CLINICAL REVIEW

Application Type	pediatric efficacy supplement
Application Number(s)	NDA 21-730/S-036
Priority or Standard	Standard
Submit Date(s)	May 27, 2014
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Division / Office	DPARP / ODEII
Reviewer Name(s)	Stacy Chin, M.D.
Review Completion Date	February 18, 2015
Established Name	levalbuterol tartrate HFA MDI
Trade Name	Xopenex HFA Inhalation Aerosol
Therapeutic Class	beta-2 agonist / bronchodilator
Applicant	Sunovion Pharmaceuticals Inc.
Formulation(s)	45 mcg (levalbuterol free base) per actuation (or inhalation)
Dosing Regimen	1-2 inhalations every 4-6 hours
Indication(s)	Reversible obstructive airway disease
Intended Population(s)	≥ 4 years of age

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, the recommended regulatory action for this supplemental NDA is Approval. This sNDA adequately fulfills the postmarketing pediatric research equity act (PREA) requirement in patients under 4 years of age. The data submitted, however, do not support extension of the Xopenex HFA indication to pediatric patients under 4 years of age.

1.2 Risk Benefit Assessment

The application contains clinical data from one of two PREA-required trials in patients less than 4 years of age with asthma or reactive airway disease. Study 051-359 was a modified-blind, placebo-controlled trial that evaluated the effectiveness of Xopenex HFA 45-90 mcg three times daily over 4 weeks compared with placebo in reducing asthma symptoms as measured by the daily Pediatric Asthma Caregiver Assessment (PACA) composite score. The study failed to meet the primary endpoint as there was no significant difference in the mean PACA score change from baseline at 4 weeks between treatment groups.

Regarding safety in patients less than 4 years of age, there was a small, but consistent, increase in asthma-related treatment-emergent adverse events and treatment discontinuations due to asthma in patients receiving Xopenex compared to placebo. This, along with the lack of consistent efficacy, does not support approval for use in pediatric patients less than 4 years of age and warrants inclusion in the product label. Based on the submitted data, the Applicant has not requested an indication in this younger age group. However, the risk benefit profile of Xopenex HFA in the approved population of patients 4 years of age and older remains favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for additional postmarketing risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

Study 051-359 represents the first of two consecutive PREA-required studies in patients less than 4 years of age. The second PREA requirement, Study 051-361, is designed to evaluate the safety and efficacy of cumulative dosing with Xopenex HFA compared to racemic albuterol for acute asthma exacerbations and was initiated after the completion

of Study 051-359. However, after reviewing data from Study 051-359 in this submission, no substantial efficacy or safety information is expected to be gained from additional postmarketing studies in patients under 4 years of age. Therefore, we recommend waiving the requirement for PREA Study 051-361.

2 Introduction and Regulatory Background

2.1 Product Information

Xopenex (levalbuterol tartrate) HFA Inhalation Aerosol was approved on March 11, 2005, for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older. Levalbuterol tartrate is a relatively selective β_2-adrenergic receptor agonist supplied as a pressurized aluminum canister containing either 80 or 200 metered actuations. After priming, each actuation of the inhaler deliver 67.8 mcg levalbuterol tartrate (equivalent to 51.6 mcg of levalbuterol free base) from the valve and 59 mcg levalbuterol tartrate (equivalent to 45 mcg of levalbuterol free base) from the actuator mouthpiece. Doses discussed in the remainder of this review will refer to the amount of levalbuterol free base delivered from the actuator. The recommended dose for adults and children 4 years of age and older is 2 inhalations (90 mcg) repeated every 4 to 6 hours, although in some patients 1 inhalation may be sufficient. More frequent administration or larger number of inhalations is not routinely recommended.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following table lists the available products approved for the prevention, treatment, or relief of bronchospasm in patients with reversible obstructive airway disease including asthma. The table does not include maintenance treatments for asthma, such as inhaled corticosteroids or long-acting beta agonists (LABAs), or products used off-label for this indication such as inhaled epinephrine.

Table 1. Products Available for Treatment of Bronchospasm

Drug	Trade Name	Formulation	Age Range (years)
Albuterol sulfate	AccuNeb and multiple generic brands	aqueous solution in unit-dose vials	≥ 2
	ProAir HFA	microcrystalline suspension in metered-dose aerosol for oral inhalation	≥ 4
	Proventil HFA	microcrystalline suspension in metered-dose aerosol for oral inhalation	≥ 4
	Ventolin HFA	microcrystalline suspension in	≥ 4

Drug	Trade Name	Formulation	Age Range (years)
		metered-dose aerosol for oral inhalation	
	Vospire ER*	extended release oral tablet	≥ 6
	generic	oral tablet	≥ 6
	generic	oral syrup	≥ 2
Levalbuterol tartrate	Xopenex HFA	micronized suspension in metered-dose aerosol for oral inhalation	≥ 4
Levalbuterol HCl	Xopenex Inhalation Solution*	aqueous solution in unit-dose vials	≥ 6
Montelukast**	Singulair*	oral chewable tablet, oral film-coated tablet, oral granules	≥ 6

*Generics available
**Acute prevention of exercise-induced bronchoconstriction (EIB)

2.3 Availability of Proposed Active Ingredient in the United States

Levalbuterol is present in one additional FDA-approved product, Xopenex Inhalation Solution (levalbuterol hydrochloride), which was approved on March 25, 1999, for the treatment and prevention of bronchospasm in patients 12 years of age and older with reversible airway disease, and on January 30, 2002, for children 6 to 11 years of age. No major safety issues have arisen since its approval; however, a recent review of PREA-required pediatric trials in patients under 6 years of age revealed an increased number of asthma-related adverse reactions in levalbuterol-treated subjects.

2.4 Important Safety Issues With Consideration to Related Drugs

Selective β_2-receptor agonists have been reported to cause "paradoxical worsening" of asthma symptoms with continued use or overuse. While racemic albuterol contains a 50:50 mixture of the (R)- and the (S)- enantiomers, levalbuterol contains only the purified (R)-enantiomer. Of the two isomers, the (R)-enantiomer is considered active, whereas the (S)-enantiomer is considered to have little or no activity at the β_2-receptor.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following is an abbreviated timeline of regulatory interactions related to the Xopenex HFA pediatric development program.

3/11/2005	Approved for patients 4 years of age and older; pediatric studies in patients < 4 years

	deferred with final study report due March 31, 2008
1/10/2006 5/15/2006 9/12/2007	Type C Meetings to discuss PPSR for sequential Studies 051-359 and 051-361; no Written Request issued due to lack of public health need
1/18/2008	Initial protocol for Study 051-359 submitted for comment
11/4/2008	Final protocol for Study 051-359 submitted
1/9/2009	Study 051-359 commenced (projected completion date of January 2011 with final study report by December 2011)
11/12/2012	Agency issued a Deferral Extension Notice regarding the outstanding PREA requirement
12/21/2012	Sponsor (b) (4)
5/29/2013	Division presented Sponsor's proposal to PeRC, recommending (b) (4) Agreed to close Study 051-359 early, but stated Study 051-361 should still be conducted. PeRC concurred with the Division's approach.
5/31/2013	Division provided Sponsor with preliminary comments regarding agreement to close Study 051-359 and recommended timeline for conducting Study 051-361
12/26/2013	Clinical study report for 051-359 submitted (per Division, must be re-submitted as efficacy supplement)
5/27/2014	Study 051-359 submitted as efficacy supplement with proposed labeling
07/2014	Study 051-361 initiated

2.6 Other Relevant Background Information

Study 051-359 was also submitted to NDA 20-837 for Xopenex Inhalation Solution (IS) as part of an efficacy supplement (S-041) to fulfill the PREA requirement for pediatric patients under 6 years of age. Safety results from this study have been included in the Pediatric Use section of the Xopenex IS product label.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA was submitted electronically and included the complete study report, appropriate case report forms, and proposed labeling. The submission was appropriately indexed and organized to permit clinical review. Review of the application did not raise any data integrity concerns, and Xopenex HFA is already an approved

product for the treatment of bronchospasm. For these reasons, the Division did not request an audit by the Division of Scientific Investigations (DSI) for this supplement.

3.2 Compliance with Good Clinical Practices

The Applicant stated that the clinical trial was conducted in compliance with Good Clinical Practices and submitted a statement certifying that no debarred individuals participated in the conduct of trials included in this NDA. Prior to trial initiation, the clinical study protocol and written informed consent form were reviewed and approved by an IRB.

3.3 Financial Disclosures

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. None of the principle investigators or sub-investigators who participated in the clinical trials referenced in this sNDA disclosed receiving significant financial compensation from Sunovion. The financial disclosure checklist is provided below. The disclosed financial interests raise no questions about the integrity of the data and do not affect the approvability of this application.

Table 2. Financial Disclosure Checklist

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 39		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☒ (NA)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (NA)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (NA)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Applicant submitted in vitro characterization studies performed in 2007 with Xopenex HFA employing two commercially available valve-mask holding chambers, AeroChamber Z-Stat Plus™ and AeroChamber Max™. Results from the studies demonstrated that Xopenex HFA can be administered to children under 4 years of age using the valve-mask holding chambers above. Otherwise, no new quality data was submitted or required, and the supplement is acceptable from the CMC perspective.

4.2 Clinical Microbiology

Xopenex HFA is an approved product; therefore, no new microbiology data was submitted or required.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology/toxicology data was submitted or required in this supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

As described in previous reviews, levalbuterol is the (R)-enantiomer of the drug substance racemic albuterol. Levalbuterol is a relatively selective β_2-adrenergic receptor agonist. Activation of β_2-adrenergic receptors on airway smooth muscle leads to activation of adenylate cyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits phosphorylation of myosin and lowers intracellular ionic calcium concentrations, ultimately resulting in smooth muscle relaxation in the airways. Increased cyclic AMP concentrations are also associated with inhibited release of mediators from mast cells in the airway.

4.4.2 Pharmacodynamics

No new pharmacodynamic information was submitted or required with this supplement.

4.4.3 Pharmacokinetics

Limited data from pharmacokinetic (PK) sampling was obtained in Study 051-359. Measurable (R)-albuterol concentrations were present in both levalbuterol treatment groups and in the placebo treatment group, although at much lower levels in the latter. These findings may reflect use of rescue albuterol or potentially contamination. Given the limitations of the sampling and the findings, no conclusions can be drawn from the PK data, and therefore no PK information will be added to the label.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3. Source of Clinical Data

Study	Dates	Design	Age (months)	Treatments: N[1]	Duration	Objective	Primary Endpoint
051-359	01/2009-06/2013	R, MB, PC, PG, AC	0-47	Xopenex HFA[2]: 65 PBO HFA[2]: 68 Levalbuterol IS[3]: 63	TID x 28 days	Safety and efficacy	Mean Δ in PACA score

Abbreviations: R=randomized, MB=modified-blind, PC=placebo-controlled, PG=parallel group, AC=active control, Lev MDI=levalbuterol MDI, PBO MDI=placebo MDI, Levalbuterol IS=leva buterol inhalation solution, TID=three times daily, PACA=pediatric asthma caregiver assessment
[1]N=Randomized subjects
[2]Double-blind; number of actuations based on age: 0-23 mo, 1 actuation (45 mcg), 24-47 mo, 2 actuations (90 mcg)
[3]Open-label; 0.31 mg dose for all ages
Source: Module 5.3.5.4, Study 051-359 CSR

5.2 Review Strategy

The focus of this review is on safety since the Applicant is not seeking an indication for this younger age group.

5.3 Discussion of Individual Studies/Clinical Trials

Protocol #	059-351
Title	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
Study dates	Study initiated: January 9, 2009 Study completed: June 5, 2013 Final study report: December 12, 2013
Sites	39 clinical study sites in the U.S.
IND	62,906

IRB (Site)	• (b) (4) •

Amendments
The Sponsor amended the protocol four times. Based on FDA feedback, amendment #1, dated July 29, 2008, increased the minimum number of patients under 1 year of age to 10, increased target enrollment to 65 randomized subjects per treatment arm (195 total) to achieve a total of 150 subjects completing the study, added a lower dose of levalbuterol for younger patients and an additional PK sample at Visit 2. Amendment #2, dated October 15, 2009, added influenza testing for symptomatic patients and decreased blood volume requirements for PK sampling. Amendment #3, dated October 26, 2009, added back language regarding review of clinical laboratory tests and rating of abnormal lab values that was inadvertently removed in the previously amended protocol. Amendment #4, dated February 11, 2010, removed the minimum number of patients required to perform PEF due to difficulty with recruitment, and clarified target enrollment numbers (30 patients aged 0 to 11 months and no more than 30 subjects aged 12 to 23 months).

Objectives
The objectives were to examine the safety, tolerability, and efficacy of Xopenex HFA using a facemask and holding chamber in subjects aged birth to 47 months with asthma.

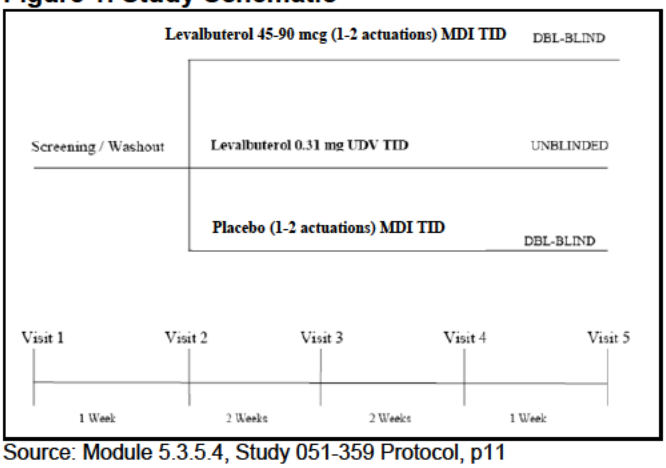
Study Design
This was a modified-blind, randomized, placebo-controlled, multicenter, parallel-group trial. Subjects were screened at Visit 1 after which eligible subjects entered a 7-day placebo washout period and returned for randomization at Visit 2. Subjects who had no clinically significant adverse events and disallowed medication use during the washout period were randomized equally to one of three study treatments: Xopenex HFA 45-90 mcg (1-2 actuations), Levalbuterol IS 0.31 mg, or placebo HFA 1-2 actuations. All study treatments were administered three times daily for 4 weeks. The HFA dose was based on age; subjects 0 to 23 months received 1 actuation (45 mcg levalbuterol) TID while subjects 24 to 47 months received 2 actuations (90 mcg levalbuterol) TID. The HFA treatment arms were double-blind while the levalbuterol IS treatment arm was open-

label with the same 0.31 mg dose administered regardless of age. Approximately 65 subjects were to be randomized to each treatment (195 subjects total) with the following distribution by age: 45 subjects aged 24 to 47 months and 20 subjects aged 0 to 23 months with at least half being under 12 months of age.

Reviewer comment: It should be noted that although levalbuterol IS was included as an active-control, pediatric trials evaluating levalbuterol IS in patients less than 6 years of age did not establish safety or efficacy in this age group.

Subjects received their first dose of study medication in clinic. Parents/legal guardians were instructed to complete the Pediatric Asthma Caregiver Assessments (PACA) questionnaire daily. Subjects 24 to 47 months of age who were capable of performing acceptable and reproducible PEF maneuvers were instructed to perform PEF maneuvers throughout the study. Follow-up visits occurred at 2-week intervals during the 4-week treatment period (Visits 3 and 4) and then 7 days after end of study drug treatment (Visit 5). A study schematic and schedule of assessments are shown below.

Figure 1. Study Schematic



Source: Module 5.3.5.4, Study 051-359 Protocol, p11

Table 4. Schedule of Study Assessments

Period	Period I		Period II		
Clinic Visit	1	2[a]	3[b]	4[a]	5[b]
Day	-7	0	14	28	35
Assessment	Screening Visit	Start of Randomization	Randomization Period	End of Treatment	End of Study
Informed Consent	X				
Inclusion / Exclusion	X	X			
Medical History	X				
Physical Exam	X			X	
Dispense Rescue Medication	X	X	X	X	
Dispense Washout Medication	X				
Dispense Randomization Medication		X	X		
ECGs	X	X[c]		X[c]	
Adverse Event Assessment	X	X	X	X	X
Vital Signs	X	X[d]	X	X[d]	X
Serum Chemistry/Hematology[f]	X	X[e]		X[e]	X
(R)-albuterol measurement[f]				X[g]	
Influenza test[h]	X	X	X	X	X
In-clinic administration of study medication		X			
PACQLQ		X[i]	X[i]	X[i]	
Investigator and Caregiver Global Evaluations				X	
Pediatric Asthma Questionnaire[j]	X	X	X	X	
Pediatric Asthma Caregiver Assessments Questionnaire[j]	X	X	X	X	
In-clinic PEF	X[k]	X[l]	X[m]	X[l]	
At Home PEF Begin	X[n]				
At Home PEF End				X	
Review of Safety Assessments	X	X	X	X	
Dispense/Review of Diary Card and MEC	X	X	X	X	
Assess Compliance		X	X	X	
Assess Concomitant Medications	X	X	X	X	X

ECG = electrocardiogram, MEC = Medical Events Calendar, PACQLQ = Pediatric Asthma Caregiver's Quality of Life Questionnaire, PEF = peak expiratory flow

a. Length of visit: 7 hours: ~ 1 hr predose, 6 hrs postdose.
b. Length of visit: 3 hours
c. ECGs will be collected predose and 1 hour postdose.
d. Vital Signs (HR and RR) will be recorded prior to dosing; at every 15 minutes for the first hour postdose, and then once an hour until the end of the visit (6 hours postdose).
e. Blood samples only for potassium and glucose will be obtained predose and at approximately 1 hour postdose.
f. See Appendix X for blood draw volumes.
g. Blood samples for levalbuterol concentrations will be obtained at Visit 4 predose and at approximately 1 and 4 hours postdose. Samples may be obtained within the window of 30-60 minutes for the 1 hour sample, and 4-6 hours for the 4 hour sample.
h. Performed as needed only as either an unscheduled visit or at the scheduled clinic visit, in patients with current influenza symptoms.
i. Performed as the first procedure
j. Questionnaires will be completed daily and collected at the next visit through visit 4.
k. In subjects 24 to <48 months of age - perform PEF before and 30 minutes after a 0.31 mg dose of levalbuterol inhalation solution.
l. In those subjects (24 to <48 months of age) able to perform PEF - perform PEF predose, and 30 minutes, 1 hour, 4 hours, and 6 hours postdose.
m. In those subjects (24 to <48 months of age) able to perform PEF - perform PEF predose only.
n. In those subjects (24 to <48 months of age) able to perform PEF – perform PEF daily prior to first morning dose.

Source: Module 5.3.5.4, Study 051-359 Protocol, p16

Study Population

A total of 197 subjects were randomized to study treatment: 65 to Xopenex HFA, 64 to levalbuterol IS, and 68 to placebo HFA. Of the 65 patients randomized to Xopenex HFA, 9 patients were under 12 months of age, 14 patients were between 12 and 23 months of age, and 42 patients were between 24 and 47 months of age.

Main Inclusion Criteria

1. Male or female between the ages of birth and 47 months at the time of consent
2. For subjects 24 to 47 months of age, a physician diagnosis of asthma (defined as at least 3 episodes of respiratory symptoms consistent with asthma symptoms including, but not limited to, cough, wheeze, or dyspnea)
3. For subjects 0 to 23 months of age, a history of 3 episodes of respiratory symptoms that in the judgment of the investigator could be consistent with asthma or reactive airways disease
4. No other chronic conditions other than asthma
5. No evidence of chronic cardiopulmonary conditions other than asthma on chest radiograph

Main Exclusion Criteria

1. Requires or may require disallowed medications
2. History of hospitalization for asthma, reactive airway disease, or bronchospasm within 4 weeks prior to Visit 1 or scheduled in-patient hospitalization, including elective surgery, during the study period
3. Clinical diagnosis of cystic fibrosis
4. Premature birth, defined as less than 38 weeks gestational birth and under 1 year of age at Visit 1

5. Body weight less than 7.0 kg at Visit 1
6. History of life-threatening asthma, defined as previous asthma episodes requiring intubation or associated with hypercapnia, respiratory arrest, or hypoxic seizures
7. History of cancer
8. Any chronic or congenital cardiorespiratory condition other than asthma, including bronchopulmonary dysplasia and congenital heart disease
9. Upper or lower respiratory tract infection in the 3 weeks prior to Visit 1
10. History of ventilation for a respiratory condition occurring at or near birth; ventilatory support for elective non-cardiopulmonary surgery was acceptable
11. Clinically significant laboratory or 12-lead ECG abnormality
12. Use of prescription drug with which levalbuterol or racemic albuterol administration is contraindicated
13. Clinically significant abnormalities that may interfere with study drug metabolism or excretion

Withdrawal Criteria

Subjects were discontinued for any of the reasons listed below. Prematurely terminated subjects were not replaced.

- Adverse event
- Protocol violation
- Withdrawal of consent
- Lost to follow-up
- Treatment failure/lack of efficacy
- No longer meets entry criteria
- Investigator's judgment/other

Prohibited Medications

The following table lists disallowed medications during the study.

Table 5. Disallowed Medications

Medications Disallowed for Study Duration	Required Withholding Interval Prior to Visit 1
Corticosteroids (oral or parenteral)	4 weeks
Inhaled, short-acting adrenergic bronchodilators	≥ 8 hours
Nebulized, short-acting adrenergic bronchodilators	≥ 10 hours
Inhaled, long-acting adrenergic bronchodilators	≥ 2 weeks
Oral adrenergic bronchodilators QID or TID preparations BID preparations	 ≥ 24 hours ≥ 36 hours
OTC asthma medications (e.g. Primatene mist and homeopathic remedies)	≥ 48 hours
Theophylline	1 week
Ipratropium bromide	8 hours
ADHD medications (e.g., Ritalin)	48 hours

Source: Module 5.3.5.4, Study 051-359 Protocol, p24

The following concomitant medications were allowed at the investigator's discretion if the dose had been stable for the month prior to Visit 1 (if applicable): leukotriene inhibitors, inhaled or nasal corticosteroids, topical corticosteroids, mucolytics and expectorants, antihistamines, immunotherapy, antibiotics, and other medications to treat chronic conditions.

Treatments
The study included three treatment groups:

- Xopenex HFA MDI 45mcg or 90 mcg (1-2 actuations) TID
- Levalbuterol IS 0.31 mg TID
- Placebo HFA MDI (1-2 actuations) TID

The HFA MDI dose was based on age: subjects 0 to 23 months received 1 actuation (45 mcg levalbuterol) TID while subjects 24 to 47 months received 2 actuations (90 mcg levalbuterol) TID. Although the HFA treatment arms were double-blind, the levalbuterol IS treatment arm was open-label with the same 0.31 mg dose administered regardless of age.

Rescue medication consisted of levalbuterol IS 0.31 mg for use as needed for all treatment groups.

HFA MDI treatments were administered via the Monaghan AeroChamber MAX™ with face mask with instructions for the face mask to be held in place for 1 minute. Levalbuterol IS was administered via mouthpiece or facemask with the TREK-S™ compressor and PARI LC PLUS™ nebulizer.

Efficacy
Evaluating the efficacy of Xopenex HFA in pediatric patients under 4 years of age was a secondary objective of this study. Efficacy assessments included daily Pediatric Asthma Caregiver Assessments (PACA), Pediatric Asthma Questionnaire (PAQ), Pediatric Asthma Quality of Life Questionnaire (PACQLQ), PEF maneuvers in subjects 24 to 47 months of age, investigator and caregiver global evaluations, and rescue medication use. The primary efficacy variable was the composite score from the PACA, a questionnaire consisting of five domains that was completed by parents/legal guardians daily (see Table 6 below). The maximum score was 19, with higher scores indicating greater symptom severity. The primary endpoint was the change in mean daily PACA score from baseline to Visit 4 between treatment groups. Baseline was defined as the mean of the daily composite scores during the placebo washout period from Visit 1 to 2, and Visit 4 was defined as the mean of the daily composite scores in the week prior to Visit 4. However, because the levalbuterol IS treatment arm was unblinded, the only relevant comparison was between the blinded Xopenex HFA and placebo HFA treatment groups.

Table 6. Pediatric Asthma Caregiver Assessments (PACA)

Domain	Score				
	0	1	2	3	4
Nocturnal awakenings due to wheeze and cough	Slept well; no cough or wheeze	awoke once; returned to sleep within 1 hour	Awoke once; stayed awake >1 hour	Awoke ≥2x; able to return to sleep	Awake most of night
Daytime wheeze	absent	barely noticeable	intermittent; no interference with daily routine	frequent; some interference with daily routine	present most of day; caused much trouble and radically changed daily routine
Daytime cough					
Shortness of breath					
Asthma symptom score	no asthma symptoms	mild asthma symptoms; easily tolerated	moderate asthma symptoms; causes discomfort and interference with daily life	severe asthma symptoms; causes much trouble and radically changed daily routine	---

Source: Module 5.3.5.4, Study 059-351 Protocol, Appendix VII, p64

Additional efficacy endpoints included the following:

- Change in the mean daily composite PACA score from baseline to Visit 3
- Changes in the mean daily composite PAQ score from baseline to Visits 3 and 4
- Change and percent change in the in-clinic PEF value from study baseline (pre-dose at Visit 2) to post-dose time points at Visits 2, 3, and 4
- Change and percent change in the at-home mean daily PEF value from study baseline (mean of the daily PEF values during placebo washout from Visit 1 to 2) to Visits 3 and 4 (mean of the daily PEF values in the week prior to each visit)
- Investigator and caregiver global evaluations
- Rescue medication use
- Change in PACQLQ composite score from baseline to Visits 3 and 4

Safety

Safety assessments included the occurrence of AEs and asthma-related AEs, protocol-defined treatment failures, vital signs, physical exams, ECGs, clinical laboratory tests, and β_2-adrenergic side effects.

6 Review of Efficacy

Efficacy Summary

The Applicant submitted one Phase 3 study (051-359) to evaluate the efficacy of Xopenex HFA for the treatment and prevention of bronchospasm in patients less than 4 years of age with reversible obstructive airway disease. In this study, subjects received one of three medications three times daily for 4 weeks: double-blind Xopenex HFA 45 mcg or 90 mcg, double-blind placebo HFA 1 or 2 actuations, or open-label levalbuterol IS 0.31 mg. The primary efficacy endpoint was the change in the mean daily composite Pediatric Asthma Caregiver Assessment (PACA) total score from run-in to its mean during Week 4 compared to placebo. Because treatment with levalbuterol IS was unblinded, the only relevant comparison was between Xopenex HFA and placebo. A secondary endpoint of interest was in clinic post-dose peak expiratory flow (PEF) measurements in the subset of children 24 to <48 months of age able to perform this maneuver.

The study failed to demonstrate a statistically significant benefit for Xopenex HFA in pediatric patients less than 4 years of age. PACA scores were relatively low at baseline in all treatment groups, and after the 4-week treatment period, there was no significant difference between Xopenex HFA and placebo with regard to the mean change in PACA score from baseline. PEF measurements obtained 1 hour post-dose at the beginning of the study and after 4 weeks showed numerical improvement in both active treatment groups compared to placebo; however, given the small number of patients with PEF observations, the results were not sufficient to establish efficacy.

The Applicant submitted this supplement to comply with PREA regulations, but based on the results from this study, is not seeking to expand the indication to patients less than 4 years of age. It is of note, however, that while this study failed to meet its primary endpoint, it is often difficult to demonstrate efficacy in younger patients by means of caregiver symptom assessments, particularly when asthma symptoms are mild at baseline.

6.1 Indication

This is a pediatric supplemental NDA for an approved drug product Xopenex HFA Inhalation Aerosol. Currently, the FDA-approved indication in the product labeling (Section 1) is “Xopenex HFA is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease”. The Applicant submitted this supplement to comply with PREA regulations, but is not seeking to expand the indication to younger age groups.

6.1.1 Methods

The efficacy review focuses on the comparison of Xopenex HFA to placebo given that the levalbuterol IS treatment arm was not blinded.

6.1.2 Demographics

Table 7 summarizes the demographic data for the ITT subject population in Study 051-359. Overall, the demographics and baseline characteristics of subjects were relatively similar across treatment groups. While the intent was to include at least 30 subjects less than 12 months of age (10 per treatment group), the Applicant was allowed to close the study early due to difficulty recruiting and enrolling subjects in this age group. Because early closure reduced the study population by only 3 subjects (1 per treatment arm), the efficacy and safety evaluation are not expected to be substantially affected.

Table 7. Subject Demographics of ITT Population

Category	Placebo N (%)	Xopenex HFA N (%)	Levalbuterol IS N (%)	Total[a] N (%)
Total (ITT population)	68	65	63	196
Age group (months)				
0 – 11	9 (13.2)	9 (13.8)	9 (14.3)	27 (13.8)
12 – 23	14 (20.5)	14 (21.5)	13 (20.6)	41 (20.9)
24 – 47	45 (66.2)	42 (64.6)	41 (65.1)	128 (65.3)
Sex				
Female	29 (42.6)	35 (53.8)	24 (38.1)	88 (44.9)
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	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)

Abbreviations: Levalbuterol IS=levalbuterol inhalation solution, ITT=intent-to-treat population, SD=standard deviation
[a] ITT population defined as any randomized subject who received at least 1 dose of study medication.
Source: Module 5.3.5.4, Study 059-351 CSR, Table 5, p47; ADSL.xpt

6.1.3 Subject Disposition

The majority of screening and randomization failures were due to failure to meet entry criteria or inability to comply with study procedures. The number of early discontinuations was greatest in the levalbuterol IS treatment group although the number of adverse drop-outs was similar across groups. Early discontinuations

categorized as "other" were related to noncompliance with study drug, inability to complete or comply with study procedures, or social/family issues.

Table 8. Disposition of Subjects

	Placebo	Xopenex HFA	Levalbuterol IS	Total
Screened	--	--	--	245
Screening/Randomization Failures	--	--	--	48
Randomized	68	65	64	197
ITT population[a]	68	65	63	196
PK population	59 (86.8)	54 (83.1)	49 (77.8)	162 (82.7)
Completed Study	62 (91.2)	60 (92.3)	53 (84.1)	175 (89.3)
Early Discontinuation	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)
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)
Other	1 (1.5)	0	3 (4.8)	4 (2.0)

Abbreviations: Levalbuterol IS=leva buterol inhalation solution, ITT=intent-to-treat population, SD=standard deviation
[a] ITT population defined as any randomized subject who received at least 1 dose of study medication.
Source: Module 5.3.5.4, Study 059-351 CSR, Table 3, p43 and ADSL.xpt

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the change in the mean daily composite Pediatric Asthma Caregiver Assessment (PACA) total score from baseline to its mean during Week 4 compared to placebo. PACA was assessed daily by parents/legal guardians and consisted of five domains: nocturnal awakenings, daytime wheeze, daytime cough, shortness of breath, and asthma symptom score (refer to Section 5.3, Table 6). The composite score was calculated as the sum of the five domains, which were rated on a scale of 0 to 4, except for asthma symptom score which was rated on a scale of 0 to 3. Therefore, the maximum score was 19, with higher scores indicating greater symptom severity. If any of the individual responses were missing, the composite score for that day was also set to missing. The primary efficacy analysis was performed on the ITT population. The 95% CI for the mean change from baseline was calculated based on the t-distribution. Pairwise comparisons between each of the 3 pairs of treatments were performed by calculating the 95% CIs for the differences in means based on the t-distribution.

Baseline PACA score was defined as the average of the daily composite scores obtained prior to the date of the first dose of study medication (Visit 1 through Visit 2). At baseline, PACA scores were low across treatment groups. The mean change from baseline to Week 4 in daily composite PACA scores are provided in Table 9. Although PACA scores decreased over the 4-week treatment period in all groups, there was no significant difference between active treatment and placebo. Similarly, there was no significant difference between Xopenex HFA and placebo when evaluated by age group

(0 to <24 months and 24 to <48 months (data not shown). See the Biometrics Review by Dr. Yu Wang for further details.

Table 9. Mean PACA Composite Score (ITT population)

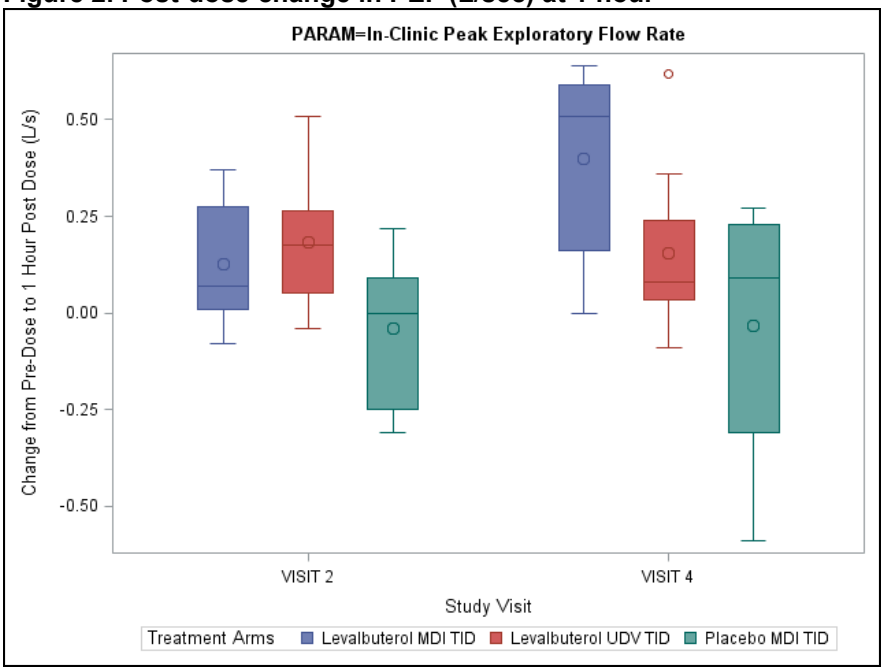
	Placebo N=68	Xopenex HFA N=65	Levalbuterol IS N=63
Baseline			
n	68	65	63
Mean (SD)	2.88 (2.84)	2.91 (2.60)	2.72 (2.50)
Median	2.27	2.00	2.14
Range	0.0 –11.7	0.0 – 10.6	0.0 – 10.2
Week 4			
n	62	59	54
Mean change from baseline (SD)	-1.21 (2.72)	-0.67 (2.09)	-0.52 (2.84)
95% CI	-1.901, -0.518	-1.219, -0.129	-1.296, 0.256
Mean difference vs Placebo (95% CI)		0.54 (-0.34,1.42)	0.69 (-0.34,1.71)

Source: Biometrics Review by Dr. Yu Wang

6.1.5 Analysis of Secondary Endpoints(s)

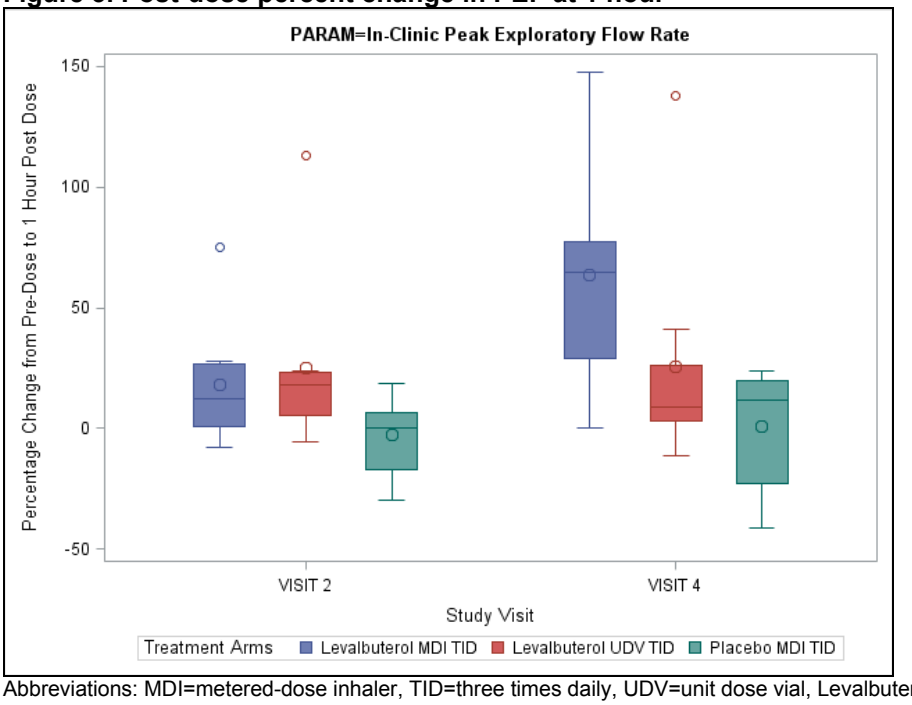
A secondary endpoint of interest was the change and percent change in the in-clinic PEF value from pre-dose to 1 hour post-dose at Visits 2 and 4. Analyses of PEF were based on the subset of subjects (aged 24 to <48 months) able to perform acceptable and reproducible PEF maneuvers. The baseline pre-dose PEF was defined as the measurement obtained at Visit 2. The PEF efficacy results showed numerical improvement in both active treatment groups compared to placebo; however, the small number of patients is not sufficient to establish efficacy based on this endpoint.

Figure 2. Post-dose change in PEF (L/sec) at 1 hour



Abbreviations: MDI=metered-dose inhaler, TID=three times daily, UDV=unit dose vial, Levalbuterol UDV=leva buterol inhalation solution
Source: Biometrics review by Dr. Yu Wang

Figure 3. Post-dose percent change in PEF at 1 hour



Abbreviations: MDI=metered-dose inhaler, TID=three times daily, UDV=unit dose vial, Levalbuterol UDV=leva buterol inhalation solution
Source: Biometrics review by Dr. Yu Wang

6.1.6 Other Endpoints

Although the Applicant analyzed additional efficacy endpoints (See Section 5.3), these were not reviewed in detail given the lack of statistical significance of the primary endpoint and the Applicant's decision to seek no further indication based on the results of this study.

6.1.7 Subpopulations

Because the study did not demonstrate overall effectiveness for Xopenex HFA in patients less than 4 years of age, differences by gender, race, or geographic region were not examined for this review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Subjects 0 to <24 months of age received low dose Xopenex HFA (45 mcg) while older subjects 24 to <48 months of age received the currently approved dose of Xopenex HFA (90 mcg). Although any dose-related efficacy findings are potentially confounded by age, there was no difference in the primary endpoint of PACA composite score at Week 4 based on dose/age group.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Current guidelines recommend that these short-acting β_2-adrenergic agonists be used as-needed rather than continuously.. In the small subset of patients with PEF measurements, the mean change in PEF from pre-dose to 1 hour post-dose increased from Visit 2 to 4. However, this may be a result of improved technique over the course of the study.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

This sNDA submission contains adequate data to update the Xopenex HFA product label regarding use in patients less than 4 years of age.

No deaths were reported in this study, and nonfatal serious adverse events (SAEs) were rare overall. However, SAEs only occurred with active treatment arms and primarily involved hospitalization for asthma or other respiratory illnesses such as pneumonia. In addition, safety data revealed a numerical increase in asthma-related

treatment-emergent adverse events and treatment discontinuations due to asthma in patients receiving Xopenex compared to placebo. Although the overall number of patients is small, the pattern is consistent with safety findings observed in the levalbuterol IS pediatric trials in patients under 6 years of age. Therefore, this safety information will be added to the product label. Furthermore, there was no substantial difference in the occurrence of hypokalemia, cardiovascular effects, or hyperglycemia among treatment groups, even though a decrease in β_2-agonist associated side effects is an often touted safety benefit of Xopenex use.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The single clinical trial submitted to this application (Study 051-359) was used to evaluate the safety of Xopenex HFA in pediatric patients less than 4 years of age; details of the study protocol are located in Section 5.1.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were defined as any reaction, side effect, or other undesirable event that occurred in conjunction with the use of study medication, whether or not the event was considered related to study medication. Adverse events were considered serious if the event was fatal or life-threatening, permanently disabling, required or prolonged hospitalization, represented a congenital anomaly, or required intervention to prevent permanent damage. Adverse events were collected from time of informed consent to the end of study. Serious adverse events (SAEs) were collected through 30 days after the last dose and followed until resolution or lost to follow up. The Applicant coded AEs using MedDRA version 16.0. Treatment emergent adverse events (TEAEs) were defined as AEs that occurred or worsened on or after the first dose of study medication.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Only a single study was included in this submission; therefore, pooling of data was not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 10 shows the overall exposure to each study treatment by age group, sex, race, and ethnicity as well as duration of exposure and completion rates. The total exposure was adequate to evaluate the safety of Xopenex HFA in patients under 4 years of age for the purposes of updating the label. As mentioned in Section 6.1.2, the early closure of the study which reduced the number of subjects in the youngest age group by a total of 3 is not expected to substantially affect the safety evaluation of Xopenex HFA.

Table 10. Demographics and Extent of Exposure

Category	Placebo N (%)	Xopenex HFA N (%)	Levalbuterol IS N (%)	Total[a] N (%)
Total (ITT population)	68	65	63	196
Age group (months)				
0 – 11	9 (13.2)	9 (13.8)	9 (14.3)	27 (13.8)
12 – 23	14 (20.5)	14 (21.5)	13 (20.6)	41 (20.9)
24 – 47	45 (66.2)	42 (64.6)	41 (65.1)	128 (65.3)
Sex				
Female	29 (42.6)	35 (53.8)	24 (38.1)	88 (44.9)
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	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)
Exposure				
Completed study, overall (%)	62 (91.2)	60 (92.3)	53 (84.1)	175 (89.3)
Mean exposure in days (SD)[b]	28.1 (4.5)	28.2 (4.2)	26.6 (6.9)	27.6 (5.3)
Mean number of doses received (SD)	80.9 (14.0)	81.5 (12.5)	76.9 (20.3)	79.8 (16)

Abbreviations: PBO=placebo, Levalbuterol IS=levalbuterol inhalation solution, ITT=intent-to-treat population, SD=standard deviation
[a]ITT population defined as any randomized subject who received at least 1 dose of study medication.
[b]Number of days on which at least one dose was received from Visit 1 through Visit 4 (includes placebo washout period)
Source: Module 5.3.5.4, Study 059-351 CSR, Table 5, p47; Table 17, p75; ADSL.xpt

7.2.2 Explorations for Dose Response

Two Xopenex HFA doses were evaluated in this study: 45 mcg TID in patients under 24 months of age and 90 mcg TID in patients 24 months of age and older. Following chronic dosing, there was no appreciable dose response in terms of efficacy or safety; however, fewer patients received the 45 mcg dose.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was submitted as part of this application.

7.2.4 Routine Clinical Testing

The safety evaluation in the Sponsor-initiated studies included monitoring of adverse events, vital signs, physical exam, and clinical laboratory tests. The methods used and the frequency of assessments provided an adequate assessment of the safety of Xopenex HFA in the treatment of asthma or reactive airway disease.

7.2.5 Metabolic, Clearance, and Interaction Workup

Appropriate studies to assess the absorption, distribution, metabolism, and clearance of levalbuterol tartrate were submitted by the Applicant in support of the original NDA for the use of Xopenex HFA to treat adult and adolescent patients with reversible obstructive airway disease.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As mentioned in Section 2.4, β_2-adrenergic agonists have the potential to cause paradoxical bronchospasm, particularly with continued or scheduled use. The Sponsor assessed for β_2-agonist related TEAEs, treatment failures, and asthma-related TEAEs; these findings are discussed in Section 7.3.5. In addition, the Sponsor included vital signs, clinical labs, and EKG to assess for common side effects such as tachycardia and hypokalemia as well as other cardiovascular effects; these results are discussed in Section 7.4.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in this study.

7.3.2 Nonfatal Serious Adverse Events

The number of nonfatal serious adverse events (SAEs) was low overall. However, SAEs only occurred in the Xopenex treatment arms, and the majority of events involved hospitalization for asthma exacerbations or other respiratory illnesses such as pneumonia.

Table 11. Nonfatal Serious Adverse Events

	Placebo N=68	Xopenex HFA N=65	Levalbuterol IS N=63	Total N=196

System Organ Class/ Preferred Term	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n
Overall	0	0	1 (1.5)	3	3 (4.8)	4	4 (2.0)	7
Infections and Infestations	0	0	1 (1.5)	1	2 (3.2)	2	3 (1.5)	3
Metapneumovirus infection	0	0	1 (1.5)	1	0	0	1 (0.5)	1
Pneumonia	0	0	0	0	1 (1.6)	1	1 (0.5)	1
UTI	0	0	0	0	1 (1.6)	1	1 (0.5)	1
Respiratory, Thoracic, and Mediastinal Disorders	0	0	1 (1.5)	2	2 (3.2)	2	3 (1.5)	4
Asthma	0	0	0	0	2 (3.2)	2	2 (1.0)	2
Hypoxia	0	0	1 (1.5)	1	0	0	1 (0.5)	1
Status asthmaticus	0	0	1 (1.5)	1	0	0	1 (0.5)	1

Abbreviations: IS=inhalation solution
N=ITT population
Sources: Module 5.3.5.4, Data Analysis Data, Analysis Dataset Legacy, ADAE.xpt and Study 059-351 CSR, Table 22, p81

A brief narrative for each nonfatal SAE is provided below:

Subject 0060/S041 (Xopenex HFA): This was an 18-month-old female with a history of asthma, RSV infection, GERD, and pneumonia on concomitant inhaled corticosteroid therapy. On Day (b) (6) she experienced fever, respiratory distress, cough, post-tussive emesis, and decreased activity/alertness. She was hospitalized for treatment of status asthmaticus with hypoxia (92% on room air) secondary to a meta-pneumovirus infection. A chest x-ray showing perihilar and peribronchiolar infiltrates was consistent with her diagnosis. No action was taken with the study medication due to the SAEs; however, she was discontinued from the study due to receiving disallowed medications (prednisolone) during the hospitalization.

Subject 0032/S013 (Levalbuterol IS): This was a 27-month old male with a history of exomphalos, asthma, and eczema who was not on concomitant inhaled corticosteroid controller therapy. On Day (b) (6) he experienced an acute asthma exacerbation which did not improve with ipratropium/albuterol and prednisolone treatment in the ED. He was admitted to the hospital for continued treatment and started on inhaled budesonide. Study medication was interrupted during the hospitalization, and he was subsequently discontinued from the study due to receiving disallowed medications (prednisone) during the hospitalization.

Subject 0060/S008 (Levalbuterol IS): This was a 43-month old male with history of recurrent otitis media, food allergy, allergic rhinitis, and asthma. Concomitant medications included montelukast but not an inhaled corticosteroid. On Day (b) (6) he presented to the ED with an acute asthma exacerbation with fever and hypoxia (94% on

room air) and found to have bi-basilar pneumonia on chest x-ray. Due to continued hypoxia despite continuous nebulization treatments in the ED, he was hospitalized for further treatment. He was discharged 3 days later, and these events led to discontinuation from the study.

Subject 0065/S001 (Levalbuterol IS): This was a 37-month-old female with history of recurrent otitis media, recurrent UTI, GERD, and asthma. On Day 29, she developed an E.coli UTI of moderate intensity that was treated with Bactrim. On Day (b) (6) she presented to the ED with persistent fever and ill appearance; a clean-catch urine culture revealed revealed E.coli resistant to Bactrim. She was hospitalized for treatment of her UTI, and discharged 2 days later once afebrile. She received her last dose of study medication on Day 26 and completed the study.

7.3.3 Dropouts and/or Discontinuations

The number of subjects who prematurely discontinued study medication due to an adverse event are displayed in the table below. Reviewer analysis of the Applicant's datasets did not reveal any additional adverse dropouts. Although the numbers are small, there are nominally more adverse drop-outs in the Xopenex treatment groups compared to placebo. Furthermore, treatment discontinuations due to asthma only occurred in Xopenex (levalbuterol) treatment groups. This trend was also observed in pediatric trials for levalbuterol IS in patients under 6 years of age (NDA 20-837, Supplement 041).

Table 12. Premature Treatment Discontinuations

Early Discontinuations	Placebo N=68		Xopenex HFA N=65		Levalbuterol IS N=63		Total N=196	
Overall, n(%)	6 (8.8)		5 (7.7)		10 (15.9)		21 (10.7)	
By age group								
0 to 11 months	0		0		0		0	
12 to 23 months	3 (4.4)		2 (3.0)		1 (1.6)		6 (3.1)	
24 to 47 months	3 (4.4)		3 (4.6)		9 (14.3)		15 (7.7)	
Early discontinuations due to AEs	**Subject n(%)**	**Event n**	**Subject n(%)**	**Event n**	**Subject n(%)**	**Event n**	**Subject n(%)**	**Event n**
Overall*	2 (2.9)	2	3 (4.6)	3	3 (4.8)	6	8 (4.1)	11
By Preferred Term								
Asthma	0	0	1 (1.5)	1	2 (3.2)	2	3 (1.5)	3
Pneumonia	1 (1.5)	1	1 (1.5)	1	2 (3.2)	2	4 (2.0)	4

Pyrexia	0	0	0	0	1 (1.6)	1	1 (0.5)	1
Sinusitis	0	0	1 (1.5)	1	0	0	1 (0.5)	1
Urticaria	1 (1.5)	1	0	0	0	0	1 (0.5)	1
Vomiting	0	0	0	0	1 (1.6)	1	1 (0.5)	1

*Some subjects reported more than one AE leading to discontinuation
Abbreviations: IS=inhalation solution
Source: Module 5.43.5.1, Study 051-359 CSR, Table 24, p83, and reviewer analysis of ADSL and ADAE datasets

7.3.4 Significant Adverse Events

In this study, a total of six TEAEs were reported as severe in intensity, all of which occurred in the Xopenex treatment groups (5 HFA, 1 inhalation solution). Pneumonia was the only severe TEAE reported in more than one patient (2 HFA, 1 inhalation solution). The remaining TEAEs graded as severe in intensity in the Xopenex HFA group included metapneumovirus, status asthmaticus, staphylococcal skin infection, eczema, epistaxis, hypoxia, diarrhea, and vomiting.

7.3.5 Submission Specific Primary Safety Concerns

Based on safety findings from the review of PREA-required pediatric trials for Levalbuterol IS (NDA 20-837, supplement 041), which included Study 051-359, the safety review of this application also focuses on evaluating the potential safety signal of asthma-related AEs. The following table lists asthma-related TEAEs by PT, regardless of whether or not the investigator considered the event to be drug-related. Similar to the pattern observed in reported SAEs and adverse drop-outs, there is a small increase the number of TEAEs related to asthma in the Xopenex treatment groups. Furthermore, all of the events in the placebo group were reports of cough, mild to moderate in severity. Similar results were observed in the number of protocol-defined treatment failures, defined as an increase in respiratory symptoms that necessitated a change in disease-related medication or necessitated study discontinuation for a respiratory-related adverse events/lack of efficacy. A total of 12 subjects were considered treatment failures: 1 placebo, 5 Xopenex HFA, and 6 levalbuterol IS.

Table 13. Asthma-related TEAEs

	Placebo N=68		**Xopenex HFA N=65**		**Levalbuterol IS N=63**		**Total N=196**	
	Subject n(%)	**Event n**	**Subject n(%)**	**Event n**	**Subject n(%)**	**Event n**	**Subject n(%)**	**Event n**
Overall*	3 (4.4)	3	8 (12.3)	10	6 (9.5)	6	17 (8.7)	19
Preferred Term								

Asthma	0	0	3 (4.6)	3	4 (6.3)	4	7 (3.6)	7
Cough	3 (4.4)	3	4 (6.2)	4	2 (3.2)	2	9 (4.6)	9
Hypoxia	0	0	1 (1.5)	1	0	0	1 (0.5)	1
Status Asthmaticus	0	0	1 (1.5)	1	0	0	1 (0.5)	1
Tachypnea	0	0	1 (1.5)	1	0	0	1 (0.5)	1

Abbreviations: IS=inhalation solution, N=ITT population
*One subject reported more than one asthma-related TEAE
Source: Module 5.43.5.1, Study 051-359 CSR, Table 27, p86, and reviewer analysis of ADAE dataset

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common AEs reported in this study were pyrexia, otitis media, and upper respiratory tract infection. Overall, the type and frequency of common adverse events generally appears similar to those observed in the clinical trials of Xopenex HFA in patients ≥4 years of age, although there were fewer reports of β2-agonist side effects such as tremor and tachycardia. Table 14 displays TEAEs that occurred in ≥2% of overall subjects while Figure 4 displays the number of potential β_2-agonist mediated TEAEs.

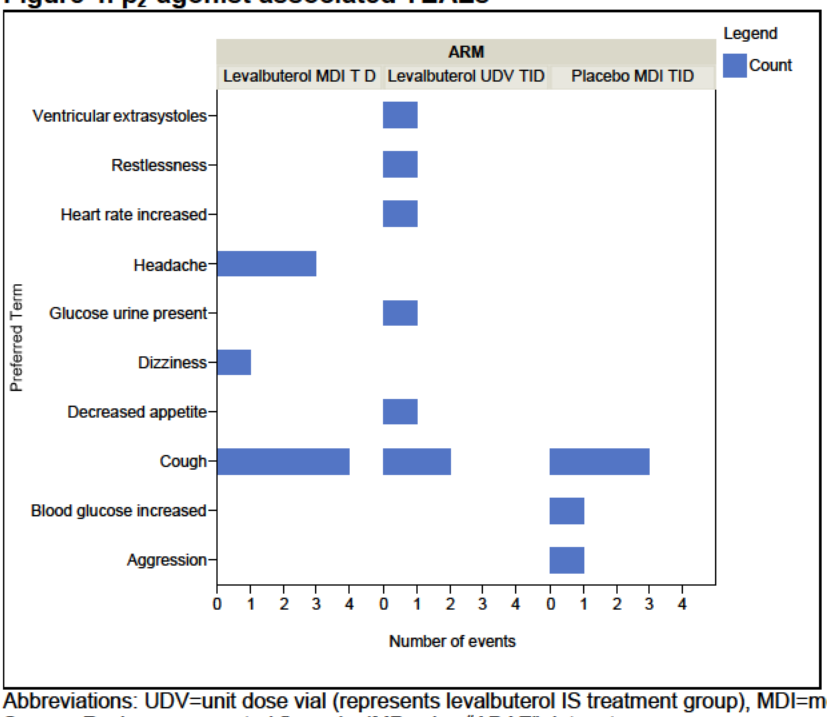
Table 14. Common TEAEs occurring in ≥2% of subjects overall

	Placebo N=68		Xopenex HFA N=65		Levalbuterol IS N=63		Total N=196	
System Organ Class Preferred Term	**Subject n (%)**	**Event n**	**Subject n (%)**	**Event n**	**Subject n (%)**	**Event n**	**Subject n (%)**	**Event n**
Overall	28 (41.2)	52	31 (47.7)	83	29 (46.0)	55	88 (44.9)	190
Gastrointestinal Disorders	7 (10.3)	9	8 (12.3)	14	4 (6.3)	5	19 (9.7)	28
Diarrhea	3 (4.4)	4	6 (9.2)	8	2 (3.2)	2	11 (5.6)	14
Vomiting	2 (2.9)	2	3 (4.6)	3	2 (3.2)	2	7 (3.6)	7
General Disorders and Administration Site Conditions	7 (10.3)	7	4 (6.2)	4	7 (11.1)	7	18 (9.2)	18
Pyrexia	6(8.8)	6	3 (4.6)	3	7 (11.1)	7	16 (8.2)	16
Infections and Infestations	15 (22.1)	20	17 (26.2)	28	19 (30.2)	22	51 (26.0)	70
Nasopharyngitis	3 (4.4)	3	1 (1.5)	1	1 (1.6)	1	5 (2.6)	5
Otitis media/Acute otitis media*	5 (7.4)	6	6 (9.2)	7	8 (12.7)	8	19 (9.7)	21
Pneumonia	1 (1.5)	1	2 (3.1)	2	2 (3.2)	2	5 (2.6)	5
Sinusitis/Bacterial Sinusitis*	1 (1.5)	1	4 (6.2)	4	0	0	5 (2.6)	5
Upper respiratory tract infection/Viral upper respiratory tract infection*	4 (5.9)	4	5 (7.7)	5	6 (9.2)	6	15 (7.7)	15
Respiratory, Thoracic, and Mediastinal Disorders	6 (8.8)	7	12 (18.5)	19	6 (9.5)	6	24 (12.2)	32

Asthma/Status asthmaticus*	0	0	4 (6.2)	4	4 (6.3)	4	8 (4.1)	8
Cough	3 (4.4)	3	4 (6.2)	4	2 (3.2)	2	9 (4.6)	9
Rhinorrhea/Respiratory tract congestion/Nasal congestion*	3 (4.4)	3	6 (9.2)	7	0	0	9 (4.6)	10

*Similar PT have been combined; therefore frequencies differ slightly from those presented by the Applicant.
Abbreviations: IS=inhalation solution,N=ITT population
Sources: Module 5.3.5.4, Data Analysis Data, Analysis Dataset Legacy, ADAE.xpt and Study 059-351 CSR, Table 19, p77

Figure 4. β_2-agonist associated TEAEs



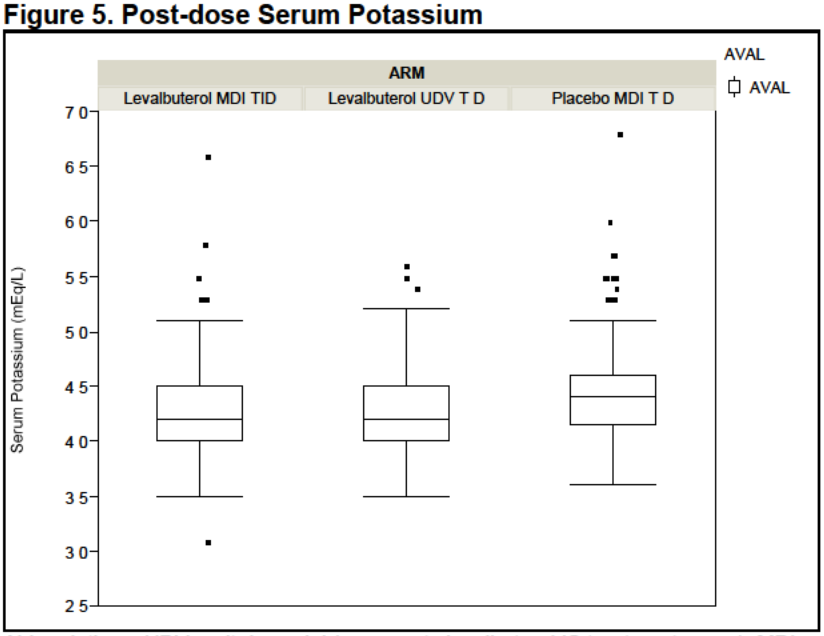
Abbreviations: UDV=unit dose vial (represents levalbuterol IS treatment group), MDI=metered dose inhaler, TID=three times daily
Source: Reviewer generated figure in JMP using "ADAE" dataset

7.4.2 Laboratory Findings

As with other β-adrenergic agonists, Xopenex HFA may cause hypokalemia through intracellular shunting, which could potentially result in adverse cardiovascular effects. In addition, activation of the β_2-adrenergic receptor in the liver and skeletal muscles can promote breakdown of glycogen into glucose leading to hyperglycemia, although this phenomenon is typically observed only in diabetic patients.

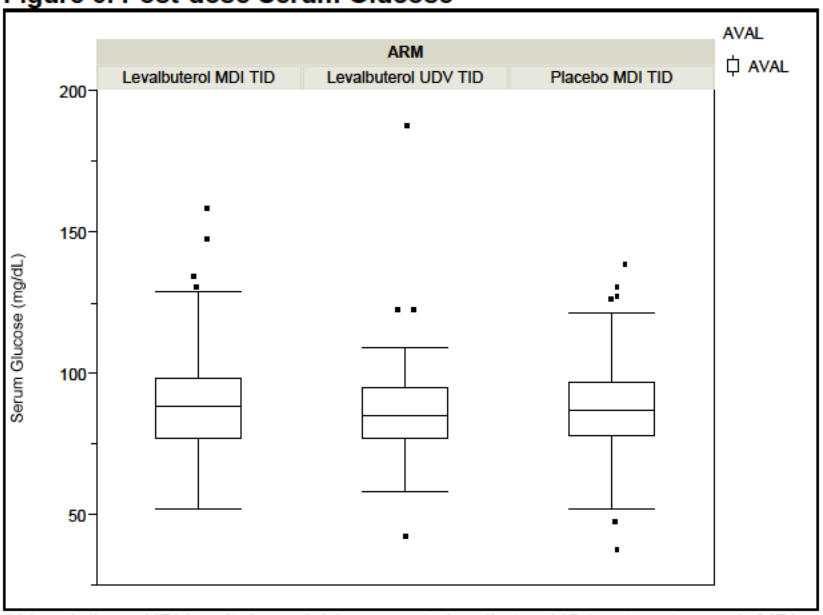
Serum potassium and glucose levels obtained post-dose are shown below. There was no apparent clinically significant difference in average potassium or glucose levels among treatment groups observed in this study.

Figure 5. Post-dose Serum Potassium



Abbreviations: UDV=unit dose vial (represents levalbuterol IS treatment group), MDI=metered dose inhaler, TID=three times daily
The figure displays an outlier box plot of the serum potassium levels measured 1 hour postdose in the ITT population from Visits 2 and 4. The vertical line represents the median while the box represents the interquartile range. The whiskers extend to 1.5x the interquartile range with outliers represented by individual data points. The figure includes a total of 323 observations with approximately 100 per treatment group.
Source: Reviewer generated figure in JMP using "ADLB" dataset

Figure 6. Post-dose Serum Glucose

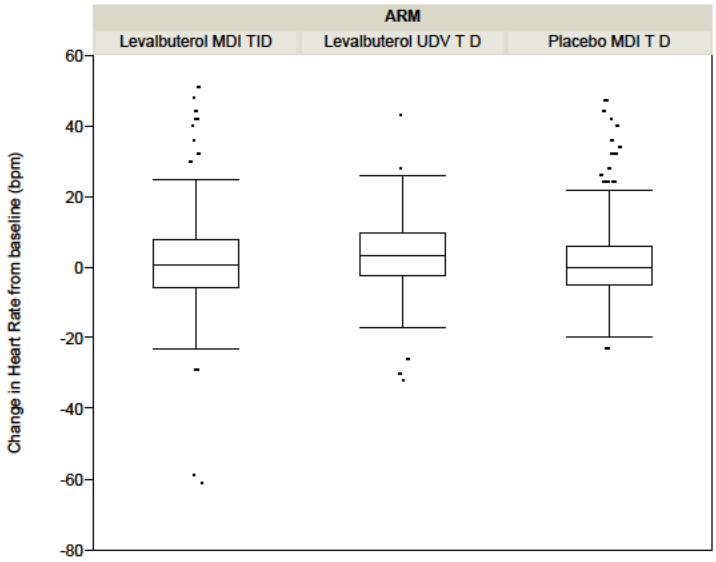


Abbreviations: UDV=unit dose vial (represents levalbuterol IS treatment group), MDI=metered dose inhaler, TID=three times daily
The figure displays an outlier box plot of the serum glucose levels measured 1 hour postdose in the ITT population from Visits 2 and 4. The vertical line represents the median while the box represents the interquartile range. The whiskers extend to 1.5x the interquartile range with outliers represented by individual data points. The figure includes a total of 323 observations with approximately 100 per treatment group.
Source: Reviewer generated figure in JMP using "ADLB" dataset

7.4.3 Vital Signs

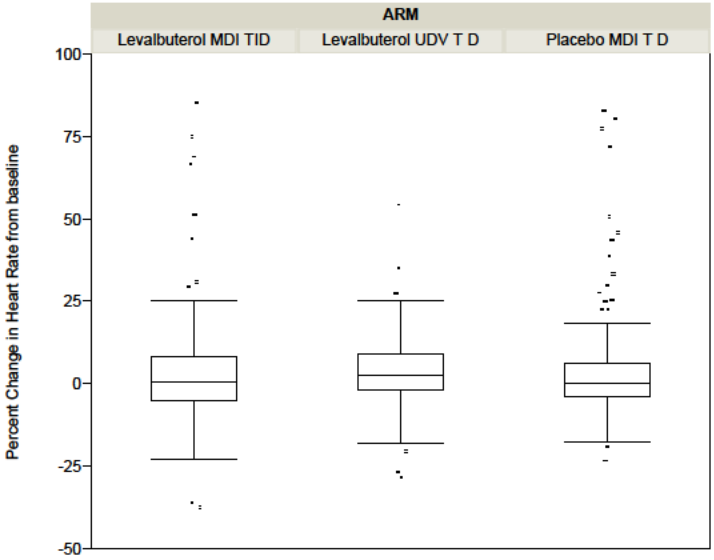
Binding to β-receptors on cardiac tissue, β-adrenergic agonists may cause cardiac stimulation with increased heart rate, contractility, conduction velocity and systemic vasodilation. The figures below display the post-dose change and percent change in heart rate measurements from baseline. There was no apparent clinically significant difference in the heart rate measurements among treatment groups. Moreover, the often purported safety advantage that Xopenex causes fewer cardiovascular side effects was not observed in this study, as the mean change was similar to placebo.

Figure 7. Post-dose Heart Rate, change from baseline



Abbreviations: UDV=unit dose vial (represents Leva buterol IS treatment group), MDI=metered dose inhaler, TID=three times daily
The figure displays an outlier box plot of the absolute change from baseline in heart rate measurements 15 and 30 minutes postdose in the ITT population from Visit 2. Baseline was defined as the pre-dose measurement at Visit 2. The vertical line represents the median while the box represents the interquartile range. The whiskers extend to 1.5x the interquartile range with outliers represented by individual data points. The figure includes a total of 392 observations.
Source: Reviewer generated figure in JMP using "ADVS" dataset

Figure 8. Post-dose Heart Rate, percent change from baseline



Abbreviations: UDV=unit dose vial (represents Leva buterol IS treatment group), MDI=metered dose inhaler, TID=three times daily
The figure displays an outlier box plot of the percent change from baseline in heart rate measurements 15 and 30 minutes postdose in the ITT population from Visit 2. Baseline was defined as the pre-dose measurement at Visit 2. The vertical line represents the median while the box represents the interquartile range. The whiskers extend to 1.5x the interquartile range with outliers represented by individual data points. The figure includes a total of 392 observations.
Source: Reviewer generated figure in JMP using "ADVS" dataset

7.4.4 Electrocardiograms (ECGs)

β-adrenergic agonists have been reported to produce ECG changes such as flattening of the t-wave, prolongation of the QTc interval, and ST segment depression. Standard 12-lead ECGs were performed pre-dose and 1 hour post-dose at Visits 1, 2, and 4. A small number of patients with baseline QTc <450 ms experienced QTc prolongation >450 ms using Bazett's correction (2 placebo, 4 Xopenex HFA); however, the occurrences were sporadic and do not appear to be clinically significant.

7.4.5 Special Safety Studies/Clinical Trials

No additional special safety studies were included or required in this submission.

7.4.6 Immunogenicity

Immunogenicity was not specifically addressed as levalbuterol tartrate is a small molecular entity with no known immunogenic potential.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The lower Xopenex HFA 45 mcg dose was only administered to younger subjects (< 24 months of age), who represented a smaller proportion of the overall study population. Acknowledging this limitation, there was no clear dose dependency for adverse events.

7.5.2 Time Dependency for Adverse Events

There was no apparent time dependency for adverse events.

7.5.3 Drug-Demographic Interactions

There were no apparent drug-demographic interactions based on limited subgroup analyses.

7.5.4 Drug-Disease Interactions

There was no assessment of drug-disease interactions in this submission.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were included in this submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity studies were included in this submission. Levalbuterol has demonstrated no carcinogenic potential in nonclinical studies.

7.6.2 Human Reproduction and Pregnancy Data

The use of Xopenex HFA during pregnancy and lactation has not been evaluated in any adequate and well-controlled studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

No growth studies were included in this submission as no growth effects are known to occur with the use of Xopenex HFA.

Reference ID: 3704097

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The expected symptoms of overdosage are those of excessive β-adrenergic receptor stimulation or exaggeration of any of the adverse reactions currently listed in the product label. Treatment consists of discontinuation of Xopenex HFA together with appropriate symptomatic therapy. No additional data on the effects of acute or chronic overdosage, abuse, or dependence potential were included or required in this submission.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a Periodic Adverse Experience Report on May 7, 2014, covering the reporting period of March 11, 2013 through March 10, 2014. Of the 40 spontaneous reports received, three were considered serious, none of which involved patients less than 4 years of age. Additionally, none of the non-serious reports were explicitly for patients less than 4 years of age; however, a number of reports were missing information regarding patient age.

8 Postmarket Experience

The Applicant estimated the commercial usage of Xopenex HFA from January 2006 to September 2013 in patients below 4 years of age to be 5.9% based on number of prescriptions dispensed and surveys from panel doctors. A total of 8 postmarketing events were spontaneously reported for Xopenex HFA in this age group: 2 events in the birth to <1 year olds, 0 events in the 1 to <2 year olds, 6 events in the 2 to <4 year olds. In addition, there were 34 events reported in patients 4 to <6 years old. The most frequently reported events were cough, drug ineffective, wheezing, asthma, dyspnea, and vomiting. While the utility of spontaneous postmarketing reports is limited by the variability in reporting rates and lack of a control or a denominator to determine frequency, the postmarketing experience with Xopenex HFA after nearly 10 years of commercial availability suggests that the safety profile in pediatric patients below 4 years of age is generally similar to the adverse event profile observed in controlled clinical trials in this age group. Although asthma-related adverse reactions were reported following off-label use in children under 4 years, the relatively small number of events does not support inclusion of (b) (4)

9 Appendices

9.1 Literature Review/References

A PubMed search using the terms “levalbuterol AND pediatric” and “levalbuterol metered dose inhaler” retrieved 38 and 9 articles, respectively. None of the published articles change the risk-benefit assessment any further.

9.2 Labeling Recommendations

Major labeling changes included updating Section 8.4 with efficacy and safety data for pediatric patients <4 years of age, specifically with information regarding the increased number of asthma-related adverse reactions in the Xopenex treatment groups. In addition, the label was revised to incorporate format changes to conform with the Agency’s best labeling practice initiative. The Office of Prescription Drug Promotion (OPDP), the Division of Medical Policy Programs (DMPP), and the Division of Medication Error Prevention and Analysis (DMEPA) had no further recommendations following review of the revised label and package insert.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not held for this supplemental NDA. Xopenex HFA is already approved for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease, and the Applicant is not seeking to expand the indication.

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/s/

STACY J CHIN
02/19/2015

ANTHONY G DURMOWICZ
02/19/2015