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 021-730
Supplement #:	S-036
Drug Name:	Xopenex HFA® (levalbuterol tartrate)
Indication(s):	Reversible Obstructive Airway Disease
Applicant:	Sunovion Pharmaceuticals Inc.
Date(s):	Submit Date: May 27, 2014 Received Date: May 27, 2014 PDUFA Goal Date: March 27, 2015
Review Priority:	Standard
Biometrics Division:	OB/DB II
Statistical Reviewer:	Yu (Jade) Wang, Ph.D.
Concurring Reviewers:	David Petullo, M.S.
Statistics Supervisor:	Thomas Permutt, Ph.D. (Division Director)
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Stacy Chin, M.D. (Medical Reviewer) Anthony Durmowicz, M.D. (Team Leader) Badrul A Chowdhury, M.D., Ph.D. (Medical Division Director)
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Keywords:

Link to keywords: NDA review, clinical studies, adaptive allocation

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1 EXECUTIVE SUMMARY

Xopenex HFA (levalbuterol tartrate) Inhalation Aerosol was approved for the treatment or prevention of bronchospasm in adults, adolescents and children 4 years of age and older with reversible obstructive airway disease on March 11, 2005. This approval included a Post Marketing Requirement (PMR) under the Pediatric Research Equity Act (PREA). The current submission contains one Study 051-039 of two sequential pediatric studies that were conducted to fulfill this PMR. This was a phase 3 study conducted to examine the safety, efficacy, and tolerability of daily dosing with Xopenex HFA administered using a facemask and Monaghan AeroChamber MAX holding chamber in subjects aged birth to <48 months with asthma. Study 051-039 failed to demonstrate a statistically significant benefit of Xopenex HFA in children aged birth to <48 months. Xopenex HFA did not improve asthma symptoms relative to placebo or the active control levalbuterol unit dose vial (UDV) in terms of the mean Pediatric Asthma Caregiver Assessments (PACA) score during the fourth week after commencement of treatment which was the primary efficacy endpoint.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Xopenex HFA (levalbuterol tartrate) Inhalation Aerosol contains levalbuterol, a short acting beta2-adrenergic receptor agonist for the prevention and relief of bronchospasm in patients with reversible obstructive airway disease. This supplemental NDA evaluated Xopenex HFA in a pediatric population, for safety, tolerability, and efficacy following daily dosing.

2.1.2 History of Drug Development

Xopenex HFA Inhalation Aerosol, for the treatment and prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease was introduced to the Division under IND 62,906, and was approved for use in patients 4 years of age and older under NDA 21-730 on March 11, 2005. In the approval letter, the Division deferred the submission of pediatric studies and considered them to be a PREA PMR.

On October 19, 2005 the sponsor submitted Proposed Pediatric Study Request (PPSR) containing three studies, safety and exposure of levalbuterol in obstructive airway disease in children from birth to <2 years old (study 051-358), safety and exposure of levalbuterol in obstructive airway disease in children from 2 to <4 years old (study 051-359), and safety and PK of levalbuterol tartrate in children from 2 to 4 years old (study 051-360).

Three Type C PPSR review meetings and several correspondences were conducted between the sponsor and the Division before the finalization of the pediatric development program plan. During the process, comments from the Division regarding the sponsor's proposals and inquiries were discussed.

The final pediatric development plan includes two sequential studies:

- Study 1 (051-359): A safety, Efficacy, and Tolerability Study of Daily Dosing with Levalbuterol Tartrate HFA MDI and Placebo in Subjects Aged Birth to <48 Months with Asthma

Study2 (051-361) : A safety and Tolerability Study of Levalbuterol Tartrate HFA Inhalation Aerosol Metered Dose Inhaler (MDI) in Pediatric Subjects Birth to <-48 Months of Age with Reactive Airways Disease in an Acute Setting
Regarding the general design of study 359, the following recommendations were given

- The Division recommend the program should include at least 50 subjects in each of the age ranges of 0 to <2 and 2 to <4 years (including reasonable number of subjects age 0 to <1 year). The sponsor raised concern over patient recruitment. The division first expressed a willingness to consider 50 per treatment group for the entire 0-4 age range. Upon the review of study protocol, the Division required that increase target enrollment to achieve 50 completers per treatment group.

- Active treatment control group recommended
- Include PK assessment
- Consider including asthma symptom scores as primary efficacy variable

In terms of the application of PREA or Best Pharmaceuticals for Children Act (BPCA), the Division stated that

- Written request for Xopenex HFA will not be issued; pediatric studies for Xopenex HFA are not necessary and do not meet a public health need; information is available for albuterol moiety and requesting studies with MDIs does not rise to a level to obtain a WR/exclusivity.

2.1.3 Current Submission

The current submission provides the results from one modified-blind, stratified-randomized, placebo-controlled, multicenter, parallel-group trial that evaluated Xopenex HFA, levalbuterol unit dose vial (UDV), and placebo. Administered using a facemask and holding chamber in subjects aged birth to <48 months with asthma (**Error! Reference source not found.**).

In study 359, the first patient was randomized to treatment February 05, 2009 and the last patient was randomized to treatment on May 01, 2013. The study was conducted at multiple sites in the United States.

2.2 Data Sources

Data for study 359 was provided by the sponsor and is currently located at:

\\cdsesub1\evsprod\NDA021730\0057\m5\datasets\study-051-359

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and analysis quality were adequate in this submission.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 359 was a modified-blind, randomized, placebo-controlled, multicenter, parallel-group phase 3 study. Key design criteria are shown in **Error! Reference source not found.**.

Table 1. Design of study 359

Design	Population	Endpoints
Dosing based on age: 0 - <2 Yrs. 2 - <4 Yrs. **Arms:** DB Xopenex HFA (45/90 μg TID) OL LEV IS UDV (0.31 mg TID) DB Placebo (1/2 Actuations TID) **Parallel Arm** **Modified Blind**	Asthma 0 - <4 Yrs. N=197 1:1:1	**Primary:** Week 4 change from baseline Pediatric Asthma Caregiver Assessments (PACA) **Key Secondary:** Change from baseline and percentage change from baseline in-clinic PEF at week 4 for subjects age 2 to <4 Yrs.

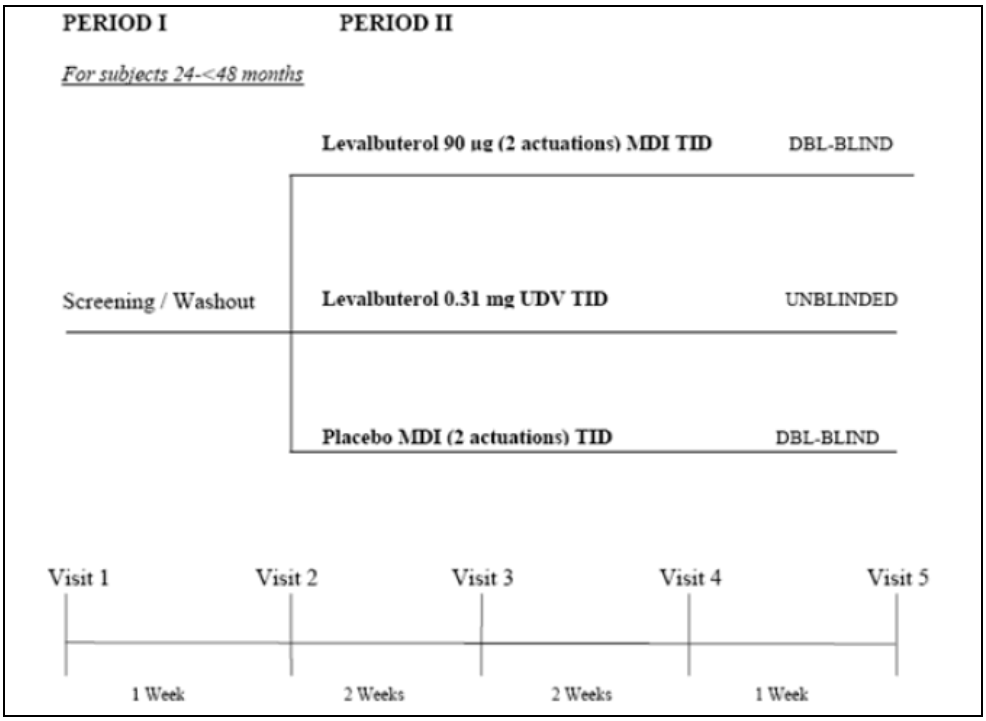
Source: Reviewer
Abbreviations: Yrs. = Years; DB = Double Blind; OL = Open Label; IS = Inhalation Solution; TID = Three times a day; LEV = Levalbuterol.

For subjects randomized to placebo or Xopenex HFA, study drug was administered in a double--blind fashion using a metered dose inhaler three times a day (TID). Actuations were introduced into the holding chamber with the facemask held in place for one minute. Levalbuterol was administered in an open label fashion using a nebulizer with a mouthpiece or facemask TID.

The study was comprised of two study periods and five study visits. A study schematic for the subjects between 2 and 4 years of age is provided in

Figure 1. Period I (Visit 1 – 2) was a one week screening/washout period. During this period, subjects were provided with the placebo MDI valved holding chamber and facemask, and instructed on how to use them. Subjects 0 to < 24 months of age were administered placebo MDI TID (1 actuation) for 7 days and subjects 24 to 48 months were administered placebo MDI TID (2 actuations) for 7 days. Period II (V2 – V5) was comprised of a four week treatment period (V2 – V4) plus a one week follow up (V4 – V5). The study schematic for the younger subjects (birth to less than 24 months) is identical except for the dose of Xopenex HFA administered, 45 µg versus 90 µg and the number actuations received, 1 versus 2.

Figure 1 Study Schematic



Source: Adapted from Figure 1 in applicant's CSR

Among the 3 treatment arms, the LEV MDI and PBO MDI arms are double blind while the IS UDV arm is open label.

It was planned that 195 subjects that met enrollment criteria (65 per treatment arm) would be randomized in order to have at least 150 subjects complete the study (50 per treatment arm). Subjects were randomized in a 1:1:1 ratio at Visit 2 to either placebo, Xopenex HFA, or levalbuterol UDV. Randomization was stratified according to age, 0 - <12 months, 12 - <24 months, and 24 - <48 months. Within the older children (2-4 years of age), randomization was further stratified by whether the child was able to perform peak expiratory flow (PEF) maneuvers. Although there was no formal sample size calculation, during the course of the trial, enrollment into the younger age group became an issue. The Division recommended at least 30 children (10 per treatment arm) be evaluated in the youngest age group. To ensure the study would meet enrollment targets for each age group, the initial 1:1:1 randomization scheme was revised to include an adaptive randomization process was implemented that stratified by age group and PEF status. The randomization weighted the probabilities of assigning a subject to a treatment based on the number of subjects enrolled in each treatment arm within a particular stratum and the total number of subjects to be enrolled in that stratum. Due to the difficulty with enrollment of younger subjects, the study finally was able to enroll only 27 subjects in this age group.

During the study, rescue medication consisted of 0.31 mg levalbuterol IS was provided for use on an as needed basis but subjects were asked not to use within eight hours of a study visit.

Efficacy was evaluated using asthma PACA, Pediatric Asthma Questionnaire (PAQ), PEF measurements, Investigator and Caregiver Global Evaluations (ICGE), Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQOL) composite score, and rescue medication use.

The primary efficacy endpoint was the change from baseline to Visit 4 (Week 4) in the mean daily composite score based on PACA. The daily composite scores were calculated as the sum of the scores of five domains: nocturnal awakening due to wheeze and cough, daytime wheeze, daytime cough, shortness of breath, and asthma symptom score. The mean daily composite score at baseline was defined as the mean of the daily composite scores from Visit 1 to Visit 2, and the mean daily composite score at Visit 4 was defined as the mean of the daily composite scores in the week prior to Visit 4.

The secondary endpoints were mainly comprised of the change from baseline to different time-points of questionnaire scores in the span of the four week trial. As the primary endpoint failed to show efficacy of the study drug over the controls (placebo and LEV UDV), and given that it is difficult to show efficacy in the pediatric population, among the secondary endpoints, the medical reviewer chose change and percentage change from study baseline (Visit 2 pre-dose) in the in-clinic PEF as endpoints of interest. The PEF time points of interest were the 1 hour post-dose at Visit 2 (week 1) and Visit 4 (week 4). Note, PEF assessments were only measured in the older subjects who were able to perform acceptable and reproducible PEF maneuvers.

3.2.2 Statistical Methodologies

All efficacy and safety analyses were conducted using the sponsor defined Intent-to-Treat (ITT) population, which are all randomized subjects who received at least one dose of study medication. The PEF analyses were conducted based on the PEF cohort, which included all subjects (24 - <48 months of age) who were part of the ITT population and were able to perform acceptable and reproducible PEF maneuvers.

For PACA composite scores, both baseline and change from baseline to Visit 4 (Week 4) in the mean daily scores were summarized by treatment group using descriptive statistics. The 95% confidence intervals for the mean change from baseline were calculated based on the t-distribution. Pairwise comparisons between each of the 3 pairs of treatments were performed by calculating the 95% confidence intervals for the differences in means based on the t-distribution. There was no adjustment for stratification factors and/or covariates in the analysis. No adjustment of multiple comparisons was implemented.

The continuous secondary variables were analyzed in the same approach.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Demographics and baseline characteristics for all randomized and treated subjects are shown in Table 2. There were no obvious differences between treatment groups for demographic and baseline characteristics.

Table 2. Demographic and Baseline Characteristics (ITT Population)

Parameter	Placebo MDI N = 68 n (%)	Levalbuterol MDI N = 65 n (%)	Levalbuterol UDV N = 63 n (%)	Total N = 196 n (%)
Gender				
Female	29 (42.6%)	35 (53.8%)	24 (38.1%)	88 (44.9%)
Male	39 (57.4%)	30 (46.2%)	39 (61.9%)	108 (55.1%)
Age (months)				
Mean (SD)	29.2 (12.17)	29.3 (12.57)	28.4 (12.48)	29.0 (12.35)
Median	32.0	32.0	31.0	31.0
Range	5 to 47	6 to 46	4 to 47	4 to 47
0 - < 12 months	9 (13.2%)	9 (13.8%)	9 (14.3%)	27 (13.8%)
12 - < 24 months	23 (33.8%)	23 (35.4%)	22 (34.9%)	68 (34.7%)
24 - < 48 months	45 (66.2%)	42 (64.6%)	41 (65.1%)	128 (65.3%)
Race				
White/Caucasian	46 (67.6%)	39 (60.0%)	36 (57.1%)	121 (61.7%)
Black/African American	18 (26.5%)	23 (35.4%)	24 (38.1%)	65 (33.2%)
Asian	0	0	1 (1.6%)	1 (0.5%)
American Indian/Alaska Native	0	1 (1.5%)	0	1 (0.5%)
Other	1 (1.5%)	0	0	1 (0.5%)
Multiple Races	3 (4.4%)	2 (3.1%)	2 (3.2%)	7 (3.6%)
Ethnicity				
Hispanic/Latino	16 (23.5%)	21 (32.3%)	19 (30.2%)	56 (28.6%)
Not Hispanic/Latino	52 (76.5%)	44 (67.7%)	44 (69.8%)	140 (71.4%)
Height/Length (cm)				
Mean (SD)	89.16 (12.32)	90.15 (11.84)	88.11 (11.79)	89.15 (11.96)
Range	57.9 to 111.0	61.5 to 109.2	61.5 to 109.0	57.9 to 111.0
Weight (kg)				
Mean (SD)	13.96 (3.460)	14.23 (3.765)	13.32 (2.843)	13.85 (3.388)
Range	7.0 to 27.8	7.4 to 24.1	7.3 to 18.6	7.0 to 27.8
BMI (kg/m^2)				
Mean (SD)	17.51 (2.177)	17.30 (1.786)	17.17 (1.960)	17.33 (1.979)
Range	14.1 to 23.5	13.9 to 22.0	13.7 to 21.7	13.7 to 23.5

Source: Table 14.1.4.1 from applicant's CSR
Abbreviations: BMI=body mass index

Discontinuation rates for subjects randomized to placebo and Xopenex HFA were less than 10%, 9% and 8 %, respectively. There were slightly more discontinuations in the levalbuterol UDV treatment arm, 16%. Pattern of patient disposition did not appear to favor or disfavor use of study drug. Reasons for discontinuations are shown in Table 3.

Table 3. Subject Disposition (All Subjects Population)

Subject Disposition	**Placebo MDI**	**Levalbuterol MDI**	**Levalbuterol UDV**	**Total**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Screened	--	--	--	245
Screen Failures	--	--	--	20
Randomized Failures	--	--	--	28
Randomized	68	65	64	197
Randomized, but not dosed	0	0	1	1
ITT Population	68	65	63	196
PK Population	59 (86.8%)	54 (83.1%)	49 (77.8%)	162 (82.7%)
Completed	62 (91.2%)	60 (92.3%)	53 (84.1%)	175 (89.3%)
Withdrew	6 (8.8%)	5 (7.7%)	10 (15.9%)	21 (10.7%)
Adverse Event	2 (2.9%)	3 (4.6%)	3 (4.8%)	8 (4.1%)
Withdrawal by Subject	2 (2.9%)	1 (1.5%)	2 (3.2%)	5 (2.6%)
Other	1 (1.5%)	0	3 (4.8%)	4 (2.0%)
Protocol Violation	1 (1.5%)	1 (1.5%)	1 (1.6%)	3 (1.5%)
Lost to Follow-up	0	0	1 (1.6%)	1 (0.5%)

Source: Table 14.1.2 from applicant's CSR

3.2.4 Results and Conclusions

Results from the pairwise comparisons of the primary endpoint (Table 4) do not support the intended efficacy of Xopenex HFA over placebo or the active control levalbuterol UDV. Both Xopenex HFA and levalbuterol UDV were numerically better than the placebo control, but didn't reach statistical significance. Results are shown in Table 4. The numbers reported below are for observed values only.

Table 4. Change from Baseline at Visit 4 in PACA Mean Daily Composite Score (ITT)

Statistic	Placebo MDI	Levalbuterol MDI	Levalbuterol UDV
n	62	59	54
Mean (SD)	-1.21 (2.722)	-0.67 9(2.092)	-0.52 (2.843)
95% CI	[-1.901, -0.518]	[-1.219, -0.129]	[-1.296, 0.256]
Mean Diff vs. Placebo MDI		0.54	0.69
95% CI vs. Placebo MDI		[-0.342, 1.412]	[-0.335, 1.714]
Mean Diff vs. Levalbuterol UDV		-0.15	
95% CI vs. Levalbuterol UDV		[-1.080, 0.771]	

Source: Reviewer

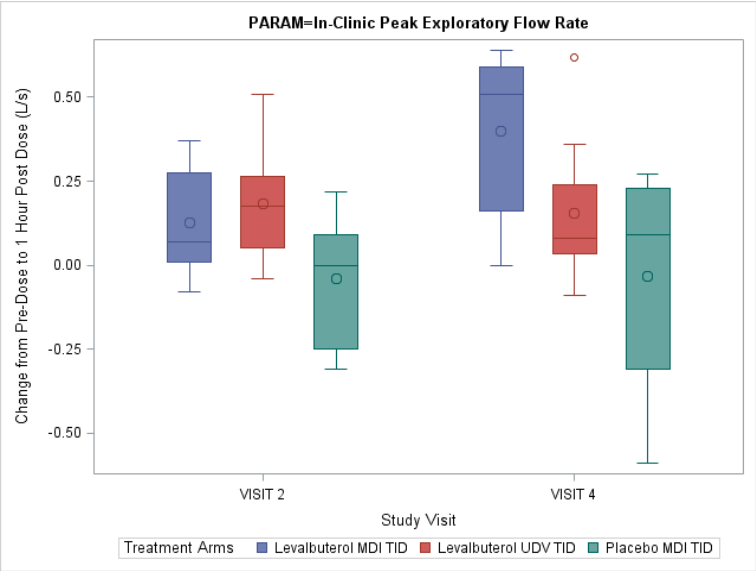
As supportive evidence, I also examined the change from baseline in PEF one hour post-dose at Weeks 1 and 4. Results are shown in Table 5. The comparison between Xopenex HFA and placebo was statistically significant at week 4 but not week 1. The comparison of levalbuterol to placebo was not significant at either week. However, this study was not designed to show a significant difference with respect to change in PEF. Percentage change from baseline results is consistent with those of change from baseline (Table 6). To show the potential trend of effects, we also included the corresponding box plots (Figure 2 and Figure 3).

Table 5. Change from Baseline in In-Clinic Peak Expiratory Flow (PEF Cohort)

Week Time Point Statistic	Placebo MDI	Levalbuterol MDI	Levalbuterol UDV
Week 1 1 Hr. Post-dose			
n	11	8	8
Mean (SD)	-0.04 (0.18)	0.13 (0.16)	0.18 (0.18)
95% CI	[-0.16, 0.08]	[-0.01, 0.26]	[0.03, 0.33]
Min, Max	-0.31, 0.22	-0.08, 0.37	-0.04, 0.51
Mean Difference vs. PBO MDI		0.17	0.22
95% CI vs. PBO MDI		[-0.01, 0.34]	[0.04, 0.40]
Mean Difference vs. LEV UDV		-0.06	
95% CI vs. LEV MDI		[-0.13, 0.24]	
Week 4 1 Hr. Post-dose			
n	9	7	8
Mean (SD)	-0.03 (0.33)	0.40 (0.24)	0.16 (0.23)
95% CI	[-0.29, 0.22]	[0.17, 0.62]	[-0.03, 0.34]
Min, Max	-0.59, 0.27	0.0, 0.64	-0.09, 0.62
Mean Difference vs. PBO MDI		0.43	0.19
95% CI vs. PBO MDI		[0.11, 0.75]	[-0.11, 0.49]
Mean Difference vs. LEV UDV		0.24	
95% CI vs. LEV MDI		[-0.02, 0.50]	

Source: Reviewer

Figure 2. Change from Baseline in In-Clinic Peak Expiratory Flow (PEF Cohort)



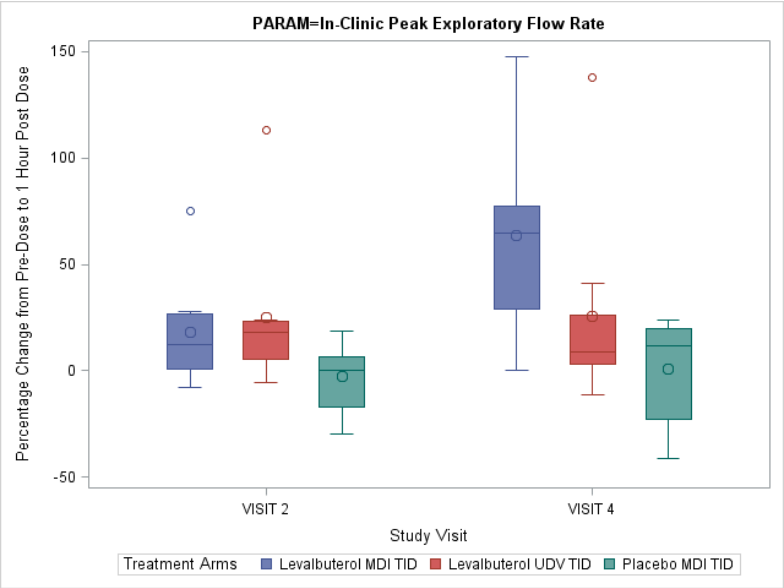
Source: Reviewer

Table 6. Percentage Change from Baseline in In-Clinic Peak Expiratory Flow (PEF Cohort)

Week Time Point Statistic	Placebo MDI N=11	Levalbuterol MDI N=8	Levalbuterol UDV N=8
Week 1			
1 Hr. Post-dose			
n	11	8	8
Mean (SD)	-2.8 (15.1)	18.2 (26.2)	25.1 (37.2)
95% CI	[-13.0, 7.3]	[-3.7, 40.1]	[-0.1, 56.2]
Min, Max	-30.0, 18.6	-7.7, 75.0	-5.8, 113.3
Mean Difference vs. PBO MDI		21.0	27.9
95% CI vs. PBO MDI		[1.1, 41.1]	[1.9, 53.9]
Mean Difference vs. LEV UDV		-6.9	
95% CI vs. LEV MDI		[-41.4, 27.7]	
Week 4			
1 Hr. Post-dose			
n	9	7	8
Mean (SD)	0.9 (24.0)	66.7 (45.6)	25.3 (47.8)
95% CI	[-17.5, 19.4]	[21.6, 105.9]	[-14.6, 65.3]
Min, Max	-41.0, 24.1	0.0, 147.5	-11.5, 137.8
Mean Difference vs. PBO MDI		62.8	24.4
95% CI vs. PBO MDI		[25.0, 100.6]	[-14.0, 62.8]
Mean Difference vs. LEV UDV		38.4	
95% CI vs. LEV MDI		[-13.9, 90.8]	

Source: Reviewer

Figure 3 Percentage Change from Baseline in In-Clinic Peak Expiratory Flow (PEF Cohort)



Source: Reviewer

3.3 Evaluation of Safety

Safety evaluations for this submission will be conducted by the medical reviewer, Stacy Chin, M.D. and will be provided in her review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Because the study did not show effectiveness of Xopenex HFA MDI, differences by gender, race, age, or geographic region were not examined for this review.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study 359 was not designed or powered to show statistical significance for either the patient asthma symptom scores or the pulmonary function test. There were no other outstanding statistical issues in the current submission.

5.2 Collective Evidence

Based on the results from the analyses of changes in PACA and PEF scores, there is no evidence of a treatment benefit in favor of Xopenex HFA in children younger than 4 years of age.

5.3 Conclusions and Recommendations

This submission fails to demonstrate statistically significant benefits of Xopenex HFA for the treatment or prevention of bronchospasm in children under four years of age who have reversible obstructive airway disease.

5.4 Labeling Recommendations (as applicable)

Because the sponsor has not proposed any claims for pediatric efficacy this information (b) (4) According to the current guidance on pediatric labeling, these results should be included in section 8.4.

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/s/

YU WANG
02/23/2015

DAVID M PETULLO
02/23/2015