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:	NDA 21861/SE5 S-002
Drug Name:	Patanase (Olopatadine Hydrochloride) Nasal Spray 0.6%
Indication(s):	Seasonal allergic rhinitis (SAR)
Applicant:	Alcon
Date(s):	Stamp date: June 1, 2009
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Keywords: NDA review, Clinical Studies, Pediatric Studies

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1.1 Conclusions and Recommendations

Patanase (Olopatadine Hydrochloride) nasal spray 0.6%: 665mcg was approved for management and treatment of the symptoms of seasonal allergic rhinitis (SAR) including itchy nose, runny nose, sneezing, nasal congestion in patients 12 years of age or older on April 15, 2008. The objective of this NDA supplement is to obtain a pediatric indication for patients (b) (4) to 11 years of age. The proposed dose for pediatric population is one spray per nostril twice daily, half of the approved adult dose. My statistical review supports the claim that Olopatadine HCl nasal spray 0.6% administered as 1 spray per nostril twice daily (B.I.D.) is statistically superior to the corresponding vehicle control in patients 6 to less than 12 years of age. No efficacy data was collected in patients 2 to less than 6 years of age. From the statistics stand point of view, there is enough evidence to support approval of Patanase for patients 6 to less than 12 years of age.

1.2 Brief Overview of Clinical Studies

Two pediatric studies, C-04-20 for safety and efficacy and C-03-51 for safety and PK, were done before the original NDA was approved. Both studies used formulation of Olopatadine HCl nasal spray that contained povidone as an excipient. The NDA was approved for reformulated drug product of Olopatadine HCl nasal spray, which does not contain povidone. After the reformulation of drug, two additional pediatric studies, C-07-01 for safety and efficacy and C-07-02 for safety and PK, were done in response to the written request for pediatric studies. Both studies used the marketing formulation, which does not contain povidone. My statistical review focuses on studies C-07-01 and C-04-20 for efficacy evaluation.

1.3 Statistical Issues and Findings

The primary efficacy endpoint for both study C-07-01 and study C-04-20 was the percent change from baseline in reflective total nasal symptom score (rTNSS), defined as the average of the AM and PM reflective severity scores for the sum of the assessments of the patient's runny nose, stuffy nose, itchy nose, and sneezing.

In study C-07-01, Olopatadine HC1 nasal spray 0.6%, administered as 1 or 2 sprays per nostril B.I.D., is superior to the corresponding dose of Olopatadine HCl nasal spray vehicle for the percent change from baseline in rTNSS. In pediatric patients, the dose approved for adult patients, 2 sprays per nostril twice daily, did not show added benefit comparing to the proposed dose for pediatric patients, 1 spray per nostril twice daily.

In study C-04-20, Olopatadine HC1 nasal spray 0.6% and 0.4% 1 spray per nostril B.I.D. showed numerical but not statistical superiority over the vehicle control for the percent change of rTNSS from baseline.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Patanase (Olopatadine Hydrochloride) nasal spray 0.6%: 665mcg was approved for management and treatment of the symptoms of seasonal allergic rhinitis (SAR) including itchy nose, runny nose, sneezing, nasal congestion in patients 12 years of age or older on April 15, 2008. The objective of this NDA supplement is to obtain a pediatric indication for patients (b) (4) to 11 years of age. The proposed dose for pediatric population is one spray per nostril twice daily, half of the approved adult dose.

Allergic rhinitis is an allergen-induced inflammatory response, a highly prevalent disorder and is one of the most common diseases encountered by primary care physicians. At the very least, the symptoms of the disease are troublesome to the patient, and under certain circumstances may lead to the development of more life threatening diseases such as asthma.

Olopatadine is both a selective antihistamine capable of antagonizing histamine and an inhibitor of release of histamine. Antihistamines are effective in reducing the nasal and ocular signs and symptoms of SAR and are recommended for use as first-line therapy.

2.1.2 History of drug development

The original NDA was submitted on December 24, 2004. A not approvable action letter was issued on October 27, 2005. The original formulation of Olopatadine HCl nasal spray contained povidone as an excipient. One of the main deficiencies identified in the original submission was the unfavorable safety profile of the povidone-containing formulation. It was found to cause nasal irritation and serious damage to the nasal mucosa. In the action letter, the division asked the applicant to reformulate the drug product to lesson the nasal toxicity and perform studies to confirm the reformulation has its intended effects.

There were various meetings between the division and applicant during November 2005 to June 2006 to discuss the path forward. The applicant reformulated the drug product and sent in the complete response to the not approvable action letter on September 27, 2007. The reformulated Olopatadine HCl nasal spray was approved on April 15, 2008 for use in patients of 12 years of age or older.

Two pediatric studies, C-04-20 for safety and efficacy and C-03-51 for safety and PK, were done before the not approvable action letter was issued, thus both study C-04-20 and C-03-51 used the povidone-containing formulation. After the reformulation of the drug product, the applicant submitted the proposed pediatric study request to IND 60,116 on March 22, 2007. The written request (WR) for pediatric studies (C-07-01 for safety and efficacy and C-07-02 for safety and PK) was issued on June 29, 2007. Clinical study C-07-01 was submitted to IND 60,116 on September 6, 2007; clinical study C-07-02 was submitted to IND 60, 116 on July 18, 2008. The pediatric supplement to NDA 21-861 was submitted on June 1, 2009.

2.1.3 Specific studies reviewed

The summary of all clinical studies the applicant submitted to support this application was given in section 5.2 (Tabular listing of all clinical studies) of the study report. My statistical review focuses on study C-07-01 and study C-04-20 for efficacy.

2.2 Data Sources

All data was supplied by the applicant on CD in SAS version 9 format. The final study reports were submitted in paper format and achieved in the document room. The information needed for this review was contained in modules 1, 2.5, 2.7, and 5.3.5.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study C-07-01

Study design and endpoints

Study C-07-01 was a study conducted in response to written request to evaluate the safety and efficacy of Olopatadine HCl nasal spray in pediatric patients (6 to <12 years of age). It was a phase 3, randomized, double blind, parallel group, vehicle-controlled, multi-center study. The study had four treatment arms: Olopatadine 0.6% 1 spray per nostril B.I.D., vehicle control 1 spray per nostril B.I.D., Olopatadine 0.6% 2 sprays per nostril B.I.D., and vehicle control 2 sprays per nostril B.I.D. The Olopatadine HCl nasal spray formulation used in this study did not contain povidone. The randomization was stratified by age groups, 6 to <9 years and 9 to <12 years. One hundred and seventy-three clinical sites in US participated in this study.

The study was conducted from September 2007 to November 2008. The study period consisted of a vehicle run-in phase and a randomized treatment phase. The vehicle run-in phase was 4 to 16 days in duration and was only blinded to patients. The run-in study medication ─ 1 spray of vehicle per nostril was administered twice daily. Patients were encouraged to maintain a 12-hour dosing frequency between the AM (awakening) and PM (bedtime) doses. Parents/caregivers were instructed to complete the symptom ratings twice daily, prior to dosing with the run-in study medication. Symptoms, including runny nose, stuffy nose, itchy nose, and sneezing, were collected for reflective (how the patient felt since the last symptom assessment) and instantaneous (how the patient felt at the time) severity scores. For each symptom, the severity was assessed using the 4-unit rating scale (0=none, 1=mild, 2=moderate, 3=sever). At the end of the run-in phase, patients' nasal symptoms scores were reviewed. Patients with a sum of reflective total nasal symptom score (rTNSS) greater than or equal to 36 units from 3 of the 4 calendar days immediately prior to the end of run-in phase visit were eligible to enter the randomization phase. During the randomized treatment phase, the study medication was administered and assessments were collected in the same way as that in the vehicle run-in phase. Patients received study medication for up to 23 days. The randomized treatment phase was double blinded. There were 4 scheduled office or phone visits during the whole duration of the study: visit 1 (screening), visit 2 (randomization, day 1, between 4 and 16 days after visit 1), visit 3 (telephone contact only, 7 ± 1 day from visit 2) and visit 4 (16 + 7 days from visit 2).

The primary efficacy endpoint was the percent change from baseline in rTNSS, defined as the average of the AM and PM reflective severity scores for the sum of the assessments of the patient's runny nose, stuffy nose, itchy nose, and sneezing. The secondary efficacy variables include: percent change from baseline in the instantaneous total nasal symptoms score (iTNSS), percent change from baseline in the reflective individual severity score, percent change from baseline in the instantaneous individual severity score, mean change from baseline in the rTNSS, mean change from baseline of the overall pediatric rhinoconjunctivitis quality-of-life questionnaire (PRQLQ).

Patient disposition, demographic and baseline characteristics

Patients with age greater than 6 years and less than 12 years and with at least a two-year history of SAR were recruited for the study. A total of 2388 patients were screened for possible study participation and were given the vehicle spray to administer as run-in treatment. Of these, 1200 patients were screen failures due to reasons including adverse event, lost to follow-up, decision unrelated to an adverse event, protocol violation, insufficient diary score, and other. The remaining 1188 patients were enrolled into the randomized treatment period. The summary of the patient disposition in the randomization phase is given in Table 1.

Intent-to-treat (ITT) population was defined as patients who received randomized study medication and had at least one on-therapy visit; with the exception of two patients that were included, but were found to have been incorrectly enrolled due to out of range bottle weight for the vehicle run-in treatment, thus the two patients were not administered test article. Per protocol (PP) population was defined as all patients who received randomized study medication, had at least one on-therapy visit, met inclusion and exclusion criteria, and completed the study with no major protocol violation.

The primary analysis and all the results reported in this review were based on ITT population. Patients who belonged to ITT population, but with no complete day (AM and PM) of diary data during the randomized treatment phase were not included in the analysis. This was a practical result of the LOCF method specified for missing data imputation.

Table 1 Study C-07-01 patient disposition.

		Olo 0.6% 1 spray	Veh 1 spray	Olo 0.6% 2 sprays	Veh 2 sprays
Randomized		298	297	296	297
Treated		298	297	296	297
ITT		298	297	296	297
No complete day diary data in the randomized phase		4	3	3	4
PP		281	283	288	283
Discontinuation	Total	17	14	8	14
	Adverse event	7	4	5	4
	Lost to follow-up	2	1	1	0
	Decision unrelated to AE	1	2	0	1
	Treatment failure	3	4	2	8
	Protocol violation	1	3	0	0
	Other	3	0	0	1

The demographic and baseline characteristics are summarized in Table 2. The study patients were mainly Caucasians (70%~75%) and not Hispanic (80%~83%). There were more children in the age group of 9 to <12 years (59%) than children in the age group of 6 to <9 years (41%) and more male (56%~59%) than female (41%~44%). Across treatment arms, patient populations were well balanced in gender, age, race, and ethnicity.

Table 2 Study C-07-01 summary of demographic and baseline characteristics.

		Olo 0.6% 1 spray	Veh 1 spray	Olo 0.6% 2 sprays	Veh 2 sprays
Gender	Male	168 (56%)	172 (58%)	174 (59%)	173 (58%)
	Female	130 (44%)	125 (42%)	122 (41%)	124 (42%)
Age	Mean (std)	8.8 (1.6)	8.8 (1.7)	8.8 (1.6)	8.8 (1.6)
	6-8 years	121 (41%)	121 (41%)	121 (41%)	121 (41%)
	9-12 years	177 (59%)	176 (59%)	175 (59%)	175 (59%)
Race	White	218 (72%)	208 (70%)	221 (75%)	217 (73%)
	Black	48 (16%)	62 (21%)	50 (17%)	57 (19%)
	Asian	6 (2%)	6 (2%)	6 (2%)	10 (3%)
	Native Hawaiian	0 (0%)	0 (0%)	1 (0.3%)	2 (0.7%)
	American Indian	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
	Other	20 (7%)	14 (5%)	10 (3%)	9 (3%)
	Multi-racial	5 (2%)	7 (2%)	8 (3%)	2 (0.7%)
Ethnicity	Hispanic	59 (20%)	54 (18%)	59 (20%)	49 (17%)
	Not Hispanic	239 (80%)	243 (82%)	237 (80%)	248 (83%)

Statistical methodologies

The primary as well as the secondary efficacy endpoints were analyzed by analysis of covariance (ANCOVA) model with treatment, the baseline variable of interest and stratification on age as covariates.

In the event of missing data, the last observation carried forward (LOCF) was used. For the diary entries, LOCF was performed separately for the vehicle run-in phase and the randomized treatment phase. Baseline values were not to be carried forward into the randomization phase. LOCF was utilized in order to obtain 14 complete days of randomized diary data for each patient. If a patient had missing on-therapy diary data (i.e. all on-therapy data was missing or no single complete day of diary data), the patient was not included in the analysis because no rTNSS was available in the randomization phase of the study.

Results and conclusions

The result of analysis on the primary efficacy endpoint is summarized in Table 3. Olopatadine HC1 nasal spray 0.6%, administered as 1 or 2 sprays per nostril B.I.D., is superior to the corresponding dose of Olopatadine HCl nasal spray vehicle for the percent change from baseline in rTNSS. The proposed dose for Olopatadine HC1 nasal spray 0.6% in pediatric patients is 1 spray per nostril twice daily. After two weeks treatment, there was a 2.2 unit (mean change) or 25% (percent change) reduction of rTNSS from baseline in patients treated with Olopatadine HCl nasal spray 0.6%, administered as 1 spray per nostril B.I.D. The reduction in the corresponding vehicle control arm was 1.7 unit (mean change) or 18% of rTNSS. The difference between Olopatadine HC1 nasal spray 0.6%, administered as 1 spray per nostril B.I.D., and the corresponding vehicle control is statistically significant (p=0.007). The dose of 2 sprays per

nostril B.I.D. was also studied to show the efficacy of adult dose in pediatric patients. No added benefit was observed for the increased dose.

Table 3 Study C-07-01 summary of analysis on the primary efficacy endpoint (rTNSS).

	Olo 0.6% 1 spray	Veh 1 spray	Olo 0.6% 2 sprays	Veh 2 sprays
N	294	294	293	293
Baseline mean (Std.)	9.0 (1.8)	9.1 (1.7)	9.2 (1.6)	8.8 (1.8)
Treatment phase mean (Std.)	6.8 (2.6)	7.4 (2.3)	6.7 (2.5)	6.9 (2.4)
Mean change from baseline	-2.2	-1.7	-2.5	-1.9
Percent change from baseline	-25%	-18%	-26%	-21%
P-value *	0.0007		0.012	

- * P-value is the result from ANCOVA based on percent change from baseline.
- The means reported in the table is the average of rTNSS without any adjustment.

The results of analysis on the secondary efficacy endpoints are summarized in Table 4.

Table 4 Study C-07-01 summary of analysis on the secondary efficacy endpoints.

	Olo 0.6% 1 spray	Veh 1 spray	Diff.	P value	Olo 0.6% 2 spray	Veh 2 spray	Diff.	P value
Percent change from baseline								
rTNSS	-25%	-18%	-7%	0.001	-26%	-21%	-5%	0.012
r.runny.nose	-24%	-17%	-7%	0.004	-25%	-20%	-4%	0.082
r.Itchy.nose	-27%	-16%	-11%	0.001	-28%	-20%	-8%	0.005
r.stuffy.nose	-18%	-15%	-3%	0.251	-22%	-19%	-3%	0.176
r.sneeze	-31%	-18%	-13%	<0.001	-26%	-23%	-3%	0.283
iTNSS	-22%	-14%	-8%	<0.001	-22	-19%	-3%	0.217
i.runny.nose	-18%	-8%	-10%	0.016	-21%	-16%	-5%	0.160
i.Itchy.nose	-22%	-10%	-12%	0.002	-22%	-16%	-6%	0.053
i.stuffy.nose	-17%	-11%	-5%	0.014	-16.6%	-17.3%	0.7%	0.809
i.sneeze	-28%	-10%	-18%	<0.001	-24%	-17%	-7%	0.140
Mean change from baseline								
rTNSS	-2.3	-1.7	-0.6	0.002	-2.4	-2.0	-0.4	0.021
PRQLQ	-0.7	-0.4	-0.3	0.001	-0.63	-0.57	-0.06	0.464

- The means reported in the table is the LS mean of ANCOVA with adjustment on age group and baseline variable of interest.

Olopatadine HCl nasal spray 0.6%, administered as 1 spray per nostril B.I.D., is superior to the corresponding vehicle control in all the secondary efficacy endpoints except on one individual symptom score, reflective stuffy nose.

Olopatadine HCl nasal spray 0.6%, administered as 2 sprays per nostril B.I.D., is not superior to the corresponding vehicle control for all the secondary efficacy endpoints, with two exceptions: mean change in rTNSS and percent change in reflective individual symptom score on itchy nose. In general, Olopatadine treatment was numerically favored compared to the corresponding

vehicle control. However, for the instantaneous individual symptom score on stuffy nose, vehicle control had a numerical higher reduction compared to Olopatadine HCl nasal spray 0.6%, administered as 2 sprays per nostril B.I.D. These results further confirmed that the increased dose did not offer added benefit for the pediatric patients.

3.1.2 Study C-04-20

Study design and endpoints

Study C-04-20 was a study conducted during March 2005 to August 2005 to evaluate the safety and efficacy of Olopatadine HCl nasal spray in pediatric patients (6 to <12 years of age). It was not a study conducted in response to the written request. The design of study C-04-20 was similar to that of study C-07-01, with two exceptions: a) there were 3 treatment arms in the study, Olopatadine 0.6% 1 spray per nostril B.I.D., Olopatadine 0.4% 1 spray per nostril B.I.D., vehicle 1 spray per nostril B.I.D.; b) the randomization was not stratified by age groups. The Olopatadine HCl nasal spray formulation used in the study contained povidone. There were 52 clinical sites participated in this study. All of them are in the United States. The efficacy endpoints in study C-04-20 were the same as those in study C-07-01. In the clinical study report, the efficacy summaries on individual symptom scores were separated by AM and PM. In this review, efficacy summaries on individual symptom scores are on daily average of AM and PM measures.

Patient disposition, demographic and baseline characteristics

The patient population in study C-04-20 was similar to that in study C-07-01. Eight hundred twenty patients were enrolled in the study and were given the vehicle run-in treatment. Of the patients enrolled, 295 were screen failures. The remaining 525 patients were randomized to treatment, received randomized study drug, and had at least one on-therapy visit. All of these patients were evaluable for the ITT analysis, 450 were evaluable for the PP analysis. The ITT and PP population were defined in the same way as that in study C-07-01. The summary of patient disposition is given in Table 5.

Table 5 Study C-04-20 patient disposition.

		Olo 0.6% 1 spray	Olo 0.4% 1 spray	Veh 1 spray
Randomized		173	176	176
Treated		173	176	176
ITT		173	176	176
No complete day diary data in the randomized phase		1	0	1
PP		142	152	156
Excluded	Total	31	24	20
	Inclusion criteria	11	11	11
	Exclusion criteria	14	6	4
	Excluded concomitant medication	6	6	5
	Other	0	1	0

The demographic and baseline characteristic are summarized in Table 6. The patient population in study C-04-20 was also dominated by Caucasians (69%~74%). There were also more children in the age group 9 to <12 years (63%~70%) than in age group 6 to <9 years (30%~37%), and more males (57~62%) than females (38%~43%). Ethnicity (Hispanic vs. not-Hispanic) information was not collected in this study.

Table 6 Study C-04-20 summary of demographic and baseline characteristics.

		Olo 0.6% 1 spray	Olo 0.4% 1 spray	Veh 1 spray
Gender	Male	101 (58%)	100 (57%)	110 (62%)
	Female	72 (42%)	76 (43%)	66 (38%)
Age	Mean (Std.)	9.0 (1.7)	9.2 (1.5)	8.9 (1.6)
	6 to <9 years	61 (35%)	53 (30%)	65 (37%)
	9 to <12 years	112 (65%)	123 (70%)	111 (63%)
Race	White	121 (70%)	131 (74%)	121 (69%)
	Black	23 (13%)	15 (9%)	19 (11%)
	Asian	5 (3%)	5 (3%)	0 (0%)
	Hispanic	19 (11%)	21 (12%)	26 (15%)
	Other	5 (3%)	4 (2%)	10 (6%)

Statistical methodologies

The missing data was imputed by LOCF, the same way as that in study C-07-01. A Dunnett's t-test was used to compare changes from baseline between the Olopatadine treatments and placebo for the primary as well as the secondary efficacy endpoints. There was no adjustment for covariates.

Results and conclusions

The summary of analysis on the primary efficacy endpoint is given in Table 7. The results showed numerical but not statistical superiority of Olopatadine 0.4% and 0.6% 1 spray per nostril B.I.D. over vehicle control for the percent change of rTNSS from baseline.

Table 7 Study C-04-20 summary of analysis on the primary efficacy endpoint (rTNSS).

	Olo 0.6% 1 spray	Olo 0.4% 1 spray	Veh 1 spray
N	172	176	175
Baseline mean (Std.)	8.3 (1.6)	8.1 (1.7)	8.2 (1.5)
Treatment phase mean (Std.)	6.5 (2.5)	6.4 (2.2)	6.7 (2.2)
Mean change from baseline	-1.8	-1.7	-1.5
Percent change from baseline	-21%	-21%	-17%
P-value (Dunnett's T test)	0.28	0.29	---
P-value (simple pair wise T test)	0.17	0.16	---

- * P-values are based on percent change from baseline.
- The means reported in this table is the average of rTNSS without any adjustment.

The summary of analysis on the secondary efficacy endpoints is given in Table 8. In general, there was numerical but not statistical superiority of Olopatadine 0.4% and 0.6% 1 spray per nostril B.I.D. over vehicle control for the various secondary efficacy endpoints. There were three exceptions: a) Olopatadine 0.6% 1 spray per nostril B.I.D. was statistically superior over vehicle control for change of PRQLQ from baseline after two weeks treatment; b) vehicle control was numerically favored over Olopatadine 0.6% 1 spray per nostril B.I.D. for one instantaneous individual symptoms score, itchy nose; c) vehicle control was numerically favored over Olopatadine 0.4% 1 spray per nostril B.I.D. for two reflective individual symptoms scores, runny nose and itchy nose.

Table 8 Study C-04-20 summary of analysis on the secondary efficacy endpoints.

	Olo 0.6% 1 spray	Veh 1 spray	Diff.	P-DT	P-PWT	Olo 0.4% 1 spray	Veh 1 spray	Diff.	P-DT	P-PWT
Percent change from baseline										
rTNSS	-21%	-17%	-4%	0.282	0.168	-21%	-17%	-4%	0.291	0.162
r.runny.nose	-20%	-16%	-4%	0.541	0.324	-15%	-16%	0.4%	0.993	0.920
r.Itchy.nose	-17%	-17%	-0.2%	0.999	0.974	-16%	-17%	0.7%	0.989	0.897
r.stuffy.nose	-13%	-11%	-2%	0.820	0.602	-13%	-11%	-2%	0.859	0.621
r.sneeze	-25%	-19%	-6%	0.246	0.149	-28%	-19%	-9%	0.078	0.049
iTNSS	-17%	-12%	-5%	0.278	0.157	-17%	-12%	-5%	0.241	0.148
i.runny.nose	-13%	-8%	-5%	0.630	0.375	-9%	-8%	-0.5%	0.994	0.934
i.Itchy.nose	-8%	-8%	0.2%	1.000	0.984	-13%	-8%	-5%	0.777	0.509
i.stuffy.nose	-12%	-10%	-2%	0.700	0.459	-11%	-10%	-1%	0.904	0.704
i.sneeze	-16%	-9%	-7%	0.708	0.501	-21%	-9%	-11%	0.363	0.234
Mean change from baseline										
rTNSS	-1.7	-1.4	-0.3	0.334	0.168	-1.7	-1.4	-0.3	0.350	0.162
PRQLQ	-0.6	-0.3	-0.3	0.005	0.005	-0.4	-0.3	-0.07	0.674	0.407

- P-DT: p value from the Dunnett's T test.
- P-PWT: p value from the simple pair wise T test.

3.2 Evaluation of Safety

The evaluation of safety was conducted by Dr. Peter Starke. No special analysis on safety evaluation was requested by the clinical review team. Reader is referred to Dr. Peter Starke's review for this section.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The summary of subgroup analysis on the primary efficacy endpoint in the two studies is given in Figure 1 and Figure 2.

The subgroups in Figure 1 are categorized by gender, age groups, race, and ethnicity based on the categories summarized in Table 2. Since most patients randomized in study C-07-01 were Caucasians and African Americans, the subgroup analysis on race was only shown on these two groups. The results presented in the plots are from the ANCOVA model, similar to the one used for primary efficacy analysis, with the additional covariate on the subgroups being analyzed.

In general, the subgroup analysis results are consistent with the results of overall population. In black or African American patients, there was barely no difference between the 2 sprays treatment groups.

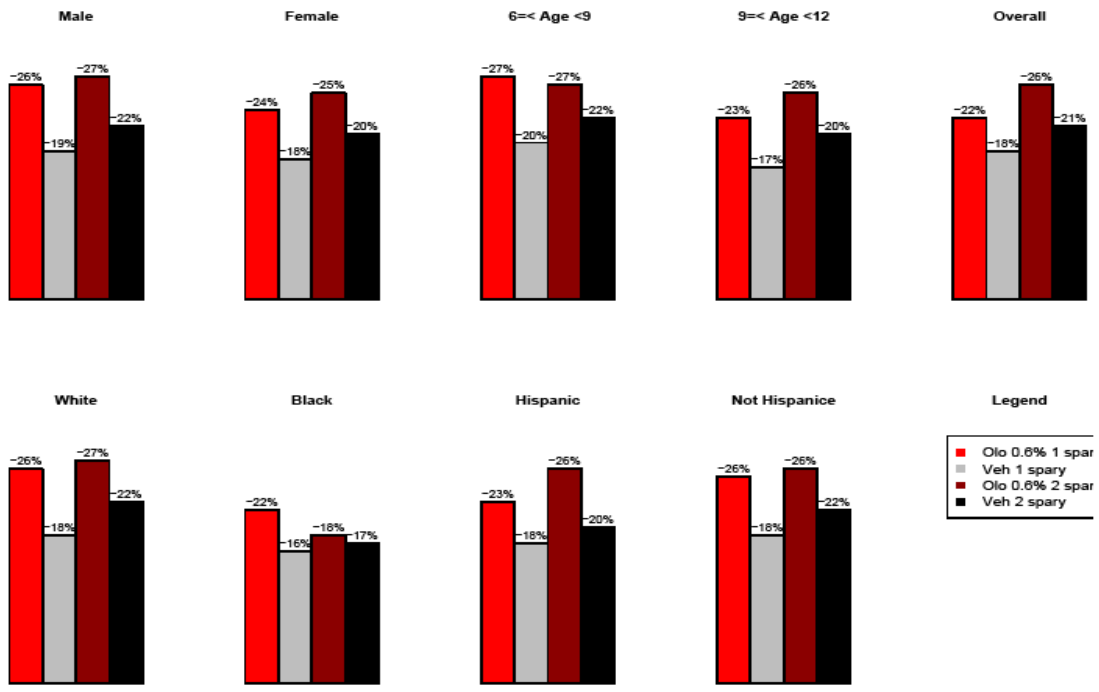

Figure 1 Study C-07-01 summary of subgroup analysis.

The subgroups in Figure 2 are categorized by gender, age groups, and race based on the categories summarized in Table 6. Since most patients randomized in study C-04-20 were Caucasians and African Americans, the subgroup analysis on race was only shown on these two groups. The results presented in the plots are from the ANCOVA model with treatment as fixed effect and additional covariate adjustment on the subgroups being analyzed.

In general, the subgroup analysis results are consistent with the results of overall population. In black or African American patients, females, and patients with age from 6 to less than 9 years old, there was a reversed numerical trend in Olopatadine 0.6% and 0.4% 1 spray treatment arms. The lower dose was favored compared to the higher dose.

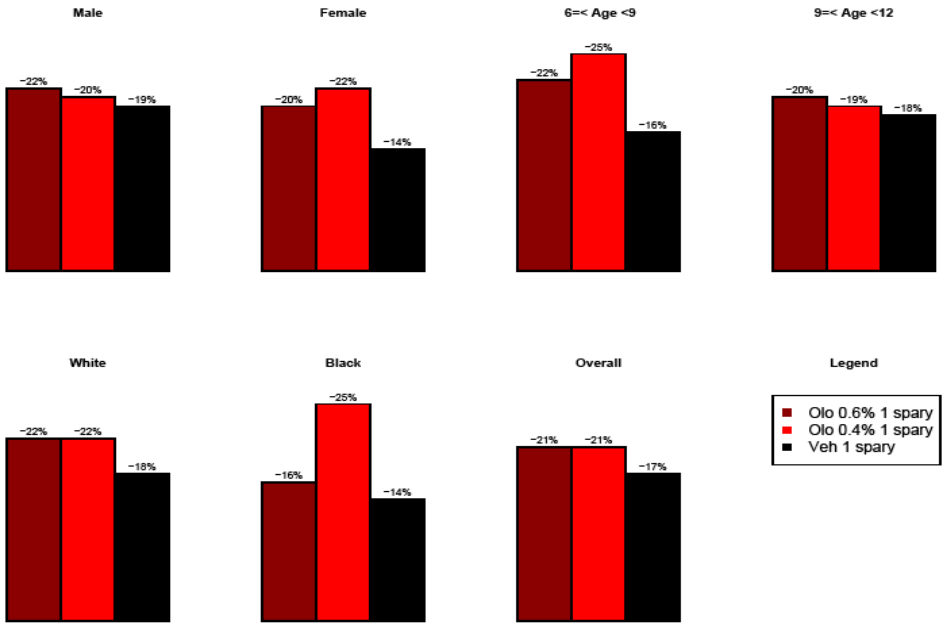

Figure 2 Study C-04-20 summary of subgroup analysis.

5 COMMENTS ON LABEL

The suggestions on the labeling revision are listed below. For section 14 Clinical studies,

1. The definition of primary efficacy endpoint in the label is wrong.

   "The primary efficacy endpoint was the difference from placebo in the percent change from baseline in the (b) (4) *of morning and evening reflective total nasal symptom score (rTNSS) averaged for the 2 –week treatment period."*

   The definition of rTNSS should be the average of morning and evening reflective total nasal symptom score, but not the sum of morning and evening reflective total nasal symptom score.

2. Analysis methods used to generate the results reported in Table 1 (Dunnett's T test) and Table 2 (ANCOVA) in section 14 Clinical studies should be included in the label.

SIGNATURES/DISTRIBUTION LIST

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Date: November 9, 2009

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21861	SUPPL-2	ALCON INC	PATANASE NASAL SPRAY (OLOPATADINE HCL)
NDA-21861	SUPPL-5	ALCON INC	PATANASE NASAL SPRAY (OLOPATADINE HCL)

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/s/

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