studies were designed to assess the efficacy and safety of Qnasl administered once daily in the morning. Study 305 had subjects apply 1 actuation per nostril each containing either 40 mcg per actuation for a total daily dose of 80 mcg per day or 80 mcg per actuation for a total daily dose of 160 mcg per day. Study 306 had subjects apply 1 actuation per nostril each containing 40 mcg per actuation for a total daily dose of 80 mcg per day. Each study consisted of a run-in period and a treatment period.

In study 305, following the run-in period, subjects were randomized to receive either Qnasl 80 mcg/day, Qnasl 160 mcg/day or placebo in a 1:1:1 ratio. In study 306, following the run-in period, subjects were randomized into treatment arms in a 2:1 ratio to receive Qnasl 80 mcg/day or placebo.

The primary efficacy endpoint in both studies was the average AM and PM subject-reported reflective Total Nasal Symptom Score (rTNSS) over the treatment period. The reflective TNSS was evaluated over the past 12 hours prior to recording of the score. TNSS was defined as the sum of the subject-reported symptom scores for the four nasal symptoms: rhinorrhea (runny nose), nasal congestion, nasal itching and sneezing. Each score was assessed on a severity scale ranging from 0 to 3 defined as:

- 0=absent (no sign/symptom present)
- 1=mild (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2=moderate (definite awareness of sign/symptom that is bothersome but tolerable)
- 3=severe (sign/symptom that is hard to tolerate; cause interference with activities of daily living and/or sleeping).

The secondary efficacy endpoint for study 305 was the average AM and PM subject-reported instantaneous Total Nasal Symptom Score (iTNSS) over the 2 week treatment period. The secondary endpoints for study 306 were average AM and PM subject-reported iTNSS over the first 6 weeks of treatment for subjects 6 to 11 years of age, average AM and PM subject-reported rTNSS over the first 6 weeks of treatment for subjects 4 to 11 years of age, and average AM and PM subject-reported iTNSS over the first 6 weeks of treatment for subjects 4 to 11 years of age.

Instantaneous Total Nasal Symptom Score is defined as the evaluation of the symptom severity over the last 10 minutes, scored using the scale above.

3.2.2 Statistical Methodologies

All efficacy analyses in study 305 were performed using the intent-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of randomized study medication and had at least one post-baseline assessment. The same definition was used to define the full analysis set (FAS) in study 306, which was used to analyze the efficacy endpoints in this study. Both studies conducted supportive analyses using the per-protocol (PP) population, defined as all data from the ITT or FAS population obtained prior to experiencing major protocol deviations.

Study 305

The protocol for study 305 specified the analysis for the primary endpoint, change from baseline in the average AM and PM daily subject-reported rTNSS over the two week treatment period, would be analyzed using a repeated measures Analysis of Covariance (ANCOVA) with covariate adjustment for baseline, day, treatment, and the treatment by day interaction using the ITT analysis set. Baseline was defined as the average reflective AM and PM TNSS over the last 4 days prior to randomization. The applicant stated that missing data was predicted to be low and would not be imputed, thus the chosen analysis, a maximum likelihood method which assumed data was missing at random, was considered valid in the current setting.

The secondary endpoint in study 305, change from baseline in the average AM and PM subject-reported iTNSS over the two-week treatment period, was analyzed in a similar way to the primary endpoint.

To account for multiple comparisons, two endpoints and two doses of Qnasl, a fixed sequential step-down procedure was used to control the family-wise error rate at 5% for the primary and secondary endpoints. If the treatment comparison for the highest dose versus placebo on the primary endpoint was less than 0.05 then the next comparison(s) of interest was made (Figure 1). The process continued until either all comparisons of interest were made or until the point at which the resulting two-sided p-value for a comparison(s) of interest was greater than 0.05. At the point where the p-value was greater than 0.05, no further comparisons were interpreted inferentially. This procedure allowed for control of the Type I error within a particular treatment comparison, as well as within a particular endpoint, however this procedure does not control the overall Type I error.

Figure 1. Multiplicity Adjustment for Primary and Secondary Efficacy Endpoints Study 305

	Treatment Comparison	
Endpoint	160 mcg vs. Placebo	80 mcg vs. Placebo
Change from baseline in the average AM and PM daily patient-reported reflective TNSS (Primary)	↓ →	↓
Change from baseline in the average AM and PM daily patient-reported instantaneous TNSS (Secondary)	→	

Source: Protocol No.: BDP-AR-305 Table 12.5.1-1, page 60

Study 306

The protocol for study 306 specified the analysis for the primary endpoint, change from baseline in the average AM and PM daily subject-reported rTNSS over the first six weeks of treatment for subjects 6 to 11 years of age, would be analyzed using a repeated measures ANCOVA with covariate adjustment for baseline, day, treatment, and the treatment by day interaction using the FAS for children 6 to 11 years of age. Baseline was defined as the average reflective AM and PM TNSS over the last 4 days prior to randomization. Similar to study 305, the applicant stated that missing data was predicted to be low and would not be imputed. Thus, the chosen analysis, a maximum likelihood method which assumed data was missing at random, was valid in the current setting.

The secondary endpoints in study 306, the average AM and PM subject-reported iTNSS over the first 6 weeks of treatment for subjects 6 to 11 years of age, average AM and PM subject-reported rTNSS over the first 6 weeks of treatment for subjects 4 to 11 years of age, and average AM and PM subject-reported iTNSS over the first 6 weeks of treatment for subjects 4 to 11 years of age, were analyzed in a similar way to the primary endpoint. Similar to the primary analysis, missing data was not imputed.

A fixed sequential step-down procedure was used to control the family-wise error rate at 5% for the primary and secondary endpoints. If the primary efficacy analysis was significant in favor of Qnasl, then the first secondary endpoint was tested. This process continued until all endpoints had been tested and non-significance was noted. The secondary endpoints were tested in the following order.

1. Average AM and PM subject-reported iTNSS over the first 6 weeks of treatment for subjects 6 to 11 years of age
2. Average AM and PM subject-reported rTNSS over the first 6 weeks of treatment for subjects 4 to 11 years of age
3. Average AM and PM subject-reported iTNSS over the first 6 weeks of treatment for subjects 4 to 11 years of age

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study 305

The summary of the subject disposition in study 305 is given in Table 2. One subject randomized to Qnasl 160 mcg/day was randomized in error and never received any study medication. This subject was not included in the ITT population. Another subject treated with Qnasl 80 mcg/day had no post-baseline efficacy data and was also excluded from the ITT population. Approximately 3% of the subjects discontinued study medication. The primary reason for discontinuation in the Qnasl 80 mcg group was adverse advents (AE), approximately 1%. The primary reason for discontinuation in the Qnasl 160 mcg and the placebo groups was due to other, 1% in each group. Protocol violations accounted for less than 1% of the overall discontinuations.

Table 2. Summary of Subject Disposition Study 305

	BDP HFA 80 mcg/day n (%)	BDP HFA 160 mcg/day n (%)	Placebo n (%)
Randomized	239	242	234
ITT	238 (99.6)	241 (99.6)	234 (100)
Completed	235 (98)	234 (97)	227 (97)
Discontinued	4 (2)	7 (3)	7 (3)
Adverse Event	2 (<1)	2 (<1)	1 (<1)
Lost to Follow-up	1 (<1)	0	1 (<1)
Protocol Violation	1 (<1)	1 (<1)	0
Consent Withdrawn	0	1 (<1)	2 (<1)
Other	0	3 (1)	3 (1)

Source: Clinical Trial Report-Protocol Number BDP-AR-305 (24-Apr-2012) Table 5, page 57
BDP HFA = Qnasl

Most subjects were white (71%) with a mean age of approximately 9 years. These factors were generally well-balanced across the treatment groups. The summary of the demographics is given in Table 3.

Table 3. Demographics and Baseline Characteristics Study 305 (ITT Population)

		BDP HFA 80 mcg/day N=238	BDP HFA 160 mcg/day N=241	Placebo N=234
Age (years)	Mean (SD)	9 (2)	9 (2)	9 (2)
Gender, n (%)	Male	133 (56)	125 (52)	123 (53)
	Female	105 (44)	116 (48)	111 (47)
Height (cm)	Mean (SD)	137 (13)	139 (12)	138 (12)
Weight (kg)	Mean (SD)	37 (13)	38 (13)	37 (12)
Ethnicity	Hispanic or Latino	40 (17)	53 (22)	45 (19)
	Not Hispanic, Not Latino	198 (83)	188 (78)	189 (81)
Race	White	169 (71)	172 (71)	164 (70)
	Asian	2 (1)	4 (2)	6 (3)
	Black or African American	55 (23)	55 (23)	52 (22)
	Other	12 (5)	10 (4)	12 (5)
BMI (kg/m^2)	Mean (SD)	19 (4)	19 (5)	19 (5)

Source: Study BDP-AR-305 Table 14.1.2.2, page 5
BDP HFA = Qnasl

3.2.3.2 Study 306

Approximately 10% of the subjects discontinued study medication. The primary reason for discontinuation in both groups was withdrawal by subject, 3% in the Qnasl 80 mcg/day group and 4% in the placebo group. More subjects discontinued due to AEs in the Qnasl 80 mcg/day group with 8 subjects (2%) than the placebo group with 4 subjects (2%). Protocol violations accounted for less than 1% of the overall discontinuations. The summary of the demographics is given in Table 4.

Table 4. Summary of Subject Disposition Study 306

	BDP HFA 80 mcg/day n (%)	Placebo n (%)
Randomized (ITT Population)	362 (100)	185 (100)
FAS	358 (99)	184 (>99)
Completed	328 (91)	167 (90)
Discontinued	34 (9)	18 (10)
Adverse Event	8 (2)	4 (2)
Lost to Follow-up	8 (2)	3 (2)
Protocol Violation	2 (<1)	2 (1)
Withdrawal by Subject	11 (3)	8 (4)
Non-compliance	4 (1)	0
Lack of Efficacy	1 (<1)	1 (<1)

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 4, page 75
BDP HFA = Qnasl

Most subjects were white (76%) with a mean age of approximately 8 years. These factors were generally well-balanced across the treatment groups. The summary of the demographics is given in Table 5.

Table 5. Demographics and Baseline Characteristics Study 306 (ITT Population)

		BDP HFA 80 mcg/day	Placebo
		N=362	N=185
Age (years)	Mean (SD)	8 (2)	8 (2)
Age Group, n (%)	4 to 5 years	62 (17)	31 (17)
	6 to 11 years	300 (83)	154 (83)
Gender, n (%)	Female	175 (48)	71 (38)
	Male	187 (52)	114 (62)
Race, n (%)	White	272 (75)	145 (78)
	Black	65 (18)	25 (14)
	Other	25 (7)	15 (8)
Ethnicity, n (%)	Hispanic	144 (40)	75 (41)
	Not Hispanic, not Latino	217 (60)	110 (59)
Weight (kg)	Mean (SD)	33 (13)	34 (13)
BMI (kg/m^2)	Mean (SD)	19 (4)	19 (4)

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 6, page 79
BDP HFA = Qnasl

3.2.4 Results and Conclusions

3.2.4.1 Study 305

The results from the primary efficacy analysis will be shown in the order of the hierarchical testing procedure. Change from baseline in the average of the subject-assessed AM and PM daily rTNSS over the 2-week treatment period for the Qnasl 160 mcg/day group and Qnasl 80 mcg/day group were tested first, if significant, the secondary endpoint iTNSS was tested within each dose group.

The results of the primary and secondary efficacy analyses for subjects with SAR are shown in Table 6. Baseline scores for the primary endpoint, rTNSS, were comparable between the three groups. There were significantly greater decreases from baseline in both Qnasl 160 mcg/day and Qnasl 80 mcg/day when compared to placebo. There was also a statistically significant difference between Qnasl 160 mcg/day and placebo, as well as between Qnasl 80 mcg/day and placebo for rTNSS over the two week treatment period. The results from the PP analysis were consistent with the ITT analysis, results not shown.

Since the by-treatment group comparison for the primary efficacy endpoint, change from baseline in the average of the subject-assessed AM and PM daily rTNSS over the 2-week treatment period was statistically significant for Qnasl 160 mcg/day followed by Qnasl 80 mcg/day and according to the pre-specified multiplicity plan, inferential statistical analysis may proceed to the secondary efficacy endpoint, change from baseline in the average of the subject-assessed AM and PM daily iTNSS over the 2-week treatment period. The results for the secondary efficacy endpoint were consistent with the primary efficacy results, with a statistically significant treatment difference between Qnasl 160 mcg/day and placebo as well as Qnasl 80 mcg/day and placebo in the ITT analysis. Again, the results from the PP analysis were consistent with the ITT analysis, results not shown.

Table 6. SAR Efficacy Results- 2 Weeks Study 305 (ITT Population)

Treatment	N	Baseline (SD)	Mean (SE) Change from Baseline	Difference From Placebo		
				Mean	95% CI	P Value
Primary: Reflective Total Nasal Symptom Scores (rTNSS)						
BDP HFA 80 mcg/day	238	8.9 (1.62)	-1.9 (0.14)	-0.71	-1.1, -0.3	<0.001
BDP HFA 160 mcg/day	241	9.0 (1.71)	-2.0 (0.14)	-0.76	-1.1, -0.4	<0.001
Placebo	234	9.0 (1.70)	-1.2 (0.14)			
Secondary: Instantaneous Total Nasal Symptom Scores (iTNSS)						
BDP HFA 80 mcg/day	238	8.1 (1.99)	-1.6 (0.13)	-0.63	-1.0, -0.3	<0.001
BDP HFA 160 mcg/day	241	8.1 (2.13)	-1.7 (0.13)	-0.73	-1.1, -0.4	<0.001
Placebo	234	8.2 (2.10)	-1.0 (0.13)			

Source: Clinical Trial Report-Protocol Number BDP-AR-305 (24-Apr-2012) Tables 12-13, pages 64 and 66
BDP HFA = Qnasl

3.2.4.2 Study 306

The results from the primary efficacy analysis will be shown in the order of the hierarchical testing procedure. Change from baseline in the average of the subject-assessed AM and PM daily rTNSS over the first 6 weeks of treatment in subjects 6 to 11 years of age for Qnasl 80 mcg/day was tested first, if significant, the secondary endpoints were tested.

The primary efficacy analyses for subjects with PAR are shown in Table 7. There was a significantly greater decrease from baseline in Qnasl 80 mcg/day group than placebo group. For the primary efficacy endpoint, change from baseline in the average of the subject-assessed AM and PM daily rTNSS over the first 6 weeks, there was a statistically significant difference between Qnasl 80 mcg/day and placebo. The results from the PP analysis were consistent with the ITT analysis, results not shown.

Table 7. Summary of Primary Efficacy Analysis rTNSS Ages 6 to 11 Study 306 (FAS)

Treatment	N	Baseline (SD)	Mean (SE) Change from Baseline	Difference From Placebo		
				Mean	95% CI	P Value
BDP HFA 80 mcg/day	296	8.6 (1.56)	-2.3 (0.12)	-0.66	-1.08, -0.24	0.002
Placebo	153	8.6 (1.60)	-1.6 (0.17)			

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 12, page 87
BDP HFA = Qnasl

Since the by-treatment group comparison for the primary efficacy endpoint was statistically significant for the Qnasl 80 mcg/day group and according to the pre-specified multiplicity plan, inferential statistical analysis may proceed to the analysis of the secondary efficacy endpoints listed in Table 8. These secondary endpoints were tested in the pre-specified order. The results for the analysis of the secondary efficacy endpoints were consistent with the primary efficacy analysis. There was a statistically significant treatment difference between Qnasl 80 mcg/day and

placebo using the FAS population. The results from the PP analysis were consistent with the FAS analysis.

Table 8. Summary of Secondary Efficacy Analyses Study 306 (FAS)

Treatment	N	Baseline (SD)	LS Mean (SE) Change from Baseline	Difference From Placebo		
				LS Mean	95% CI	P Value
Average AM and PM subject-reported iTNSS over the first 6 weeks of treatment for subjects 6-11 years of age						
BDP HFA 80 mcg/day	296	7.9 (2.05)	-2.0 (0.12)	-0.58	-0.99, -0.18	0.004
Placebo	153	7.8 (2.12)	-1.4 (0.17)			
Average AM and PM subject-reported rTNSS over the first 6 weeks of treatment for subjects 4-11 years of age						
BDP HFA 80 mcg/day	358	8.7 (1.53)	-2.3 (0.11)	-0.62	-1.0, -0.23	0.002
Placebo	184	8.7 (1.66)	-1.7 (0.16)			
Average AM and PM subject-reported iTNSS over the first 6 weeks of treatment for subjects 4-11 years of age						
BDP HFA 80 mcg/day	358	8.0 (2.00)	-2.1 (0.11)	-0.54	-0.91, -0.17	0.004
Placebo	184	7.8 (2.16)	-1.5 (0.15)			

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 13, page 89
BDP HFA = Qnasl

3.3 Evaluation of Safety

The evaluation of safety was conducted by Dr. Xu Wang. Reader is referred to Dr. Xu Wang's review for this section.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses on the primary (rTNSS) and secondary efficacy (iTNSS) endpoints were performed by gender (male and female) and race (white, black, and other) in studies 305 and 306. Study 306 conducted an additional analysis on both the average AM and PM subject-reported rTNSS and iTNSS over the first 6 weeks of treatment for subjects 4 to 5 years of age.

4.1 Gender, Race and Age

Gender

Tables 9 and 10 summarize the subgroup analysis by gender for study 305 in patients with SAR for rTNSS and iTNSS, respectively. There was a statistically significant difference in favor of Qnasl 80 mcg/day and Qnasl 160 mcg/day over placebo for males but not for females in rTNSS, however, the effects were in the same direction as the primary endpoint. This non-significant result is probably due to the study not being powered to detect differences in gender. There was a statistically significant difference in favor of both Qnasl 80 mcg/day and Qnasl 160 mcg/day for both males and females for iTNSS.

Table 9. Subgroup Analysis for rTNSS by Gender for Study 305 (ITT Population)

	BDP HFA 80 mcg	BDP HFA 160 mg	Placebo
Females			
N	105	116	111
Baseline mean (SD)	8.8 (1.6)	9.0 (1.7)	8.9 (1.7)
Overall LS mean (SE) change from Baseline[1]	-2.0 (0.2)	-1.9 (0.2)	-1.4 (0.2)
LS mean treatment difference from placebo (95% CI)	-0.6 (-1.2, -0.0)	-0.5 (-1.1, 0.0)	
p-value	0.047	0.069	
Males			
N	133	125	123
Baseline mean (SD)	8.9 (1.7)	9.1 (1.7)	9.1 (1.7)
Overall LS mean (SE) change from Baseline[1]	-1.9 (0.2)	-2.0 (0.2)	-1.1 (0.2)
LS mean treatment difference from placebo (95% CI)	-0.8 (-1.3, -0.3)	-1.0 (-1.4, -0.5)	
p-value	<0.001	<0.001	

Source: Clinical Trial Report-Protocol Number BDP-AR-305 (24-Apr-2012) Table 14.2.4.1, pages 265-272
BDP HFA = Qnasl

Table 10. Subgroup Analysis for iTNSS by Gender for Study 305 (ITT Population)

	BDP HFA 80 mcg	BDP HFA 160 mg	Placebo
Females			
N	105	116	111
Baseline mean (SD)	8.1 (1.9)	8.2 (2.1)	8.1 (2.1)
Overall LS mean (SE) change from Baseline[1]	-1.7 (0.2)	-1.7 (0.2)	-1.1 (0.2)
LS mean treatment difference from placebo (95% CI)	-0.6 (-1.2, -0.1)	-0.6 (-1.2, -0.1)	
p-value	0.032	0.025	
Males			
N	133	125	123
Baseline mean (SD)	8.1 (2.1)	8.0 (2.1)	8.2 (2.2)
Overall LS mean (SE) change from Baseline[1]	-1.6 (0.2)	-1.7 (0.2)	-0.9 (0.2)
LS mean treatment difference from placebo (95% CI)	-0.66 (-1.1, -0.2)	-0.81 (-1.3, -0.4)	
p-value	0.004	<0.001	

Source: Clinical Trial Report-Protocol Number BDP-AR-305 (24-Apr-2012) Table 14.2.4.3 Pages 285-292
BDP HFA = Qnasl

Tables 11 and 12 summarize the subgroup analysis by gender for study 306 in subjects with PAR for rTNSS ages 6 to 11 and 4 to 11, respectively. Tables 13 and 14 summarize the subgroup analysis by gender for study 306 in subjects with PAR for iTNSS ages 6 to 11 and 4 to 11, respectively. There was a statistically significant difference in favor of Qnasl 80 mcg/day for males but not for females in both rTNSS and iTNSS in both ages 6 to 11 and 4 to 11, probably due to the study not being powered to detect differences in gender. However, there was a greater effect in the LS means for rTNSS and iTNSS with Qnasl 80 mcg/day than with placebo for females.

Table 11. Subgroup Analysis for rTNSS by Gender over the First 6 Weeks of Treatment for Subjects 6 to 11 Years of Age in Study 306 (FAS)

	BDP HFA 80 mcg		Placebo
Females			
N	142		56
Baseline mean (SD)	8.8 (1.6)		8.8 (1.5)
Overall LS mean (SE) change from Baseline[1]	-2.1 (0.2)		-1.9 (0.3)
LS mean treatment difference from placebo (95% CI)		-0.23 (-0.88, 0.41)	
p-value		0.480	
Males			
N	154		97
Baseline mean (SD)	8.5 (1.5)		8.5 (1.6)
Overall LS mean (SE) change from Baseline[1]	-2.4 (0.2)		-1.5 (0.2)
LS mean treatment difference from placebo (95% CI)		-0.98 (-1.55, -0.42)	
p-value		<0.001	

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 15.8.1.7.1 Pages 269-277 and Table 15.8.1.7.2 Pages 278-286
BDP HFA = Qnasl

Table 12. Subgroup Analysis for rTNSS by Gender over the First 6 Weeks of Treatment for Subjects 4 to 11 years of Age in Study 306 (FAS)

	BDP HFA 80 mcg		Placebo
Females			
N	173		70
Baseline mean (SD)	8.8 (1.6)		8.9 (1.6)
Overall LS mean (SE) change from Baseline[1]	-2.2 (0.2)		-1.8 (0.3)
LS mean treatment difference from placebo (95% CI)		-0.37 (-0.95, 0.21)	
p-value		0.480	
Males			
N	185		114
Baseline mean (SD)	8.6 (1.5)		8.5 (1.7)
Overall LS mean (SE) change from Baseline[1]	-2.4 (0.2)		-1.6 (0.2)
LS mean treatment difference from placebo (95% CI)		-0.81 (-1.33, -0.29)	
p-value		0.002	

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Tables 15.8.1.8.1 Pages 287-295 and Table 15.8.1.8.2 Pages 296-304
BDP HFA = Qnasl

Table 13. Subgroup Analysis for iTNSS by Gender Over the First 6 Weeks of Treatment for Subjects 6 to 11 Years of Age Study 306 (FAS)

	BDP HFA 80 mcg		Placebo
Females			
N	142		56
Baseline mean (SD)	8.0 (2.2)		8.0 (2.0)
Overall LS mean (SE) change from Baseline[1]	-1.8 (0.2)		-1.7 (0.3)
LS mean treatment difference from placebo (95% CI)		-0.1 (-0.72, 0.53)	
p-value		0.764	
Males			
N	154		97
Baseline mean (SD)	7.8 (1.9)		7.7 (2.2)
Overall LS mean (SE) change from Baseline[1]	-2.2 (0.2)		-1.2 (0.2)
LS mean treatment difference from placebo (95% CI)		-0.95 (-1.47, -0.42)	
p-value		<0.001	

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 15.10.1.7.1 Pages 575-583 and Table 15.10.1.7.2 Pages 584-592
BDP HFA = Qnasl

Table 14. Subgroup Analysis for iTNSS by Gender Over the First 6 Weeks of Treatment for Subjects 4 to 11 Years of Age Study 306 (FAS)

	BDP HFA 80 mcg		Placebo
Females			
N	173		70
Baseline mean (SD)	8.0 (2.1)		8.0 (2.2)
Overall LS mean (SE) change from Baseline[1]	-2.0 (0.2)		-1.7 (0.2)
LS mean treatment difference from placebo (95% CI)		-0.2 (-0.77, 0.37)	
p-value		0.483	
Males			
N	185		114
Baseline mean (SD)	7.9 (1.9)		7.7 (2.2)
Overall LS mean (SE) change from Baseline[1]	-2.2 (0.2)		-1.4 (0.2)
LS mean treatment difference from placebo (95% CI)		-0.79 (-1.28, -0.30)	
p-value		0.002	

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 15.10.1.8.1 Pages 593-601 and Table 15.10.1.8.2 Pages 602-610
BDP HFA = Qnasl

Race

Tables 15 and 16 summarize the subgroup analysis by race for study 305 in subjects with SAR for rTNSS and iTNSS, respectively. There were numerically greater differences in Qnasl 160 mcg/day and Qnasl 80 mcg/day over placebo in all the race subgroups for both rTNSS and iTNSS.

Table 15. Subgroup Analysis for rTNSS by Race for Study 305 (ITT Population)

	BDP HFA 80 mcg	BDP HFA 160 mg	Placebo
White			
N	169	172	164
Baseline mean (SD)	8.7 (1.6)	8.9 (1.7)	8.9 (1.7)
Overall LS mean (SE) change from Baseline[1]	-1.8(0.2)	-2.1 (0.2)	-1.1 (0.2)
LS mean treatment difference from placebo (95% CI)	-0.7 (-1.1, -0.2)	-0.9 (-1.4, -0.5)	
p-value	0.003	<0.001	
Black			
N	55	55	52
Baseline mean (SD)	9.3 (1.4)	9.4 (1.9)	9.3 (1.6)
Overall LS mean (SE) change from Baseline[1]	-2.1 (0.3)	-1.7 (0.3)	-1.6 (0.3)
LS mean treatment difference from placebo (95% CI)	-0.5 (-1.4, 0.4)	-0.14 (-1.0, 0.7)	
p-value	0.271	0.746	
Other			
N	14	14	18
Baseline mean (SD)	8.9 (1.8)	9.1 (1.6)	9.1 (1.8)
Overall LS mean (SE) change from Baseline[1]	-2.7 (0.4)	-1.6 (0.4)	-0.7 (0.4)
LS mean treatment difference from placebo (95% CI)	-2.0 (-3.1, -0.9)	-0.9 (-2.0, 0.2)	
p-value	<0.001	0.124	

Source: Clinical Trial Report-Protocol Number BDP-AR-305 (24-Apr-2012) Table 14.2.4.2, pages 273-284
BDP HFA = Qnasl

Table 16. Subgroup Analysis for iTNSS by Race for Study 305 (ITT Population)

	BDP HFA 80 mcg	BDP HFA 160 mg	Placebo
White			
N	169	172	164
Baseline mean (SD)	7.9 (2.0)	7.8 (2.1)	7.9 (2.1)
Overall LS mean (SE) change from Baseline[1]	-1.5(0.2)	-1.8 (0.2)	-0.9 (0.2)
LS mean treatment difference from placebo (95% CI)	-067 (-1.0, -0.2)	-0.9 (-1.3, -0.5)	
p-value	0.004	<0.001	
Black			
N	55	55	52
Baseline mean (SD)	8.7 (1.9)	8.9 (2.2)	9.0 (1.9)
Overall LS mean (SE) change from Baseline[1]	-1.6 (0.3)	-1.4 (0.3)	-1.4 (0.3)
LS mean treatment difference from placebo (95% CI)	-0.2 (-1.0, 0.6)	-0.02 (-0.8, 0.8)	
p-value	0.611	0.957	
Other			
N	14	14	18
Baseline mean (SD)	7.7 (2.2)	8.5 (1.9)	8.1 (2.5)
Overall LS mean (SE) change from Baseline[1]	-2.7 (0.4)	-1.3 (0.4)	-0.4 (0.4)
LS mean treatment difference from placebo (95% CI)	-2.3 (-3.4, -1.2)	-1.0 (-2.0, 0.1)	
p-value	<0.001	0.077	

Source: Clinical Trial Report-Protocol Number BDP-AR-305 (24-Apr-2012) Table 14.2.4.4, pages 293-304
BDP HFA = Qnasl

Tables 17 and 18 summarize the subgroup analysis by race for study 306 in subjects with SAR for rTNSS ages 6 to 11 and 4 to 11, respectively. Tables 19 and 20 summarize the subgroup analysis by race for study 306 in subjects with SAR for iTNSS ages 6 to 11 and 4 to 11, respectively. There were numerically greater differences in Qnasl 80 mcg/day in all the race subgroups for both rTNSS and iTNSS.

Table 17. Subgroup Analysis for rTNSS by Race Over the First 6 Weeks of Treatment for Subjects 6 to 11 Years of Age Study 306 (FAS)

	BDP HFA 80 mcg		Placebo
White			
N	227		123
Baseline mean (SD)	8.6 (1.6)		8.5 (1.6)
Overall LS mean (SE) change from Baseline[1]	-2.4 (0.1)		-1.8 (0.2)
LS mean treatment difference from placebo (95% CI)		-0.6 (-1.1, -0.1)	
p-value		0.016	
Black			
N	53		18
Baseline mean (SD)	8.8 (1.6)		9.2 (1.6)
Overall LS mean (SE) change from Baseline[1]	-1.8 (0.3)		-1.2 (0.5)
LS mean treatment difference from placebo (95% CI)		-0.6 (-1.7, 0.5)	
p-value		0.293	
Other			
N	16		12
Baseline mean (SD)	8.6 (1.4)		8.7 (1.5)
Overall LS mean (SE) change from Baseline[1]	-2.6 (0.5)		-0.6 (0.6)
LS mean treatment difference from placebo (95% CI)		-2.0 (-3.5, -0.5)	
p-value		0.011	

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 15.8.1.9.1 Page 305-313, Table 15.8.1.9.2 page 314-322, Table 15.8.1.9.3 page 323-331
BDP HFA = Qnasl

Table 18 Subgroup Analysis for rTNSS by Race Over the First 6 Weeks of Treatment for Subjects 4 to 11 Years of Age Study 306 (FAS)

	BDP HFA 80 mcg		Placebo
White			
N	271		144
Baseline mean (SD)	8.6 (1.5)		8.6 (1.7)
Overall LS mean (SE) change from Baseline[1]	-2.4 (0.1)		-1.8 (0.2)
LS mean treatment difference from placebo (95% CI)		-0.5 (-1.0, -0.1)	
p-value		0.013	
Black			
N	63		25
Baseline mean (SD)	9.0 (1.5)		9.1 (1.7)
Overall LS mean (SE) change from Baseline[1]	-1.9 (0.3)		-1.4 (0.4)
LS mean treatment difference from placebo (95% CI)		-0.4 (-1.4, 0.5)	
p-value		0.376	
Other			
N	24		15
Baseline mean (SD)	8.5 (1.3)		8.5 (1.4)
Overall LS mean (SE) change from Baseline[1]	-3.1 (0.4)		-0.9 (0.6)
LS mean treatment difference from placebo (95% CI)		-2.1 (-3.5, -0.7)	
p-value		0.005	

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 15.8.1.10.1 Page 332-340, Table 15.8.1.10.2 page 341-349, Table 15.8.1.10.3 page 350-358
BDP HFA = Qnasl

Table 19. Subgroup Analysis for iTNSS by Race Over the First 6 Weeks of Treatment for Subjects 6 to 11 Years of Age Study 306 (FAS)

	BDP HFA 80 mcg		Placebo
White			
N	227		123
Baseline mean (SD)	7.8 (2.1)		7.7 (2.1)
Overall LS mean (SE) change from Baseline[1]	-2.1 (0.1)		-1.5 (0.2)
LS mean treatment difference from placebo (95% CI)		-0.5 (-1.0, -0.1)	
p-value		0.020	
Black			
N	53		18
Baseline mean (SD)	8.2 (2.0)		8.4 (2.5)
Overall LS mean (SE) change from Baseline[1]	-1.6 (0.3)		-1.1 (0.4)
LS mean treatment difference from placebo (95% CI)		-0.5 (-1.5, 0.6)	
p-value		0.377	
Other			
N	16		12
Baseline mean (SD)	7.9 (1.6)		7.7 (2.2)
Overall LS mean (SE) change from Baseline[1]	-2.3 (0.5)		-0.7 (0.6)
LS mean treatment difference from placebo (95% CI)		-1.6 (-3.2, -0.01)	
p-value		0.042	

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 15.10.1.9.1 Page 611-619, Table 15.10.1.9.2 page 620-628, Table 15.10.1.9.3 page 629-637
BDP HFA = Qnasl

Table 20 Subgroup Analysis for iTNSS by Race Over the First 6 Weeks of Treatment for Subjects 4 to 11 Years of Age Study 306 (FAS)

	BDP HFA 80 mcg		Placebo
White			
N	271		144
Baseline mean (SD)	7.9 (2.0)		7.8 (2.1)
Overall LS mean (SE) change from Baseline[1]	-2.1 (0.1)		-1.6 (0.2)
LS mean treatment difference from placebo (95% CI)		-0.5 (-0.9, -0.1)	
p-value		0.021	
Black			
N	63		25
Baseline mean (SD)	8.4 (1.9)		8.4 (2.4)
Overall LS mean (SE) change from Baseline[1]	-1.6 (0.2)		-1.3 (0.4)
LS mean treatment difference from placebo (95% CI)		-0.3 (-1.1, 0.6)	
p-value		0.495	
Other			
N	24		15
Baseline mean (SD)	8.0 (1.8)		7.2 (2.4)
Overall LS mean (SE) change from Baseline[1]	-2.8 (0.5)		-1.1 (0.6)
LS mean treatment difference from placebo (95% CI)		-1.6 (-3.1, -0.1)	
p-value		0.034	

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 15.10.1.10.1 Page 638-646, Table 15.10.1.10.2 page 647-655, Table 15.10.1.10.3 page 656-664
BDP HFA = Qnasl

Table 21 summarizes the additional subgroup analysis for rTNSS and iTNSS for study 306 in subjects with PAR for ages 4 to 5 years of age. There were numerically greater differences in Qnasl 80 mcg/day than placebo for both rTNSS and iTNSS.

Table 21 Subgroup Analysis by Treatment Group Over the First 6 Weeks of Treatment for Subjects 4 to 5 Years of Age Study 306 (FAS)

	BDP HFA 80 mcg N=62		Placebo N=31
rTNSS			
Baseline mean (SD)	8.8 (1.4)		8.9 (1.9)
Overall LS mean (SE) change from Baseline[1]	-2.6 (0.3)		-2.2 (0.4)
LS mean treatment difference from placebo (95% CI)		-0.4 (-1.3, -0.6)	
p-value		0.416	
iTNSS			
Baseline mean (SD)	8.4 (1.8)		8.0 (2.4)
Overall LS mean (SE) change from Baseline[1]	-2.5 (0.3)		-2.2 (0.4)
LS mean treatment difference from placebo (95% CI)		-0.3 (-1.3, 0.6)	
p-value		0.490	

Source: Clinical Trial Report-Protocol Number BDP-AR-306 (11-Feb-2014) Table 15.8.1.11 Page 359-367, Table 15.10.1.11 page 665-673
BDP HFA = Qnasl

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

The two studies that evaluated Qnasl for treating nasal symptoms associated with SAR and PAR demonstrated a statistically significant treatment effect. Even though there were concerns that the applicant did not impute missing data, missing data was not an issue. Of the 715 subjects randomized in study 305, only 3% dropped out. The most common reason for early termination in placebo and in Qnasl 160 mcg was other. There were only two drop outs due to AEs in each of Qnasl groups. Of the 547 subjects randomized in study 306, 10% dropped out of the study. Withdrawal by subject was the overall common reason for early termination in both treatment groups; 11 (3%) subjects in the Qnasl 80 mcg/day group and 8 (4%) in the placebo group. Therefore, missing data was not an issue with this application and the repeated measures ANCOVA which assumed data was missing at random was considered valid.

5.2. Conclusions and Recommendations

In study 305, analysis of the primary endpoint, change from baseline in the average of the subject-assessed AM and PM daily rTNSS over the 2-week treatment period for Qnasl 160 mcg/day and Qnasl 80 mcg/day both demonstrated a statistically significant treatment effect in favor of Qnasl over placebo in 6 to 11 years of age. The secondary endpoint, change from baseline in the average of the subject-assessed AM and PM daily iTNSS over the 2-week treatment period was consistent with the primary efficacy results, with a statistically significant treatment difference between Qnasl 160 mcg/day and placebo as well as Qnasl 80 mcg/day and placebo.

In study 306, analysis of the primary efficacy endpoint, change from baseline in the average of the subject-assessed AM and PM daily rTNSS over the first 6 weeks of treatment in subjects 6 to 11 years of age demonstrated a statistically significant treatment effect in favor of Qnasl 80 mcg/day over placebo. The secondary endpoints, which included rTNSS and iTNSS over the first 6 weeks of treatment for patients 4 to 11 years of age, also demonstrated a significant treatment effect in favor of Qnasl 80 mcg/day over placebo.

This statistical review of the two clinical studies supports the claim of the treatment of nasal symptoms of SAR and PAR in patients 4 years of age and older.

5.3. Comment on the Proposed Label

Based on review of the submitted data, below are the edits to the proposed label dated March 27, 2014 under Section14. Comments and suggestions are in **BOLD**.

14 CLINICAL STUDIES

14.1 Seasonal and Perennial Allergic Rhinitis

Adult and Adolescent Patients Aged 12 Years and Older: The efficacy and safety of QNASL Nasal Aerosol have been evaluated in 3 randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials of 2 to 6 weeks duration in adult and adolescent patients 12 years and older with symptoms of seasonal or perennial allergic rhinitis. The 3 clinical trials included one 2-week dose-ranging trial in patients with seasonal allergic rhinitis, one 2-week efficacy trial in patients with seasonal allergic rhinitis, and one 6-week efficacy trial in patients with perennial allergic rhinitis. The trials included a total of 1049 patients (366 males and 683 females). About 81% of patients were Caucasian and 17% African American, the mean age was approximately 38 years. Of these patients 521 received QNASL Nasal Aerosol 320 mcg once daily administered as 2 actuations in each nostril.

Assessment of efficacy was based on the total nasal symptom score (TNSS). TNSS is calculated as the sum of the patients' scoring of the 4 individual nasal symptoms (rhinorrhea, sneezing, nasal congestion, and nasal itching) on a 0 to 3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) as reflective (rTNSS) or instantaneous (iTNSS). rTNSS required the patients to record symptom severity over the previous 12 hours; iTNSS required the patients to record symptom severity over the previous 10 minutes. Morning and evening TNSS scores were averaged over the treatment period and the difference from placebo in the change from baseline rTNSS was the primary efficacy endpoint. The morning iTNSS reflects the TNSS at the end of the 24-hour dosing interval and is an indication of whether the effect was maintained over the 24-hour dosing interval.

Dose-Ranging Trial: The dose-ranging trial was a 2-week trial that evaluated the efficacy of 3 doses of beclomethasone dipropionate nasal aerosol (80, 160, and 320 mcg, once daily) in patients with seasonal allergic rhinitis. In this trial, only treatment with beclomethasone dipropionate nasal aerosol at the dose of 320 mcg/day resulted in statistically significant improvements compared with placebo in the primary efficacy endpoint, rTNSS (Table 3).

Table 3. Mean Changes from Baseline in Reflective Total Nasal Symptom Score Over 2 Weeks in Adult and Adolescent Patients with Seasonal Allergic Rhinitis (ITT Population)						
Treatment	**N**	**Baseline (SD)**	**LS Mean (SE) Change from Baseline**	**Difference From Placebo**		(b) (4)
				LS Mean	**95% CI**	
Beclomethasone dipropionate 320 mcg/day	122	9.17 (1.66)	-2.22 (0.18)	-0.63	-1.13, 0.13	
Beclomethasone dipropionate 160 mcg/day	123	9.24 (1.57)	-1.87 (0.18)	-0.29	-0.78, 0.21	
Beclomethasone dipropionate 80 mcg/day	118	9.33 (1.72)	-1.88 (0.18)	-0.29	-0.80, 0.21	
Placebo	123	8.98 (1.47)	-1.59 (0.18)			

The 320 mcg dose also demonstrated a statistically significant decrease in morning iTNSS than placebo, indicating that the effect was maintained over the 24-hour dosing interval.

Seasonal and Perennial Allergic Rhinitis Trials: In 2 randomized, double-blind, parallel-group, multicenter, placebo-controlled efficacy trials, once-daily treatment with QNASL Nasal Aerosol for 2 weeks in patients with seasonal allergic rhinitis and for 6 weeks in patients with perennial allergic rhinitis resulted in statistically significant greater decreases from baseline in the rTNSS and morning iTNSS than placebo (Table 4).

Table 4. Mean Changes From Baseline in Reflective and Instantaneous Total Nasal Symptom Scores in Adult and Adolescent Patients with Seasonal or Perennial Allergic Rhinitis (ITT Population)						
Treatment	**N**	**Baseline (SD)**	**LS Mean (SE) Change from Baseline**	**Difference From Placebo**		(b) (4)
				LS Mean	**95% CI**	
Seasonal Allergic Rhinitis						
Reflective Total Nasal Symptom Scores (rTNSS)						
Beclomethasone dipropionate 320 mcg/day	167	9.6 (1.51)	-2.0 (0.16)	-0.91	-1.3, -0.5	
Placebo	171	9.5 (1.54)	-1.0 (0.15)			
Instantaneous Total Nasal Symptom Scores (iTNSS)						
Beclomethasone dipropionate 320 mcg/day	167	9.0 (1.74)	-1.7 (0.15)	-0.92	-1.3, -0.5	
Placebo	171	8.7 (1.81)	-0.8 (0.15)			

Table 4. Mean Changes From Baseline in Reflective and Instantaneous Total Nasal Symptom Scores in Adult and Adolescent Patients with Seasonal or Perennial Allergic Rhinitis (ITT Population)						
Perennial Allergic Rhinitis						
Reflective Total Nasal Symptom Scores (rTNSS)						(b) (4)
Beclomethasone dipropionate 320 mcg/day	232	8.9 (1.70)	-2.5 (0.14)	-0.84	-1.2, -0.5	
Placebo	234	9.0 (1.73)	-1.6 (0.14)			
Instantaneous Total Nasal Symptom Scores (iTNSS)						
Beclomethasone dipropionate 320 mcg/day	232	8.1 (1.98)	-2.1 (0.13)	-0.78	-1.1, -0.4	
Placebo	234	8.3 (1.96)	-1.4 (0.13)			

Pediatric Patients 4 to 11 Years of Age: The efficacy and safety of QNASL Nasal Aerosol have been evaluated in 2 randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials of 2 to 12 weeks duration in pediatric patients 4 to 11 years of age with symptoms of seasonal or perennial allergic rhinitis. The 2 clinical trials included one 2-week dose-ranging trial in patients with seasonal allergic rhinitis (6 - 11 years of age), and one 12-week efficacy trial in patients with perennial allergic rhinitis (4 - 11 years of age). The trials included a total of 1255 patients (680 males and 575 females). About 73% of patients were Caucasian and 20% African American, the mean age was approximately 8 years for one study and 9 years for the second study. Of these patients 596 received QNASL Nasal Aerosol 80 mcg once daily administered as 1 actuation of QNASL 40 mcg Nasal Aerosol in each nostril.

Assessment of efficacy was based on the total nasal symptom score (TNSS) as described in adult and adolescents efficacy studies.

Dose-Ranging Seasonal Allergic Rhinitis Trial: The dose-ranging trial was a 2-week trial that evaluated the efficacy of 2 doses of beclomethasone dipropionate nasal aerosol (80 and 160mcg, once daily) in patients with seasonal allergic rhinitis. In this trial, treatment with beclomethasone dipropionate nasal aerosol at the dose of 80 mcg/day resulted in statistically significant improvements compared with placebo in the primary efficacy endpoint, rTNSS (**Table 5**).

Table 5. Mean Changes from Baseline in Reflective and Instantaneous Total Nasal Symptom Scores Over 2 Weeks in Pediatric Patients with Seasonal Allergic Rhinitis (ITT Population)						
Treatment	**N**	**Baseline (SD)**	**LS Mean (SE) Change from Baseline**	**Difference From Placebo**		(b) (4)
				LS Mean	**95% CI**	
Reflective Total Nasal Symptom Scores (rTNSS)						
Beclomethasone		8.9 (1.62)	-1.9 (0.14)	-0.71	-1.1, -0.3	

Table 5. Mean Changes from Baseline in Reflective and Instantaneous Total Nasal Symptom Scores Over 2 Weeks in Pediatric Patients with Seasonal Allergic Rhinitis (ITT Population)						(b) (4)
dipropionate 80 mcg/day	**238**					
Beclomethasone dipropionate 160 mcg/day	241	9.0 (1.71)	-2.0 (0.14)	-0.76	-1.1, -0.4	
Placebo	234	9.0 (1.70)	-1.2 (0.14)	-	-	
Instantaneous Total Nasal Symptom Scores (iTNSS)						
Beclomethasone dipropionate 80 mcg/day	238	8.1 (1.99)	-1.6 (0.13)	-0.63	-1.0, -0.3	
Beclomethasone dipropionate 160 mcg/day	241	8.1 (2.13)	-1.7 (0.13)	-0.73	-1.1, -0.4	
Placebo	234	8.2 (2.10)	-1.0 (0.13)	-	-	

The 80 mcg daily dose also demonstrated a statistically significant decrease in morning iTNSS than placebo, indicating that the effect was maintained over the 24-hour dosing interval. Based on the results from the dose ranging trial, 80 mcg once daily was chosen as dose in pediatric patients.

Perennial Allergic Rhinitis Trial: In a randomized, double-blind, parallel-group, multicenter, placebo-controlled efficacy trial, treatment with QNASL Nasal Aerosol 80 mcg once daily (b) (4) in patients with perennial allergic rhinitis resulted in statistically significant greater decreases from baseline in the rTNSS than placebo (b) (4) the first six weeks of treatment (b) (4) (**Table 6**).

Table 6. Mean Changes from Baseline in Reflective Total Nasal Symptom Score Over 6 Weeks in Pediatric Patients 6 to 11 Years of Age with Perennial Allergic Rhinitis (FAS)						
Treatment	**N**	**Baseline (SD)**	**LS Mean (SE) Change from Baseline**	**Difference From Placebo**		(b) (4)
				LS Mean	**95% CI**	
Reflective Total Nasal Symptom Scores (rTNSS)						
Beclomethasone dipropionate 80 mcg/day	296	8.6 (1.56)	-2.26 (0.12)	-0.66	-1.08,-0.24	
Placebo	153	8.6 (1.60)	-1.60 (0.17)	-	-	
Instantaneous Total Nasal Symptom Scores (iTNSS)						
Beclomethasone	296	7.9 (2.05)	-1.98 (0.12)	-0.58	-0.99, -0.18	

Table 6. Mean Changes from Baseline in Reflective Total Nasal Symptom Score Over 6 Weeks in Pediatric Patients 6 to 11 Years of Age with Perennial Allergic Rhinitis (FAS)						
dipropionate 80 mcg/day						
Placebo	153	7.8 (2.12)	-1.39 (0.17)	-	-	-

FAS=full analysis set

(b) (4)

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/s/

KIYA HAMILTON
11/20/2014

DAVID M PETULLO
11/20/2014