CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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/BLA #:	NDA 209-022
Drug Name:	XHance (Fluticasone Propionate)
Indication(s):	Treatment of nasal (b) (4)
Applicant:	OptiNose US, Inc.
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Biometrics Division:	II
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Keywords:	NDA review, Clinical Studies

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1. EXECUTIVE SUMMARY

OptiNose US, Inc. submitted a New Drug Application (NDA) for OPN-375 (fluticasone propionate) seeking an indication for the treatment of nasal (b) (4) in patients 18 years of age or older. Two confirmatory phase 3 efficacy studies, Study OPN-FLU-NP-3101 (3101) and Study OPN-FLU-NP-3102 (3102), were conducted to demonstrate the efficacy of OPN-375 in comparison to placebo.

Study 3101 and Study 3102 had identical study design and efficacy analyses. Both were 16-week, randomized, double-blind, placebo-controlled, parallel group, and multicenter study evaluating the efficacy and safety of intranasal administration of three doses of OPN-375 (93, 186, and 372 mcg twice daily) using a bi-directional device in adults with bilateral nasal polyposis and nasal congestion. The two co-primary efficacy variables were reduction of nasal congestion/obstruction score at Week 4 and reduction in the nasal polyp grade at Week 16.

In both studies, the primary analyses demonstrated statistically significant reductions in nasal congestion/obstruction score at Week 4 and in total nasal polyp grade at Week 16 for the three doses of OPN-375 in comparison to placebo. In Study 3101, the treatment effect (95% confidence interval) in nasal congestion/obstruction score was -0.25 (-0.43, -0.06), -0.30 (-0.48,-0.11), and -0.38 (-0.57, -0.19) for the 93 mcg, 186 mcg, and 372 mcg, respectively. The treatment effect (95% confidence interval) in total nasal polyp grade was -0.51 (-0.86, -0.16), -0.59 (-0.93,-0.24), and -0.62 (-0.96, -0.27) for the 93 mcg, 186 mcg, and 372 mcg, respectively. In Study 3102, the treatment effect (95% confidence interval) in nasal congestion/obstruction score was -0.36 (-0.56, -0.16), -0.45 (-0.65,-0.25), and -0.38 (-0.58, -0.18) for the 93 mcg, 186 mcg, and 372 mcg, respectively. The treatment effect (95% confidence interval) in total nasal polyp grade was -0.70 (-0.99, -0.41), -0.60 (-0.89,-0.31), and -0.80 (-1.08, -0.51) for the 93 mcg, 186 mcg, and 372 mcg, respectively.

The efficacies of the three doses were similar in both studies. No apparent dose response was observed. Conclusions from the primary analyses are not sensitive to statistical methods implemented. Analyses of the secondary endpoints were also supportive to the primary analyses.

In my opinion, the two studies have demonstrated the superiority of OPN-375 over placebo in the proposed indication. The review team needs to compare the overall benefit-risk profiles of the three doses to make an approval decision. Safety evaluation will be critical during the decision-making process regarding approval and dose selection.

2. INTRODUCTION

2.1 Overview

OptiNose US, Inc. has developed OPN-375, an exhalation drug delivery system used to administer fluticasone propionate intranasally, for the treatment of nasal (b) (4) in patients 18 years of age or older. Fluticasone propionate is a synthetic corticosteroid that is currently approved as monotherapy and in various combinations, and in multiple formulations for multiple indications including creams, inhalers, and nasal sprays. The applicant states that the exhalation delivery system employed by OPN-375 is intended to improve the performance of fluticasone propionate in the treatment of serious diseases characterized by chronic nasal inflammation occurring behind the nasal valve. The product is intended to facilitate deposition of a topically-acting steroid in anatomic regions affected by local inflammation that causes or exacerbates chronic symptoms.

The clinical development program of OPN-375 was discussed with the division under IND110,089 on several occasions. At the pre-IND meeting occurred on January 20, 2011, the division advised the applicant refer to the report released by the National Academy of Science for handling missing data in the efficacy analyses. The division also recommended that the reasons for discontinuation be clearly documented to avoid less informative terms.

On August 11, 2014, the applicant submitted a statistical analysis plan (SAP) for the phase 3 Study 3101. In the advice letter dated March 9, 2015, the division informed the applicant that reduction in the nasal polyp grade should be evaluated at Week 16 rather than the average over the 16 weeks. The division also recommended the applicant conduct a tipping point analysis for the primary endpoints.

In the pre-NDA meeting held on December 3, 2015, the division requested the applicant submit a complete responder analysis for the elimination of polyps for the efficacy studies. With regard to the indication, the division clarified that the treatment of nasal (b) (4)

In this statistical review, I focused on whether data from Study 3101 and Study 3102 demonstrated the efficacy of OPN-375 in the proposed indication.

2.2 Data Sources

All data were supplied electronically by the applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR): \\Cdsesub1\evsprod\NDA209022\0001\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets and associated define files were of acceptable quality, and were sufficient for validating study results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 3101 and Study 3102 had identical study design and endpoints. Both were 16-week, randomized, double-blind, placebo-controlled, parallel group, and multicenter study evaluating the efficacy and safety of intranasal administration of three doses of OPN-375 (93, 186, and 372 mcg twice daily) using a novel bi-directional device in adults with bilateral nasal polyposis and nasal congestion. Study 3101 was performed in 54 centers across six countries (2 in Canada, 7 in the Czech Republic, 6 in South Africa, 5 in Ukraine, 6 in the United Kingdom, and 28 in the United States). Study 3102 was performed in 38 centers across five countries (9 in the United States, 12 in Poland, 6 in Romania, 6 in South Africa, and 5 in Ukraine).

Both studies consisted of a pretreatment phase (placebo run-in phase with duration of 7 to 14 days), a 16-week double-blind treatment phase, and an 8-week open-label extension phase during which all subjects received OPN-375 372 mcg. During the pretreatment phase, subjects were blinded to study treatment. The investigator, study center personnel at each center, and the applicant or its designated personnel were unblinded. The pretreatment phase was to determine eligibility and to ensure that subjects were able to comply with study procedures. At the end of the pretreatment phase, eligible subjects entered into the double-blind treatment phase. Subjects were then randomized in a ratio of 1:1:1:1 to receive placebo, 93 mcg, 186 mcg, or 372 mcg of OPN-375 twice daily.

Polyp grade of each nasal cavity was determined on a four-point polyp grading scale (0 - no polyps, 1- mild polyposis, 2 - moderate polyposis, 3 - severe polyposis) using nasoendoscopy at screening, Week 4, Week 8, Week 12, Week 16, and Week 24 visits. Electronic diaries were completed twice daily by subjects to capture symptom scores for nasal congestion/obstruction, rhinorrhea, facial pain or pressure symptoms, and sense of smell. Subjects reported nasal symptoms twice daily immediately before dosing (morning and evening). Subjects reported both instantaneous (evaluation of symptom severity immediately prior to the time of scoring) and reflective (evaluation of symptoms severity over the previous 12 hours) scores.

Before entry into this study, subjects were required to stop the use of all medications that could potentially alleviate symptoms of nasal congestion (such as intranasal steroids, oral antihistamines). Subjects were permitted continued use of saline nasal sprays and saline lavage (with some restrictions) if these were already being used before study entry. After Week 4 visit, subjects were permitted to use non-sedating antihistamines as rescue on an as-needed basis for the remainder of the study. The applicant believes that the use of non-sedating antihistamines can potentially impact the severity of associated symptoms (such as congestion, rhinorrhea) but will

not affect the size of the nasal polyps. It is for this reason that the primary time point for change in nasal congestion was at Week 4 and, for the change in nasal polyp grade, it was at Week 16. Use of approved rescue medication after the Week 4 visit was also captured.

The two co-primary efficacy variables were reduction of nasal congestion/obstruction symptoms at Week 4 and reduction in the nasal polyp grade at Week 16. The reduction of nasal congestion/obstruction symptoms at Week 4 was defined as the change from baseline in instantaneous morning diary symptom scores to the average score over the 7 days (ADS7-IA) prior to the Week 4 visit. The reduction in nasal polyp grade at Week 16 was defined as the change from baseline in the total polyp grade (sum of scores from both nasal cavities) at the Week 16 assessment. The baseline value for the nasal congestion/obstruction symptoms was the average score obtained from the values recorded during the last 7 days in the run-in period immediately prior to Day 1. The baseline value for the nasal polyp grade was the corresponding assessment score during screening visit.

The mean change in the Sinonasal Outcome Test - 22 (SNOT-22) total score at Week 16 and the mean change in the Sleep Disturbance subscale score of the MOS Sleep-R at Week 16 were identified as the key secondary endpoints in the SAP. Inferential statistics for these two variables were conducted after both primary efficacy variables were found to be statistically superior to placebo. Statistical multiplicity between the two key secondary variables was controlled using a stepdown method analogous to that utilized for the primary outcome variables.

3.2.2 Statistical Methodologies

Reduction of nasal congestion/obstruction symptoms at Week 4 was analyzed using an analysis of covariance (ANCOVA) model with the baseline nasal symptom score as a covariate, treatment and country as factors. The reduction in total polyp grade at Week 16 was analyzed using a mixed effect model for repeated measures (MMRM). The MMRM model included terms for baseline score, treatment, country, visit, and the treatment-by-visit interaction. An unstructured covariance matrix was used for the within subject correlation modelling.

Efficacy analyses was carried out using the full analysis set (FAS), defined as all randomized subjects who received at least one dose of double-blind study drug and had baseline assessments for the two co-primary endpoints.

A sequential testing procedure was implemented to control the study-wise Type I error at level 0.05. The highest dose, 372 mcg, was tested against placebo first, followed by the 186 mcg dose, and then the 93 mcg dose. The test could proceed to the next lower dose only if the higher dose was better than placebo in both co-primary endpoints with statistical significance at level 0.05.

Missing data in the primary efficacy analyses were imputed using a multiple imputation procedure based on an applicant defined pattern mixture approach. The pattern mixture approach categorized missing data into missing at random (MAR) or not missing at random (NMAR) based on reason for discontinuing the double-blind treatment. Specifically, subjects

discontinuing for adverse events (AEs), death or lack of efficacy had their missing data classified as NMAR; whereas subjects discontinuing for any other reason had their missing data classified as MAR. Additionally, intermittent missing values were all considered MAR. For MAR, the imputation values were drawn by visit from the treatment group to which the subject belonged. For NMAR, the imputation values were drawn from the lowest quartile of all observed values across treatment groups and visits. Ten imputation draws were performed using SAS PROC MI procedure. The ten imputed datasets were then analyzed and combined using SAS PROC MIANALYSIS.

To assess the sensitivity of the primary analyses to protocol violations, the applicant repeated the primary analysis using the per-protocol set (PPS), which included all FAS subjects excluding those with major protocol violations. As another sensitivity analysis, the primary analysis was repeated without missing data imputation. In addition, a tipping point analysis was carried out for each of the co-primary efficacy endpoints.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In Study 3101, a total of 323 subjects were randomized (Table 1). One subject randomized to 372 mcg discontinued the study before receiving the study medication. Overall, about 90% of the randomized subjects completed double-blind phase of the study. OPN-375 treatment groups had a higher rate of study completion than the placebo group (Table 1). The percentage of subjects who discontinued due to lack of efficacy was higher in the placebo group compared to the active treatment groups. The demographic and baseline characteristics were comparable across treatment groups (Table 2). Overall, approximately 88% of the subjects were White and 50% of the subjects were male. About 44% of the subjects were enrolled in the United States.

In Study 3102, there were also a total of 323 randomized subjects (Table 3). One subject randomized to placebo and one subject randomized to ONP-375 93 mcg did not receive study treatment. Overall, approximately 95% of the randomized subjects completed the double-blind phase of the study. A similar distribution of age, race, and ethnicity among subjects in each treatment group was reported (Table 4). In this study, there were a higher percentage of male subjects in all treatment groups, with the highest ratio occurring in the 372 mcg group. The population was predominantly white (94%). Subjects from the United States accounted for 41% of the randomized population.

Table 1: Patient Disposition- Study 3101

Population	Placebo	93 mcg	186 mcg	372 mcg	Total
All randomized (ITT)	**N=82**	**N=81**	**N=80**	**N=80**	**323**
ITT, but not treated	0	0	0	1	1
Full analysis set (FAS)	82	81	80	79	322
Completed DB phase, n (%)*	70 (85%)	75 (93%)	71 (89%)	76 (95%)	292 (90%)
Discontinued DB phase, n(%)*	12 (15%)	6 (7%)	9 (11%)	4 (5%)	31 (10%)
Adverse event	4 (5%)	2 (3%)	3 (4%)	1 (1%)	10 (3%)
Death	0	0	0	0	
Lost to follow-up	0	0	1 (1%)	0	1(0.3%)
Lack of efficacy	6 (7%)	0	3 (4%)	2 (3%)	11 (3%)
Protocol deviation	0	2 (3%)	0	1 (1%)	3 (1%)
Withdrawal by subject	2 (2%)	2 (3%)	2 (3%)	0	6 (2%)

Source: Clinical study report, Table 14.1.1
*: Percentages are based on the total number of patients in ITT population. DB: double-blind

Table 2: Demographics and Baseline Characteristics (ITT population) –Study 3101

Variable	Placebo N=82	93 mcg N=81	186 mcg N=80	372 mcg N=80	Total N=323
Age (years)					
n	82	81	80	80	
Mean (SD)	45 (13)	45 (13)	46 (13)	44 (13)	
Median	45	45	46	46	
Min, Max	18, 74	18, 68	18, 71	18, 73	
Sex [n(%)]					
Male	36 (44%)	40 (49%)	48 (60%)	38 (48%)	162 (50%)
Female	46 (56%)	41 (51%)	32 (40%)	42 (53%)	161 (50%)
Race [n(%)]					
White	68 (83%)	74 (91%)	72 (90%)	69 (86%)	283 (88%)
Black or African American	8 (10%)	3 (4%)	6 (8%)	9 (11%)	26 (8%)
Asian	5 (6%)	2 (2%)	2 (3%)	0	9 (3%)
Other	1 (1%)	2 (2%)	0	2 (3%)	5 (2%)
Ethnicity [n(%)]					
Not Hispanic or Latino	77 (94%)	78 (96%)	80 (100%)	75 (94%)	310 (96%)
Hispanic or Latino	5 (6%)	3 (4%)	0	5 (6%)	13 (4%)
Weight (kg)					
n	82	81	80	79	
Mean (SD)	81 (18)	83 (18)	81 (19)	80 (17)	
Median	80	82	81	77	
Min, Max	47, 143	51, 166	50, 131	55, 156	
Country [n(%)]					
United States	36 (44%)	36 (44%)	35 (44%)	36 (45%)	143 (44%)
Ukraine	16 (20%)	17 (21%)	16 (20%)	16 (20%)	65 (20%)
Czech Republic	14 (17%)	15 (19%)	14 (18%)	13 (16%)	56 (17%)
South Africa	9 (11%)	6 (7%)	8 (10%)	7 (9%)	30 (9%)
Canada	4 (5%)	5 (6%)	5 (6%)	4 (5%)	18 (6%)
United Kingdom	3 (4%)	2 (2%)	2 (3%)	4 (5%)	11 (3%)

Source: Clinical study report, Table 14.1.2; SD: standard deviation

Table 3: Patient Disposition- Study 3102

Population	Placebo	93 mcg	186 mcg	372 mcg	Total
All randomized (ITT)	**N=80**	**N=81**	**N=80**	**N=82**	**323**
ITT, but not treated	1	1	0	0	2
Full analysis set	79	80	80	82	321
Completed DB phase, n (%)*	70 (88%)	78 (96%)	76 (95%)	82 (100%)	306 (95%)
Discontinued DB phase, n(%)*	10 (12%)	3 (4%)	4 (5%)	0	17 (5%)
Adverse event	2 (3%)	1 (1%)	1 (4%)	0	4 (1%)
Death	0	0	0	0	
Lost to follow-up	0	0	0	0	0
Lack of efficacy	5 (6%)	1 (1%)	0	0	6 (2%)
Protocol deviation	0	1 (1%)	0	0	1 (0.3%)
Withdrawal by subject	3 (4%)	0	3 (4%)	0	6 (2%)

Source: Clinical study report, Table 14.1.1
*: Percentages are based on the total number of patients in ITT population. DB: double-blind

Table 4: Demographics and Baseline Characteristics (ITT population) –Study 3102

Variable	Placebo N=80	93 mcg N=81	186 mcg N=80	372 mcg N=82	Total N=323
Age (years)					
n	80	81	80	82	
Mean (SD)	47 (12)	47 (14)	45 (13)	45 (12)	
Median	46	46	44	43	
Min, Max	22, 76	23, 82	20, 74	18, 69	
Sex [n(%)]					
Male	42 (53%)	42 (52%)	46 (58%)	56 (68%)	186 (58%)
Female	38 (48%)	39 (48%)	34 (43%)	26 (32%)	137 (42%)
Race [n(%)]					
White	76 (95%)	76 (94%)	76 (95%)	76 (93%)	304 (94%)
Black or African American	3 (4%)	3 (4%)	3 (4%)	4 (5%)	13 (4%)
Other	1 (1%)	2 (2%)	1 (1%)	2 (2%)	6 (2%)
Ethnicity [n(%)]					
Not Hispanic or Latino	79 (99%)	81 (100%)	80 (100%)	81 (99%)	321 (99%)
Hispanic or Latino	1 (1%)	0	0	1 (1%)	2 (1%)
Weight (kg)					
n	79	80	80	82	
Mean (SD)	80 (16)	82 (19)	79 (17)	81 (15)	
Median	78	82	78	80	
Min, Max	51, 140	49, 126	49, 125	46, 125	
Country [n(%)]					
Poland	31 (39%)	34 (42%)	33 (41%)	33 (40%)	131 (41%)
Romania	15 (19%)	13 (16%)	13 (16%)	14 (17%)	55 (17%)
Ukraine	12 (15%)	14 (17%)	13 (16%)	15 (18%)	54 (17%)
South Africa	12 (15%)	10 (12%)	11 (14%)	11 (13%)	44 (14%)
United States	10 (13%)	10 (12%)	10 (13%)	9 (11%)	39 (12%)

Source: Clinical study report, Table 14.1.2; SD: standard deviation

3.2.4 Results and Conclusions

I was able to reproduce the applicant's results from the primary analyses with negligible difference for both studies. For both studies, the primary analyses demonstrated statistically significant reductions in ADS7-IA nasal congestion/obstruction score at Week 4 and in total nasal polyp grade at Week 16 in all the three active treatment groups in comparison to placebo group.

Study 3101

In Study 3101, the treatment effects of the three active doses of OPN-375 appear similar. The treatment effects of the two higher doses of OPN-375 were numerically larger than the 93 mcg dose in the two primary endpoints (Tables 5 and 6). However, the differences were not statistically significant.

Table 5: Change from Baseline to Week 4 in Nasal Congestion - Study 3101

		Placebo	93 mcg	186 mcg	372 mcg
Time point	**Statistics**	**N=82**	**N=81**	**N=80**	**N=79**
Baseline	Mean (SD)	2.3 (0.41)	2.2 (0.44)	2.2 (0.42)	2.3 (0.44)
Change from baseline to Week 4	LS mean	-0.24	-0.49	-0.54	-0.62
	Difference		-0.25	-0.30	-0.38
	95% CI		(-0.43,-0.06)	(-0.48, -0.11)	(-0.57, -0.19)
	P-values vs placebo		0.01	0.002	<0.001
	P-values vs 93 mcg			0.599	0.165

Source: Clinical study report, Table 14.2.1; CI: confidence interval; SD: standard deviation

Table 6: Change from Baseline to Week 16 in Total Nasal Polyp Grade - Study 3101

		Placebo	93 mcg	186 mcg	372 mcg
Time point	**Statistics**	**N=82**	**N=81**	**N=80**	**N=79**
Baseline	Mean (SD)	3.8 (0.94)	3.6 (1.07)	3.9 (1.08)	3.7 (0.94)
Change from baseline to Week 16	LS mean	-0.45	-0.96	-1.03	-1.06
	Difference		-0.51	-0.59	-0.62
	95% CI		(-0.86,-0.16)	(-0.93, -0.24)	(-0.96, -0.27)
	P-values vs placebo		0.004	<0.001	<0.001
	P-values vs 93 mcg			0.671	0.549

Source: Clinical study report, Table 14.2.2; CI: confidence interval; SD: standard deviation

I identified several potential issues in the applicant's analysis methods for the primary endpoints. First of all, in the analysis model for the total nasal polyp grade at Week 16, the visits were handled as numeric variables, which essentially assumed that the total polyp grade had a linear trend across visits. This is a strong assumption without justification and the treatment effect at Week 16 is hence determined by the slope of the overall linear trend over visits. Second, the multiple imputation methods for missing values could potentially produce an imputed value that

is out of the feasible range of the endpoint. For example, the imputed nasal congestion score could be negative or greater than 3, the maximum value. Third, the proposed missing value imputation method appears ad-hoc and depends on accurate documentation of reasons of dropouts. Fourth, the imputation method for the total polyp grade mixed values from all visits ignoring the longitudinal nature of the data, which does not appear theoretically sound.

I conducted sensitivity analyses to address the above potential concerns. The results were all supportive to the conclusions from the primary analyses (Appendix, Tables 17 to 18). Thus my concerns on the analysis methods are alleviated. Below, I describe the sensitivity analyses I conducted.

To address the first concern, visit was handled as a factor in all my analyses for the nasal polyp grade at Week 16, which thus does not put any assumption on the trend of the total nasal polyp grade over visits. To address the second concern, I added range restriction to the imputed values such that all imputed values would be in the feasible range. To address the third concern, I treated all dropouts the same regardless of reason of discontinuation. To address the fourth concern, in addition to imputing random values from the worst quartile as proposed in the applicant's primary analysis, I also performed a jump to placebo imputation method, where all dropouts were imputed using values from placebo completers. My sensitivity analyses produced results similar to those from the primary efficacy analyses.

To investigate whether the treatment effect on nasal congestion/obstruction was maintained even after non-sedating antihistamines rescue medication were allowed after Week 4, the mean observed weekly average of nasal congestion/obstruction score is depicted through Week 16 for each treatment group in Figure 1. It appears that treatment effects of the active doses increased over time and very similar to each other throughout the study.

The impact of treatment on polyp size was further evaluated by examining change in total polyp grade over time. The average change in total polyp grade from baseline is depicted through Week 24 for each treatment group in Figure 2. Note that all subjects received the 372 mcg dose after Week 16. Therefore, the responses of placebo subjects were improved toward the active treatments after from Week 16 to Week 24. The total polyp grade reduction generally increased over time from baseline for all treatment groups with the maximum differences from placebo observed at Week 16.

Figure 1: **Change in Nasal Congestion over Time – Study 3101**

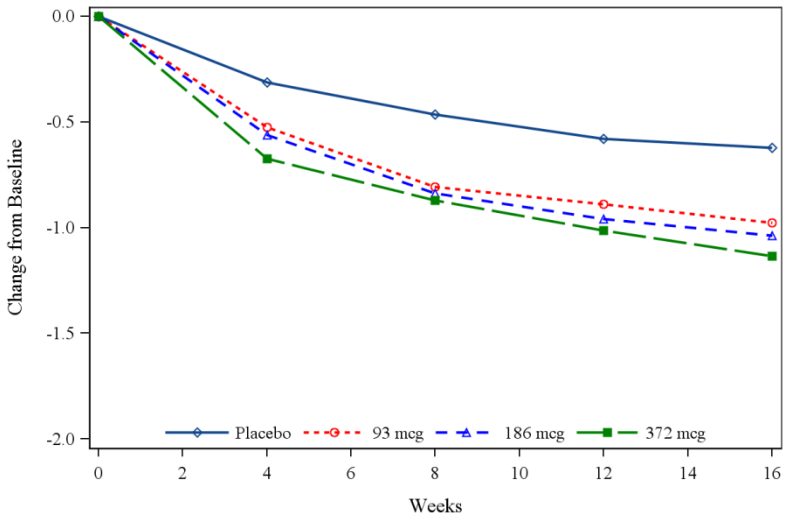
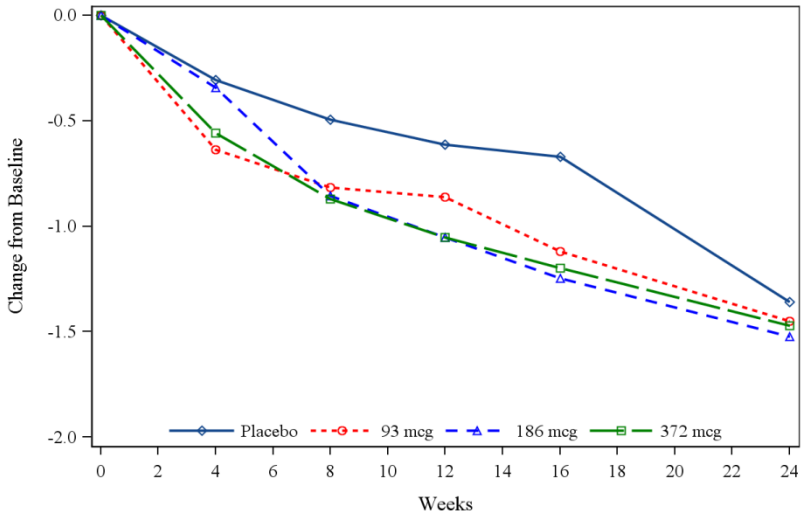
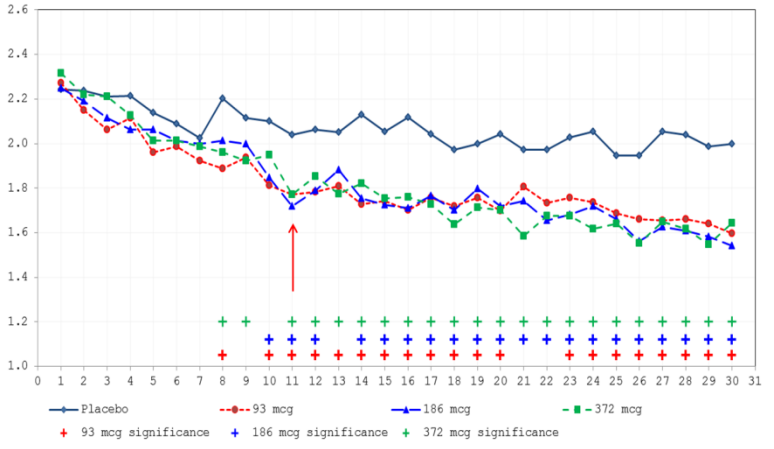


Figure 2: **Change in Total Polyp Grade over Time – Study 3101**



The average nasal congestion/obstruction score over the first 30 days of the double-blind period is presented in Figure 3 to evaluate the onset of action. The separation between the curves of the active treatments becomes apparent roughly after Day 10, where the treatment difference between all three active doses and placebo achieved statistical significance simultaneously. The treatment effects of the active treatments were thereafter roughly maintained, although statistical significance was lost occasionally due to random variation. The analyses of the nasal congestion at each day used the same method as the primary analysis.

Figure 3: Nasal Congestion Score During the First 30 Days – Study 3101



At Week 16, the percentage of subjects with a polyp grade of 0 (none) in at least one nostril was 11%, 23%, 15%, and 18% for the placebo, 93 mcg, 186 mcg, and 372 mcg group, respectively (Table 7). Both the 93 mcg and 186 mcg doses achieved nominal statistical significance with no multiplicity adjustment. A higher percentage of subjects in the three active treatment groups were dual responders than the placebo group (Table 8). A dual responder was defined as a subject who had at least 0.5 point reduction in nasal congestion/obstruction score and one point reduction in total nasal polyp grade at Week 16 in comparison to baseline. Subjects with missing values at Week 16 were defined as non-responders in the above analyses.

Table 7: Nasal Polyp Grade of None in one Nostril at Week 16 – Study 3101

Statistics	**Placebo**	**93 mcg**	**186 mcg**	**372 mcg**
N	**82**	**81**	**80**	**79**
n %)	9 (11%)	19 (23%)	12 (15%)	14 (18%)
p-value*		0.035	0.044	0.22

*: p-values are based on chi-square test for pairwise comparison with no multiplicity adjustment.

Table 8: Dual Responder at Week 16 – Study 3101

Statistics	**Placebo**	**93 mcg**	**186 mcg**	**372 mcg**
N	**82**	**81**	**80**	**79**
n %)	14 (17%)	34 (42%)	36 (45%)	42 (53%)
p-value		0.0005	0.0001	<0.0001

*: p-values are based on chi-square test for pairwise comparison with no multiplicity adjustment.

Analyses of secondary efficacy endpoints such as SNOT-22, Sleep disturbance, rhinorrhea, facial pain or pressure symptoms, and sense of smell produced results consistently in favor of the three active doses. Subjects in the active treatment groups also used less amount of rescue medications and less frequently in the study.

Study 3102

Study 3102 replicated the findings of the primary endpoints from Study 3101. All the three active doses of OPN-375 were superior to placebo with statistical significance in the two primary endpoints (Tables 9 and 10). Treatment effects of the three active doses were similar. My sensitivity analyses produced results supportive to the primary analyses (Appendix, Tables 19 to 20).

The treatment effect of each active dose on nasal congestion/obstruction was well maintained from Week 4 to Week 16 (Figure 4). Same as what were observed in Study 3101, the treatment effects of the active doses were similar throughout the study.

The total nasal polyp grade improved from baseline over time for all treatment groups (Figure 5). As shown in Figure 5, the separation between the curves of the active treatments and the curve of the placebo is apparent. The treatment effect of the 186 mcg dose was relatively smaller than the other two doses of OPN-375.

Onset of action as evaluated by analyzing nasal congestion/obstruction scores appears to occur after Day 10, where the treatment difference between each active dose and placebo started to achieve statistical significance (Figure 6). The separation between the curve of each active dose and that of placebo is roughly maintained thereafter.

The percentage of subjects who had nasal polyp grade of none in at least in one nostril at Week 16 was higher in each active treatment group than the placebo group (Table 11). However, treatment differences from placebo were not impressive. The treatment effect of the 186 mcg dose in polyp grade reduction appeared to be smaller than that of the other two doses. The active treatment groups also had higher percent of dual responders, which were subjects who had at least 0.5 point reduction from baseline in nasal congestion score and one point reduction in total polyp grade at Week 16 (Table 12).

Table 9: Change from Baseline to Week 4 in Nasal Congestion - Study 3102

		Placebo	**93 mcg**	**186 mcg**	**372 mcg**
Time point	**Statistics**	**N=79**	**N=80**	**N=80**	**N=82**
Baseline	Mean (SD)	2.3 (0.43)	2.2 (0.41)	2.2 (0.37)	2.3 (0.42)
Change from baseline to Week 4	LS mean	-0.24	-0.59	-0.68	-0.62
	Difference		-0.36	-0.45	-0.38
	95% CI		(-0.56,-0.16)	(-0.65, -0.25)	(-0.58, -0.18)
	P-values vs placebo		<0.001	<0.001	<0.001
	P-values vs 93 mcg			0.375	0.810

Source: Clinical study report, Table 14.2.1; CI: confidence interval; SD: standard deviation

Table 10: Change from Baseline to Week 16 in Total Nasal Polyp Grade - Study 3102

Time point	Statistics	Placebo N=79	93 mcg N=80	186 mcg N=80	372 mcg N=82
Baseline	Mean (SD)	3.8 (1.08)	3.6 (0.98)	3.9 (1.05)	3.9 (1.00)
Change from baseline to Week 16	LS mean	-0.61	-1.31	-1.22	-1.41
	Difference		-0.70	-0.60	-0.80
	95% CI		(-0.99,-0.41)	(-0.89, -0.31)	(-1.08, -0.51)
	P-values vs placebo		<0.001	<0.001	<0.001
	P-values vs 93 mcg			0.498	0.507

Source: Clinical study report, Table 14.2.2; CI: confidence interval; SD: standard deviation

Figure 4: **Change in Nasal Congestion over Time – Study 3102**

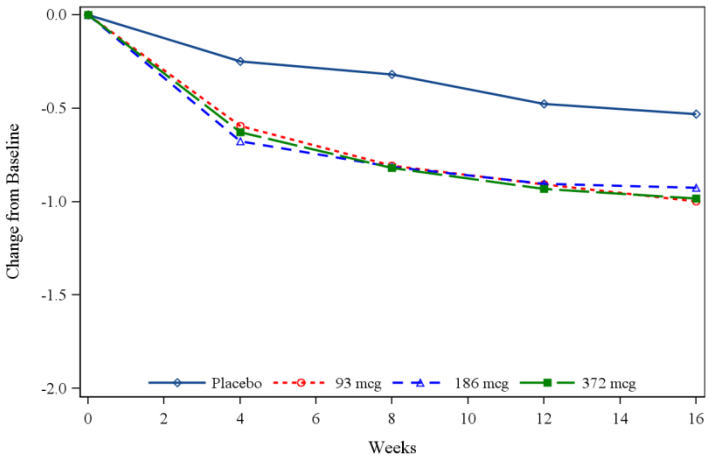


Figure 5: Change in Total Polyp Grade over Time – Study 3102

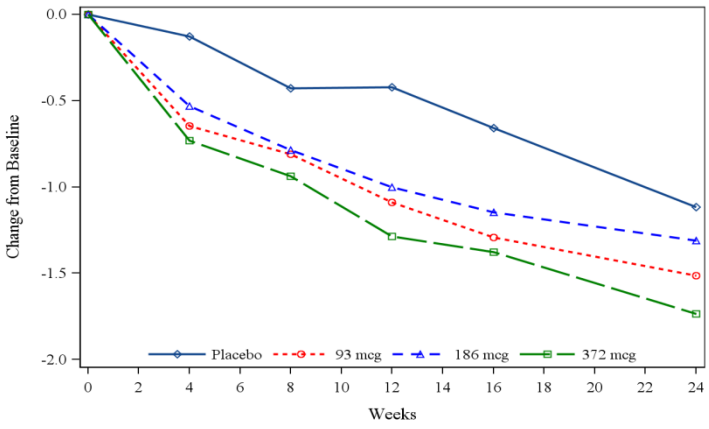


Figure 6: Nasal Congestion Score during the First 30 Days – Study 3102

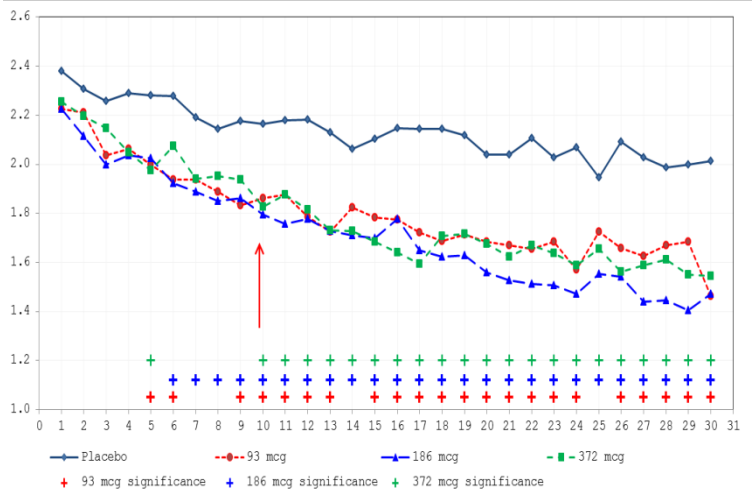


Table 11: Nasal Polyp Grade of None in at least One Nostril at Week 16 – Study 3102

Statistics	Placebo	93 mcg	186 mcg	372 mcg
N	**79**	**80**	**80**	**82**
n %)	3 (4%)	10 (12.5%)	6 (7.5%)	11 (13%)
p-value*		0.045	0.31	0.03

*: p-values are based on chi-square test for pairwise comparison with no multiplicity adjustment.

Table 12: Dual Responder at Week 16 – Study 3102

Statistics	Placebo	93 mcg	186 mcg	372 mcg
N	**79**	**80**	**80**	**82**
n %)	18 (23%)	44 (55%)	30 (37.5%)	32 (39%)
p-value		<0.0001	0.043	0.026

*: p-values are based on chi-square test for pairwise comparison with no multiplicity adjustment.

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by the clinical reviewer, Dr. Courtney McGuire. There were no major safety findings. Please refer to Dr. McGuire's review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age and Race

Subgroups summary by sex, race, age, and region are presented respectively for the two primary endpoints and two studies in Tables 13 to 16. Missing values were not imputed for these subgroup summaries. Findings from the subpopulations are generally consistent with those observed in the overall population. The active doses were consistently better than placebo in all the subpopulations except for some relative small subgroups. For example, in Study 3101, placebo was better than 93 mcg dose in the non-White population in reduction of nasal polyp grade. However, this is likely due to small sample size as there were only about 10 non-White subjects in each treatment group and only accounted for about 10% of the study population.

Table 13: Subgroup Summary for Reduction in Nasal Congestion at Week 4 - Study 3101

Subgroup		Statistics	Placebo N=82	93 mcg N=81	186 mcg N=80	372 mcg N=79
Sex	Female	n (%)	42 (51%)	39 (48%)	32 (40%)	42 (53%)
		Mean (SD)	-0.3 (0.6)	-0.6 (0.7)	-0.7 (0.8)	-0.7 (0.7)
	Male	n (%)	35 (43%)	39 (48%)	47 (59%)	36 (46%)
		Mean (SD)	-0.3 (0.6)	-0.5 (0.6)	-0.5 (0.6)	-0.7 (0.7)
Race	Non-White	n (%)	13 (16%)	7 (9%)	8 (10%)	11 (14%)
		Mean (SD)	-0.1 (0.5)	-0.1 (0.6)	-0.2 (0.5)	-0.6 (0.7)
	WHITE	n (%)	64 (78%)	71 (88%)	71 (89%)	67 (85%)
		Mean (SD)	-0.3 (0.6)	-0.6 (0.7)	-0.6 (0.7)	-0.7 (0.7)
Age	< 65	n (%)	71 (87%)	72 (89%)	74 (93%)	75 (95%)
		Mean (SD)	-0.3 (0.6)	-0.5 (0.7)	-0.6 (0.7)	-0.7 (0.7)
	>=65	n (%)	6 (7%)	6 (7%)	5 (6%)	3 (4%)
		Mean (SD)	-0.3 (0.6)	-0.6 (0.8)	-0.2 (0.7)	0 (0)
Region	USA	n (%)	34 (41%)	36 (44%)	35 (44%)	35 (44%)
		Mean (SD)	-0.2 (0.6)	-0.4 (0.6)	-0.5 (0.6)	-0.7 (0.7)
	Other	n (%)	64 (78%)	71 (88%)	71 (89%)	67 (85%)
		Mean (SD)	-0.3 (0.6)	-0.6 (0.7)	-0.6 (0.7)	-0.7 (0.7)

Table 14: Subgroup Summary for Reduction in Nasal Polyp Grade at Week 16 - Study 3101

Subgroup		Statistics	Placebo N=82	93 mcg N=81	186 mcg N=80	372 mcg N=79
Sex	Female	n (%)	36 (44%)	37 (46%)	29 (36%)	41 (52%)
		Mean (SD)	-0.7 (1.4)	-1.4 (1.6)	-1 (1.3)	-1.1 (1.1)
	Male	n (%)	32 (39%)	38 (47%)	39 (49%)	34 (43%)
		Mean (SD)	-0.6 (1.4)	-0.8 (1.2)	-1.4 (1.5)	-1.2 (0.9)
Race	Non-White	n (%)	11 (13%)	7 (9%)	7 (9%)	11 (14%)
		Mean (SD)	-0.7 (1.2)	-0.4 (0.8)	-1.3 (1.7)	-1.2 (0.9)
	WHITE	n (%)	57 (70%)	68 (84%)	61 (76%)	64 (81%)
		Mean (SD)	-0.6 (1.4)	-1.2 (1.5)	-1.2 (1.4)	-1.2 (1)
Age	< 65	n (%)	62 (76%)	69 (85%)	64 (80%)	72 (91%)
		Mean (SD)	-0.6 (1.3)	-1.1 (1.4)	-1.2 (1.5)	-1.2 (1)
	>=65	n (%)	6 (7%)	6 (7%)	4 (5%)	3 (4%)
		Mean (SD)	-1 (1.9)	-1.2 (1.6)	-1 (0.8)	-0.3 (0.6)
Region	USA	n (%)	29 (35%)	33 (41%)	26 (33%)	33 (42%)
		Mean (SD)	-0.8 (1.5)	-1.2 (1.7)	-1.3 (1.5)	-1.1 (1)
	Other	n (%)	39 (48%)	42 (52%)	42 (53%)	42 (53%)
		Mean (SD)	-0.6 (1.3)	-1 (1.2)	-1.2 (1.4)	-1.2 (1.1)

Table 15: Subgroup Summary for Reduction in Nasal Congestion at Week 4 - Study 3102

Subgroup		Statistics	Placebo N=79	93 mcg N=80	186 mcg N=80	372 mcg N=82
Sex	Female	n (%)	35 (44%)	38 (48%)	34 (43%)	26 (32%)
		Mean (SD)	-0.2 (0.7)	-0.7 (0.7)	-0.8 (0.8)	-0.7 (0.7)
	Male	n (%)	42 (53%)	41 (51%)	44 (55%)	56 (68%)
		Mean (SD)	-0.3 (0.5)	-0.5 (0.7)	-0.6 (0.6)	-0.6 (0.7)
Race	Non-White	n (%)	4 (5%)	5 (6%)	4 (5%)	6 (7%)
		Mean (SD)	-0.4 (1.1)	-0.1 (0.3)	-0.9 (0.7)	-0.5 (0.6)
	White	n (%)	73 (92%)	74 (93%)	74 (93%)	76 (93%)
		Mean (SD)	-0.2 (0.6)	-0.6 (0.7)	-0.7 (0.7)	-0.6 (0.7)
Age	< 65	n (%)	70 (89%)	72 (90%)	72 (90%)	79 (96%)
		Mean (SD)	-0.2 (0.6)	-0.6 (0.7)	-0.6 (0.7)	-0.6 (0.7)
	>=65	n (%)	7 (9%)	7 (9%)	6 (8%)	3 (4%)
		Mean (SD)	-0.3 (0.8)	-0.4 (0.6)	-1 (0.8)	-0.8 (1.1)
Region	USA	n (%)	8 (10%)	9 (11%)	8 (10%)	9 (11%)
		Mean (SD)	0.1 (0.5)	-0.5 (0.6)	-0.9 (0.7)	-0.3 (0.6)
	Other	n (%)	69 (87%)	70 (88%)	70 (88%)	73 (89%)
		Mean (SD)	-0.3 (0.6)	-0.6 (0.7)	-0.6 (0.7)	-0.7 (0.7)

Table 16: Subgroup Summary for Nasal Polyp Grade at Week 16 - Study 3102

Subgroup		Statistics	Placebo N=79	93 mcg N=80	186 mcg N=80	372 mcg N=82
Sex	Female	n (%)	33 (42%)	38 (48%)	33 (41%)	26 (32%)
		Mean (SD)	-0.3 (0.9)	-1.6 (1.4)	-1 (1.1)	-1.7 (1.4)
	Male	n (%)	37 (47%)	41 (51%)	42 (53%)	56 (68%)
		Mean (SD)	-1 (1.4)	-1 (1)	-1.3 (1.5)	-1.2 (1.2)
Race	Non-White	n (%)	4 (5%)	5 (6%)	4 (5%)	6 (7%)
		Mean (SD)	-1.3 (1.3)	-1 (1.7)	-1.8 (1.3)	-2 (1.7)
	White	n (%)	66 (84%)	74 (93%)	71 (89%)	76 (93%)
		Mean (SD)	-0.6 (1.2)	-1.3 (1.2)	-1.1 (1.4)	-1.3 (1.2)
Age	< 65	n (%)	64 (81%)	72 (90%)	69 (86%)	79 (96%)
		Mean (SD)	-0.7 (1.2)	-1.3 (1.3)	-1.2 (1.4)	-1.3 (1.2)
	>=65	n (%)	6 (8%)	7 (9%)	6 (8%)	3 (4%)
		Mean (SD)	-0.7 (1.2)	-1 (1)	-0.5 (1)	-3 (1)
Region	USA	n (%)	5 (6%)	9 (11%)	7 (9%)	9 (11%)
		Mean (SD)	0.6 (0.9)	-1.1 (1.4)	-0.3 (1)	-1.7 (1.2)
	Other	n (%)	65 (82%)	70 (88%)	68 (85%)	73 (89%)
		Mean (SD)	-0.8 (1.2)	-1.3 (1.2)	-1.2 (1.4)	-1.3 (1.3)

4.2 Other Special/Subgroup Populations

No other special subgroup summary was conducted.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Some minor statistical issues were identified in the applicant's primary efficacy analyses. However, none of the issues affected the study conclusions.

First of all, in the analysis model for the total nasal polyp grade at Week 16, the visits were handled as numeric variables, which essentially assumed that the total polyp grade had a linear trend across visits. The treatment effect at Week 16 is hence determined by the slope of the overall linear trend over visits. Second, the implemented multiple imputation methods for missing values could potentially produce an imputed value that is out of the feasible range of the endpoint. Third, the proposed missing value imputation method appears ad-hoc and depends on accurate documentation of reasons of dropouts. Fourth, the imputation method for the total polyp grade mixed values from all visits ignoring the longitudinal nature of the data, which does not appears theoretically sound.

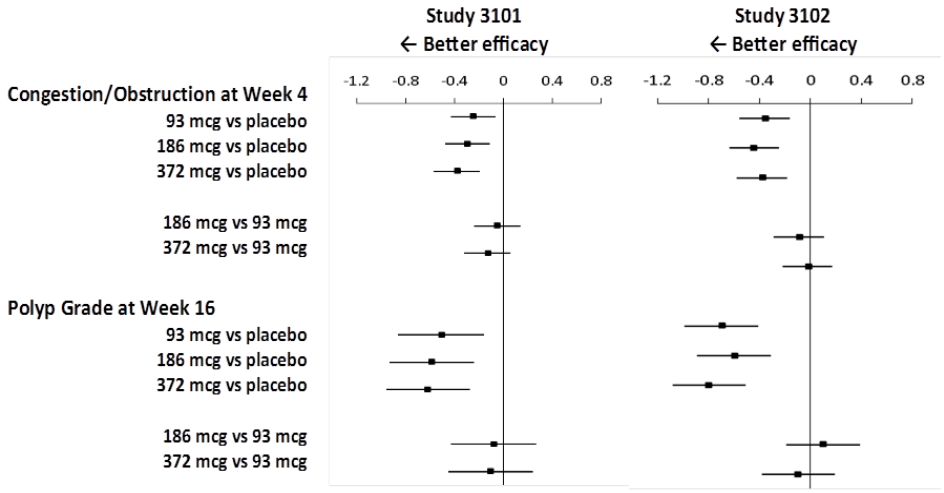
I conducted sensitivity analyses to address the above potential concerns. The results from my sensitivity analyses were supportive to the conclusion from the primary analysis. Thus my concerns on the analysis methods are alleviated.

5.2 Collective Evidence

Study 3101 and Study 3102 had identical study design and efficacy analyses. Findings from the two studies replicated each other. In both studies, the three active doses of the study drug were superior to placebo in the two primary endpoints (Figure 7). However, no apparent dose response was observed. The efficacies of the three doses were similar in both studies. Conclusions from the primary analyses are not sensitive to statistical methods implemented.

The secondary endpoints were consistently in favor of the three doses of the active drug over placebo. Subgroup analyses by sex, age, race, and region did not reveal any concerning findings.

Figure 7: Confidence Intervals of Treatment Differences



5.3 Conclusions and Recommendations

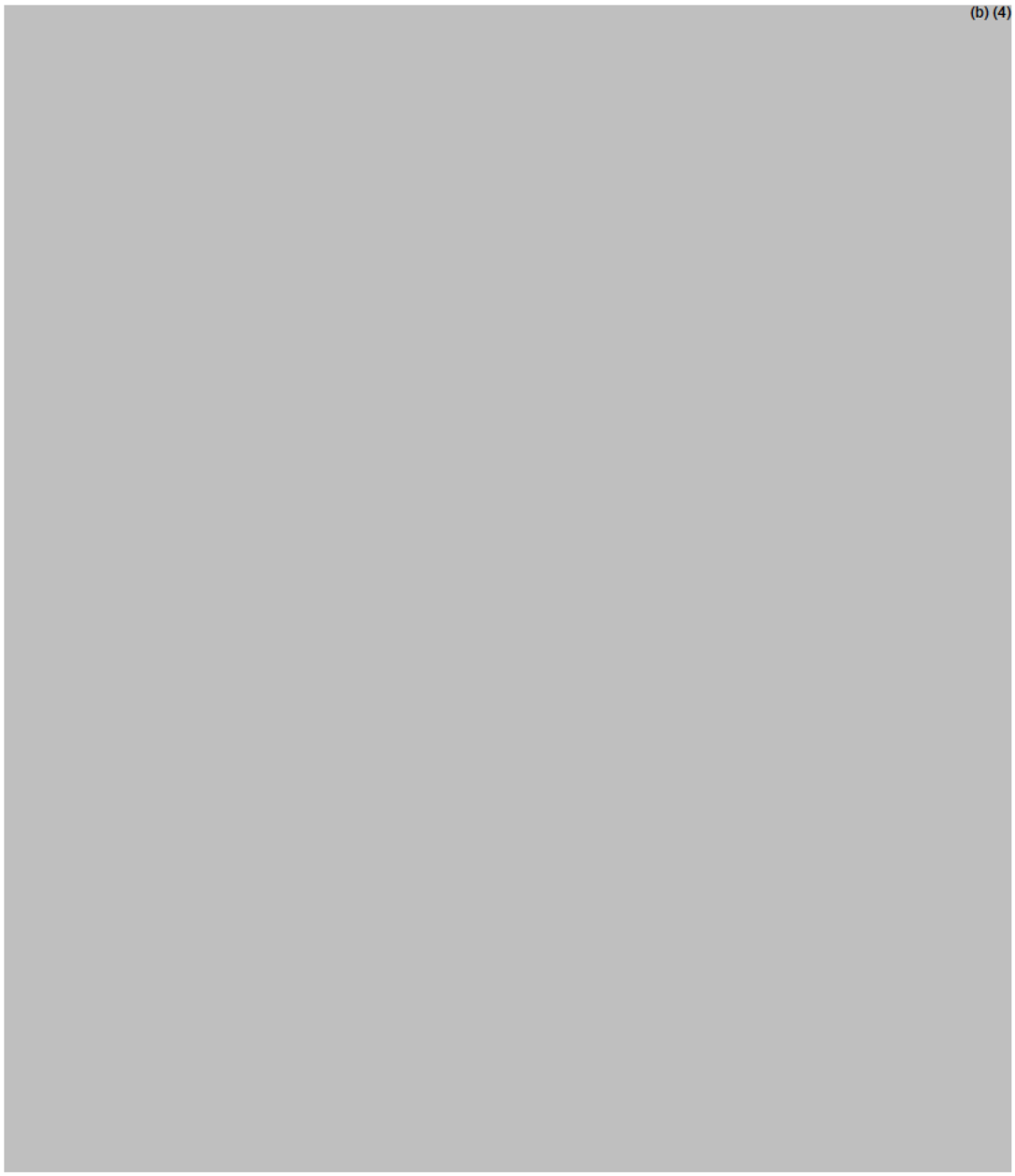
Study 3101 and Study 3102 have demonstrated the efficacy of the three doses of OPN-375 in reduction of nasal congestion/obstruction symptom and nasal polyp size. However, there was a lack of apparent dose response. The efficacy of the three doses appears similar. The review team needs to compare the overall benefit-risk profiles to make an approval decision. Safety evaluation will be critical during the decision-making process.

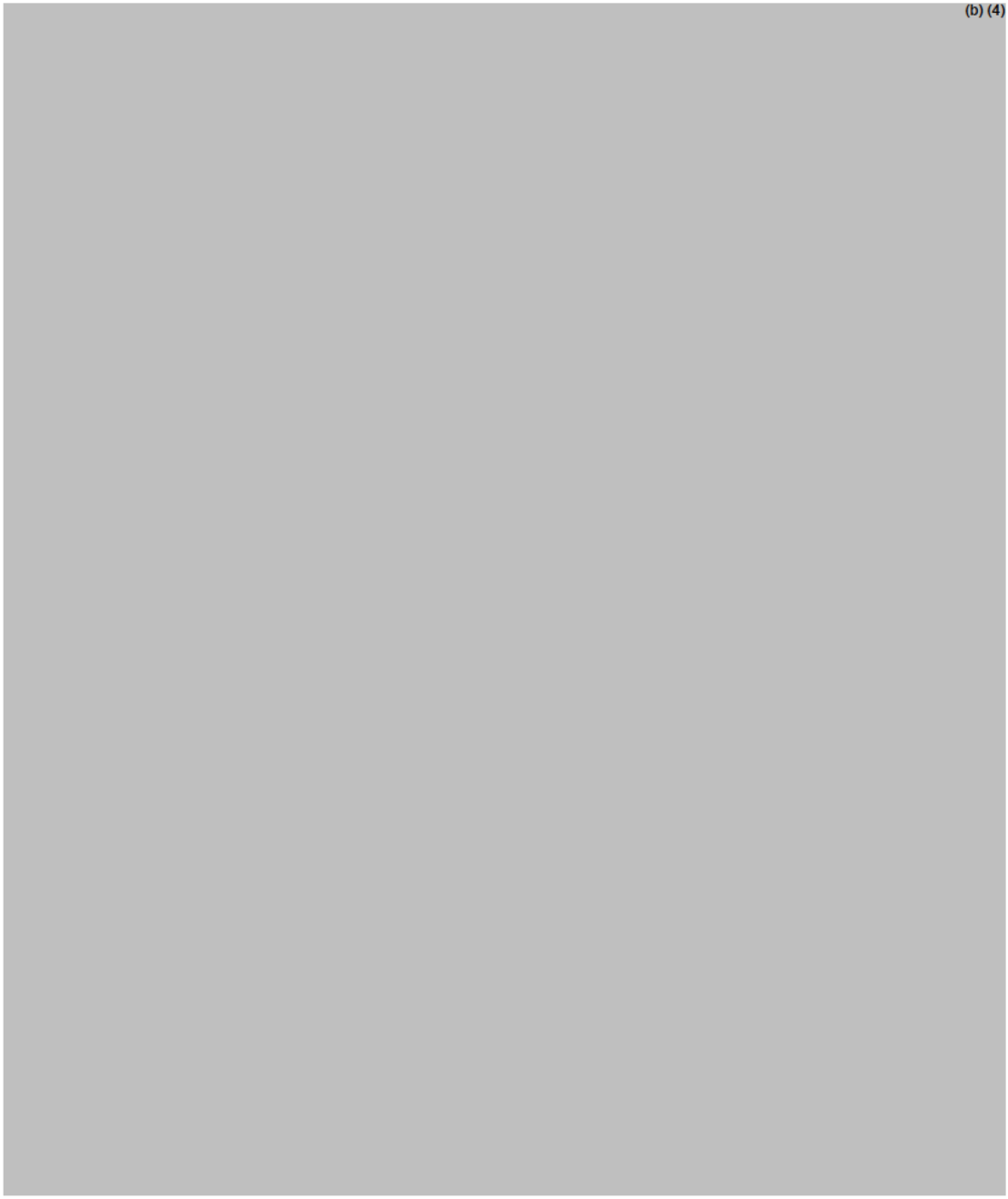
5.4 Labeling Recommendations

The applicant submitted the following for section 14 of labeling.

14 CLINICAL STUDIES

(b) (4)





I have the following recommendation:

- Remove (b) (4) from the labeling.
- Change (b) (4) to "Onset of action was generally observed within 2 weeks."
- Remove (b) (4) "
- Use observed mean instead of (b) (4) in both (b) (4).

Appendix

Table 17: Sensitivity Analysis for Week 4 Nasal Congestion Score - Study 3101

Time point	Statistics	Placebo N=82	93 mcg N=81	186 mcg N=80	372 mcg N=79
Baseline	Mean (SD)	2.3 (0.41)	2.2 (0.44)	2.2 (0.42)	2.3 (0.44)
Change from baseline to Week 4	LS mean*	-0.24	-0.48	-0.54	-0.62
	Difference		-0.24	-0.30	-0.38
	95% CI		(-0.43, -0.05)	(-0.49, -0.11)	(-0.57, -0.19)
	P-values vs placebo		0.013	0.002	<0.001
	P-values vs 93 mcg			0.513	0.144

CI: confidence interval; SD: standard deviation
*: missing values due to dropouts were imputed by drawing random samples from worst quartile regardless of dropout reasons. Other missing values were multiply imputed with restriction to [0, 3].

Table 18: Sensitivity Analyses for Week 16 Nasal Polyp Grade - Study 3101

Method	Time point	Statistics	Placebo N=82	93 mcg N=81	186 mcg N=80	372 mcg N=79
	Baseline	Mean (SD)	3.8 (0.94)	3.6 (1.07)	3.9 (1.08)	3.7 (0.94)
1	Change from baseline to Week 16	LS mean	-0.44	-0.99	-1.01	-1.01
		Difference		-0.55	-0.56	-0.57
		95% CI		(-0.92, -0.18)	(-0.94, -0.18)	(-0.94, -0.20)
		P-values vs placebo		0.004	0.004	0.003
		P-values vs 93 mcg			0.949	0.926
2	Change from baseline to Week 16	LS mean	-0.58	-1.05	-1.08	-1.08
		Difference		-0.47	-0.50	-0.50
		95% CI		(-0.85, -0.09)	(-0.91, -0.09)	(-0.88, -0.12)
		P-values vs placebo		0.015	0.017	0.009
		P-values vs 93 mcg			0.877	0.863

CI: confidence interval; SD: standard deviation
Method 1: restricted imputation value, visit as categorical variable, MMRM after imputation as in primary analysis.
Method 2: restricted imputation value, visit as categorical variable, MMRM after jump to placebo imputation.

Table 19: Sensitivity Analysis for Week 4 Nasal Congestion Score - Study 3102

Time point	Statistics	Placebo N=79	93 mcg N=80	186 mcg N=80	372 mcg N=82
Baseline	Mean (SD)	2.3 (0.43)	2.2 (0.41)	2.2 (0.37)	2.3 (0.42)
Change from baseline to Week 4	LS mean*	0.23	-0.59	-0.67	-0.61
	Difference		-0.37	-0.45	-0.39
	95% CI		(-0.56, -0.17)	(-0.65, -0.25)	(-0.58, -0.19)
	P-values vs placebo		<0.001	<0.001	<0.001
	P-values vs 93 mcg			0.41	0.83

CI: confidence interval; SD: standard deviation

*: missing values due to dropouts were imputed by drawing random samples from worst quartile regardless of dropout reasons. Other missing values were multiply imputed with restriction to [0, 3].

Table 20: Sensitivity Analyses for Week 16 Nasal Polyp Grade - Study 3102

Method	Time point	Statistics	Placebo N=79	93 mcg N=80	186 mcg N=80	372 mcg N=82
	Baseline	Mean (SD)	3.8 (1.08)	3.6 (0.98)	3.9 (1.05)	3.9 (1.00)
1	Change from baseline to Week 16	LS mean	-0.62	-1.32	-1.18	-1.36
		Difference		-0.70	-0.56	-0.75
		95% CI		(-1.01, -0.40)	(-0.87, -0.26)	(-1.05, -0.44)
		P-values vs placebo		<0.001	<0.001	<0.001
		P-values vs 93 mcg			0.373	0.779
2	Change from baseline to Week 16	LS mean	-0.62	-1.33	-1.17	-1.37
		Difference		-0.71	-0.55	-0.75
		95% CI		(-1.02, -0.40)	(-0.86, -0.24)	(-1.06, -0.44)
		P-values vs placebo		<0.001	<0.001	<0.001
		P-values vs 93 mcg			0.310	<0.799

CI: confidence interval; SD: standard deviation

Method 1: restricted imputation value, visit as categorical variable, MMRM after imputation as in primary analysis.
Method 2: restricted imputation value, visit as categorical variable, MMRM after jump to placebo imputation.

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/s/

FENG LI
08/14/2017

YONGMAN KIM
08/14/2017
I concur.

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 209022
Related IND #:	IND 110089
Product Name:	(b) (4) (Fluticasone Propionate, OPN-375)
Indication(s):	Treatment of nasal (b) (4)
Applicant:	OptiNose US, Inc.
Dates:	Received: November 18, 2016 PDUFA: September 18, 2017
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Feng Li, Ph.D.
Concurring Reviewers:	Gregory Levin, Ph.D.
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Medical Officer: Courtney McGuire, M.D. Medical Team Leader: Anthony Durmowicz, M.D.
Project Manager:	Nina Phuong Ton, Pharm.D.

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
OPN-FLU-NP-3101	MC, R, DB, PG, PC (16 weeks)	OPN-375 93 mcg / 81 OPN-375 186 mcg/80 OPN-375 372 mcg/80 Placebo/ 82	**Primary**: Reduction in nasal congestion score at Week 4 and reduction in nasal polyp grade at Week 16 Key Secondary: Change in sinonasal outcome test-22 (total score) at Week 16 and change in sleep disturbance subscale score at week 16	The primary analyses achieved statistical significance for all three active treatments.
OPN-FLU-NP-3102	MC, R, DB, PG, PC (16 weeks)	OPN-375 93 mcg / 81 OPN-375 186 mcg/80 OPN-375 372 mcg/82 Placebo/ 80	Primary: Reduction in nasal congestion score at Week 4 and reduction in nasal polyp grade at Week 16 Key Secondary: Change in sinonasal outcome test-22 (total score) at Week 16 and change in sleep disturbance subscale score at week 16	The primary analyses achieved statistical significance for all three active treatments.

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes.**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes.**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**Not applicable.**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**Yes.**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**Yes.**

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\Cdsesub1\evsprod\NDA209022\0001\m5\datasets
Were analysis datasets provided?	Yes.
Dataset structure (e.g., SDTM or ADaM)	SDTM and AdaM.
Are the define files sufficiently detailed?	Yes.
List the dataset(s) that contains the primary endpoint(s)	ADEF1 and ADEF2
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes.
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No.
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes and also refer to clinical filing review.

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	x			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			The SAPs for the ISE and ISS are provided.
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	x			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	x			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	x			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?

Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None.

5.2. Information Requests/Review Issues

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FENG LI
01/09/2017

GREGORY P LEVIN
01/09/2017