CLINICAL REVIEW

Application Type	Pediatric efficacy supplement
Application Number(s)	NDA 20-837/S-041
Priority or Standard	Standard
Submit Date(s)	3/28/2014
Received Date(s)	3/28/2014
PDUFA Goal Date	1/28/2014
Division / Office	DPARP / ODEII
Reviewer Name(s)	Stacy Chin, MD
Review Completion Date	12/19/2014
Established Name	levalbuterol hydrochloride
Trade Name	Xopenex Inhalation Solution
Therapeutic Class	β2-adrenergic agonist
Applicant	Oak Pharmaceuticals, Inc. (subsidiary of Akorn, Inc.); ownership transferred from Sunovion Pharmaceuticals Inc. on 10/1/2014
Formulation(s)	0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL, and 1.25 mg/0.5 mL unit dose vials
Dosing Regimen	0.31 mg to 1.25 mg three times daily
Indication(s)	Reversible obstructive airway disease
Intended Population(s)	≥ 6 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 6 years of age.

1.2 Risk Benefit Assessment

The application contains clinical data from five pediatric trials which enrolled patients under 6 years of age with asthma or reactive airway disease. Because these studies were not part of a planned pediatric development program, the studies were of varying design and utility to the efficacy and safety evaluation. Despite this limitation, the Agency agreed to accept all clinical data available in this age group in order to update the product label accordingly and to fulfill the long-outstanding PREA requirement for pediatric patients less than 6 years of age. The single placebo-controlled trial (051-032) evaluated the effectiveness of levalbuterol inhalation solution 0.31 mg and 0.63 mg three times daily over 3 weeks compared with placebo and racemic albuterol in reducing asthma symptoms as measured by the Pediatric Asthma Questionnaire. Neither dose of levalbuterol inhalation solution demonstrated consistent efficacy in asthmatic patients 2 to 5 years of age. Of the remaining four studies submitted, none were adequately designed to demonstrate substantial evidence of efficacy.

Regarding safety in patients less than 6 years of age, there was a small but consistent pattern of increased asthma exacerbations, asthma-related treatment-emergent adverse events, and treatment discontinuations due to asthma in patients receiving levalbuterol inhalation solution compared to placebo or racemic albuterol. This along with the lack of consistent efficacy does not support approval for use in pediatric patients under 6 years of age and warrants inclusion in the product label. Based on the submitted data, the Applicant has not requested an indication in the younger age group. The risk benefit profile of Xopenex IS in the approved population of patients 6 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

There are no recommendations for additional postmarketing requirements or commitments. This submission fulfills the outstanding PREA postmarketing requirement for studies in pediatric patients under 6 years of age.

2 Introduction and Regulatory Background

2.1 Product Information

Xopenex (levalbuterol HCl) Inhalation Solution was approved on March 25, 1999, for the treatment and prevention of bronchospasm in adults and adolescents 12 years of age or older with reversible obstructive airway disease, and on January 30, 2002, for children 6 to 11 years of age. Levalbuterol HCl is a relatively selective β_2-adrenergic receptor agonist available in dosages of 0.31 mg, 0.63 mg, and 1.25 mg in 3 mL unit-dose vials and in a concentrated formulation of 1.25 mg/0.5 mL, primarily for use in hospital settings. The recommended starting dose in adults and adolescents is 0.63 mg administered three times a day (TID) every 6 to 8 hours by nebulization, with doses of 1.25 mg TID reserved for patients with severe asthma or an inadequate response to the starting dose. The recommended starting dose for children 6 to 11 years of age is 0.31 mg TID every 6 to 8 hours, with doses not to exceed 0.63 mg TID.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following table lists the available products approved for the prevention and 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
Pirbuterol acetate	Maxair Autohaler	microcrystalline suspension in metered-dose aerosol for oral inhalation with breath-activated actuator	≥ 12

*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 HFA (levalbuterol tartrate inhalation aerosol), which was approved on March 11, 2005, for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible airway disease. No major safety issues have arisen since its approval.

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 (b) (4) While racemic albuterol contains (b) (4) (R)- and the (S)- enantiomers, levalbuterol contains only the (b) (4) (R)-enantiomer. (b) (4)

However, as suggested by some *in vitro* data, the more slowly metabolized S-enantiomer may be responsible for the adverse effects of β_2-agonists, such as increased contractility of airway smooth muscle and mediator release. Although, this finding would theoretically make levalbuterol a "safer" drug, no consistent differences have been found with levalbuterol compared with racemic albuterol in bronchodilation, bronchoprotection, or side effects.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following is an abbreviated timeline of regulatory interactions related to the levalbuterol inhalation solution (Lev IS) pediatric development program. Of note, three Written Requests (WR) were issued for Xopenex Inhalation Solution; (b) (4) and since then, all WRs have expired.

3/25/1999	Approved for the treatment and prevention of bronchospasm in adult and adolescents ≥ 12 years of age
3/16/2000	Pediatric Written Request No. 1 issued (IND# 47363) for age < 6 yrs
1/30/2002	Efficacy supplement 006 approved for children 6 to 11 years of age; the PREA requirement studies for patients <6 years of age were deferred with a final report submission due July 31, 2003
7/30/2002	Pediatric Written Request No. 2 issued (IND#47363)
9/27/2002	(b) (4)
3/12/2003	(b) (4)
8/4/2005	Pediatric Written Request No. 3 issued (IND#47363)
3/11/2005	Approval of Xopenex HFA Inhalation Aerosol (NDA #21730) for patients ≥ 4 years of age
12/14/2005	Sponsor notified FDA of plan to not fulfill Written Request for Xopenex IS
11/14/2012	Agency issued a Deferral Extension Notice regarding the outstanding PREA requirement
12/21/2012	(b) (4)
5/29/2013	(b) (4)
5/31/2013	Division provided the Sponsor with preliminary comments regarding our agreement with their proposal to submit 5 studies by March 2014 to fulfill PREA
6/5/2013	(b) (4)
6/13/2013	Notice of Non-Compliance with PREA issued
3/28/2014	Supplement 041 submitted

2.6 Other Relevant Background Information

On October 1, 2014, the Applicant (Sunovion Pharmaceuticals, Inc.) transferred ownership of this NDA (20-837) to Oak Pharmaceuticals, Inc.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA was submitted electronically and included complete study reports, 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 the majority of studies were conducted greater than 10 years ago. In addition, Xopenex Inhalation Solution 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 trials were 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 protocols and written informed consent forms 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 who participated in the clinical trials referenced in this sNDA disclosed receiving significant financial compensation from Sunovion. One sub-investigator for Study (b) (6) (b) (6) reported receiving a consultation fee of >$25,000 after study initiation. To ensure full compliance with the protocols and minimize bias of the clinical study results, the investigator and study coordinators attended an investigators' meeting where protocol specifications and regulatory responsibilities were reviewed in detail, and the study site was monitored by trained Clinical Research personnel with a 100% review of source documentation to the case record form data. 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: 94		
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): 1		
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: 1 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 interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from applicant)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Levalbuterol HCl inhalation solution is an approved product; therefore, no new quality data was submitted or required.

4.2 Clinical Microbiology

Levalbuterol HCl inhalation solution 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

This supplement included limited data from pharmacokinetic (PK) sampling in pediatric patients, primarily from Studies 051-032 and 051-359. Levalbuterol treatment groups from Study 051-032 had measurable (R)-albuterol plasma concentrations, but also had measurable (S)-albuterol plasma concentrations, albeit at lower levels than observed in the racemic albuterol group. Similarly, 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, (b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

As previously agreed upon, the Applicant submitted data from five clinical trials in patients under 6 years of age to fulfill PREA. An overview of the trials are provided in the table below.

Table 3. Sources of Clinical Data

Study	Dates	Design	Age (yrs)	Treatments: N[1]	Treatment Duration	Primary Endpoint
051-032	11/2000-11/2001	R, DB, PG, PC, AC	2-4	Lev IS 0.31mg: 58 Lev IS 0.63 mg: 51 RAC[2]: 52 PBO: 50	TID x 3 weeks[6]	Mean Δ in PAQ total score
051-033	02/2001-07/2002	R, DB, PG, AC	0-4	LD Lev IS[3]: 42 HD Lev IS[4]: 40 RAC[5]: 35	Period I: during acute exacerbation: up to 3hrs (6 doses) Period II: TID x 7-10d Period III: PRN to TID x 7-10d	Maximum decrease in RSS (Period I)
091-029	01/2008-12/2008	R. DB. XO, OL	2-11	Lev IS 0.63mg: 51 ARF 7.5µg: 52 ARF 15 µg (OL): 40	2 crossover periods: 3 doses over 1 hr OL period: 3 doses over 1 hr	Safety and PK
051-359	01/2009-06/2013	R, DB/OL, PG, PC	0-3	Lev HFA: 65 Lev IS 0.31mg: 63 PBO: 68	TID x 4 weeks[6]	Mean Δ in PACA score
051-SRC038	04/2000-01/2001	R, DB, AC, SC	2-17	Lev IS 1.25mg: 250 RAC 2.5mg: 233	During acute exacerbation: up to 6 doses in ED and PRN during 1 hr to 4 day hospitalization	Rate of hospital admissions and length of stay

Abbreviations: R=randomized, DB=double-blind, PG=parallel group, PC=placebo-controlled, OL=open label, AC=active control, SC=single center, Lev IS=levalbuterol HCl inhalation solution, Lev HFA=levalbuterol tartrate HFA MDI, RAC=racemic albuterol, PBO=placebo, LD=low-dose, HD=high-dose, ARF=arformoterol, TID=three times daily, d=days, hr=hour(s), PRN="pro re nata" (as needed),PAQ=Pediatric Asthma Questionnaire, RSS=Respiratory Status Scale, PACA=Pediatric Asthma Caregiver Assessments
[1]N=Randomized subjects
[2]Racemic albuterol dose based on weight; subjects <33 lbs. received 1.25mg, subjects ≥33 lbs. received 2.5mg
[3]Low dose Lev IS based on weight: 2.5 to 5kg – 0.15mg, >5 to 10kg – 0.31mg, >10kg – 0.63mg
[4]High dose Lev IS based on weight: 2.5 to 5kg – 0.31mg, >5 to 10 kg – 0.63mg, >10kg – 1.25mg
[5]Racemic albuterol dose based on weight: 2.5 to 5kg – 0.63mg, >5 to 10kg – 1.25mg, >10kg – 2.5mg
[6]Preceded by 1-week placebo run-in period
Source: Module 5.2 Tabular Listing of All Clinical Studies

5.2 Review Strategy

The primary focus of this review will be on safety since only Study 051-032 was adequately designed and controlled to evaluate efficacy and the Applicant is not seeking an indication for this younger age group. The majority of safety data is derived from three studies: 051-032, 051-033, and 051-359. The remaining studies, 091-029 and 051-SRC038, included a small number of patients for a brief treatment period or failed to thoroughly capture adverse events.

5.3 Discussion of Individual Studies/Clinical Trials

Because of the varying study designs, this section describes each study individually. Efficacy and safety results are presented separately in Sections 6 and 7, respectively.

5.3.1 Study 051-032

Protocol #	051-032
Title	An Efficacy, Safety, and Tolerability Study of Daily Dosing with Levalbuterol, Racemic Albuterol, and Placebo in Pediatric Subjects 2-5 Years Old with Asthma
Study dates	Study initiated: November 28, 2000 Study completed: November 30, 2001 Final study report: May 30, 2002
Sites	46 clinical study sites in the U.S.
IND	47,363
IRBs	• (b) (4) •

Amendments
The protocol was amended on December 14, 2000, to change the timing of the primary efficacy analysis and population PK analysis from the second to the third week of treatment.

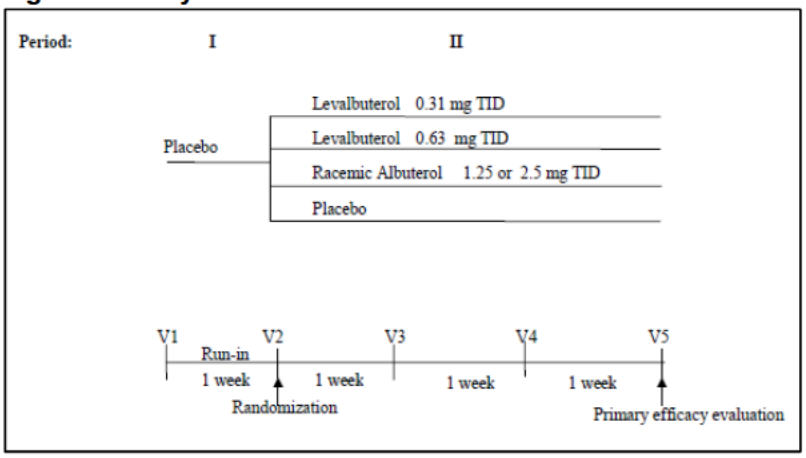
Objectives
The objectives of this study were to assess the efficacy (primary) and safety/tolerability and pharmacokinetics (secondary) of two doses of levalbuterol in pediatric subjects 2 to 5 years of age. Other secondary objectives included a comparative effectiveness evaluation of racemic albuterol versus placebo and levalbuterol versus racemic albuterol in this age group.

Study Design
This study was a multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 trial in pediatric patients 2 to 5 years of age with asthma. Subjects were screened at Visit 1 after which eligible subjects entered a 7-day placebo run-in period and returned for randomization at Visit 2. Subjects who had exhibited pre-specified asthma symptoms[1] and ≥80% compliance during the run-in period were randomized equally to one of four study treatments: a) 0.31 mg Lev IS, b) 0.63 mg Lev IS, c) racemic albuterol [1.25 mg (<33 lbs) or 2.5 mg (≥33 lbs)], or d) placebo. Rescue medication consisted of double-blind 1.25 mg Lev IS for all subjects during the placebo run-in period and for all subjects randomized to treatment with Lev IS, while the racemic albuterol and placebo treatment groups received double-blind 2.5 mg racemic albuterol

[1] Defined as cough, wheezing, shortness of breath, or nocturnal asthma awakenings requiring the use of PRN rescue medication on 3 of the previous 7 days.

for rescue medication use during the 3-week double-blind treatment period. Study medication was administered via face mask or mouthpiece with the PARI DURA-NEB 3000™ compressor and PARI LC PLUS™ nebulizer provided by the Sponsor. Follow-up visits (Visits 3-5) occurred weekly during the treatment period. A final safety evaluation was conducted by telephone 3 days after the last study visit. A schematic of the study design and a schedule of study assessments are shown below.

Figure 1. Study Schematic: 051-032



Source: Module 5.3.5.1, Study 051-032, Legacy CSR, p27

Table 4. Schedule of Assessments: Study 051-032

Study Schedule	Period I		Period II				
Clinic Visit	1	Phone	2	3	4	5	Phone
Days	-7	-4, 3, 10, 17	0	7	14	21	24
	Screening	**Telephone Evaluations**	**Randomization Period**				**Telephone Evaluation**
Informed Consent	X						
Inclusion / Exclusion	X		X				
Medical History	X						
Physical Exam	X					X	
Chest X-Ray	X[a]						
ECGs	X		X	X	X	X	
Adverse Event Assessment	X	X	X	X	X	X	X
Vital Signs	X		X	X	X	X	
Peak Flow	X[b]		X[b]	X[b]	X[b]	X[b]	
BLOOD DRAWS	X				X	X	
Chemistry	X					X	
Hematology	X					X	
Urinalysis	X					X	
PK	X[c]						
Serial PK						X[c,f]	
Theophylline Levels	X[d]					X[d]	
Outcome Questionnaires			X[e]			X[e]	
Health Status CHQ-PF50, FS-II(R)			X[e]			X[e]	
Quality of Life (PACQLQ)			X[e]			X[e]	
Global Evaluations						X[e]	
Caregiver Asthma Symptom Assessment		X					
Review of Safety Assessments	X	X	X	X	X	X	X
Review of Diary Card/Completion		X	X	X	X	X	
Start of Single-Blind	X						
Start of Double-Blind			X				
Assess Compliance			X	X	X	X	
Assess Concomitant Medications	X	X	X	X	X	X	

a. The most recent chest x-ray within 12 months was allowable.
b. At the Investigator's discretion.
c. PK samples were collected at selected sites predose at Week -1 (Visit 1) and at Week 3 (Visit 5) at the following three time points: 1) predose; 2) 30-60 minutes postdose; or 3) 180-360 minutes postdose. Samples collected between subjects were required to be staggered between the 30-60 minute and 180-360 minute intervals.
d. Samples were obtained for subjects currently on theophylline.
e. Required to be performed as the first procedure during Week 0 (Visits 2) and Week 3 (Visit 5). The physician's global evaluation was completed at the end of Visit 5.
f. Per Protocol Amendment #1, implemented 14 December 2000, serial PK sampling was changed from Day 14 to Day 21.

Source: Module 5.3.5.1, Study 051-032, Legacy CSR, Table 9.5.1-1, p35

Study Population
A total of 211 subjects were randomized to study treatment: 58 to Lev IS 0.31 mg, 51 to Lev IS 0.63 mg, 52 to racemic albuterol, and 50 to placebo.

Key Inclusion Criteria

1. Male or female between the ages of 2 and 5 years (inclusive) at the time of consent.
2. Physician-diagnosis of asthma for a minimum of 30 days prior to Visit 1. (Investigators were allowed to enroll subjects under their direct supervision with newly diagnosed asthma.)
3. Overall good health with the exception of asthma
4. Chest x-ray (within the past 12 months) with no evidence of pneumonia, atelectasis, pulmonary fibrotic disease, pneumothorax, etc.
5. Parent/legal guardian able to reliably complete diary cards and medical event calendars on a daily basis.

Key Exclusion Criteria

1. History of hospitalization for asthma within 30 days prior to Visit 1 or scheduled for in-patient hospitalization, including elective surgery, during the trial.
2. Life-threatening asthma, defined as a history of asthma episodes requiring intubation, associated with hypercapnia, respiratory arrest, or hypoxic seizures within 12 months prior to Visit 1.
3. Disallowed medication use or expected use during the trial
4. Clinically significant abnormalities that may interfere with metabolism or excretion of study drug or diseases (e.g., hyperthyroidism, diabetes, hypertension, cardiac disease, seizures) that were not well-controlled by medication or that may interfere with completion of study
5. History of cancer
6. Bronchopulmonary aspergillosis or any form of allergic alveolitis
7. Purulent respiratory tract infection in the 14 days prior to Visit 1 or during the study
8. Clinically significant laboratory or 12-lead ECG abnormality

Withdrawal Criteria
Subjects may have been discontinued from study treatment for any of the following reasons:

- Adverse event
- Intercurrent illness
- Protocol violation
- Use of disallowed medications
- Administrative reasons
- Withdrawal of consent

Subjects who were prematurely discontinued from the trial were required to be seen for the Visit 5/Early Termination procedures.

Prohibited Medications
Disallowed medications as well as the required washout period for each medication are listed in the table below.

Table 5. Disallowed Medications: Study 051-032

Medication	Wash-Out Periods
Antihistamines	
Astemizole	90 days
Corticosteroids	
Parenteral	30 days
Oral	30 days
Adrenergic bronchodilators	
Inhaled, short-acting	≥8 hours
Nebulized, short acting	≥10 hours
Inhaled, long acting	≥24 hours
Oral QID or TID preparations	≥24 hours
Oral BID preparations	≥36 hours
Nonprescription asthma medications	48 hours

Source: Module 5.3.5.1. Study 051-032 Legacy CSR, Table 9.3.2-1, p29

Concomitant Medications
The following medications were allowed at enrollment and during the study if the dose had been stable for the specified amount of time prior to Visit 1 or at the discretion of the individual investigator.

Table 6. Concomitant Medications: Study 051-032

Medication	Stable dose prior to Visit 1
Theophylline	5 days
Leukotriene inhibitor	30 days
Ipratropium bromide	5 days
Antibiotics	N/A
Inhaled corticosteroids	21 days
Topical corticosteroids	Investigator's discretion
Mucolytics, expectorants, decongestants	Investigator's discretion
Antihistamines (except astemizole)	Investigator's discretion
Nedocromil sodium and cromolyn sodium	5 days
Immunotherapy	30 days
Other medications	Investigator's discretion
Source: Module 5.3.5.1, Study 051-032, Legacy CSR, p33	

Treatments/Dosing Rationale
The study included four treatment groups:

- Levalbuterol 0.63 mg: (R)-albuterol HCl Ampule Inhalation Solution, 0.042% (w/v), 0.625 mg/3 mL in 0.9% saline

- Levalbuterol 0.31 mg: (R)-albuterol HCl Ampule Inhalation Solution, 0.0105% (w/v), 0.312 mg/3 mL in 0.9% saline
- Racemic albuterol 1.25 mg (<33 lbs) or 2.5 mg (≥33 lbs): (R,S)-albuterol HCl Ampule Inhalation Solution, 0.083% (w/v), 1.25 mg/3 mL or 2.5 mg/3 mL in 0.9% saline
- Placebo: 0.9% saline/3 mL

Rescue medication consisted of 1.25 mg Lev IS for all subjects during the placebo run-in period. Blinded rescue medication during the double-blind treatment period consisted of 1.25 mg Lev IS for both levalbuterol groups and 2.5 mg racemic albuterol for the racemic albuterol and placebo groups.

Study medication was administered using a PARI LC PLUS™ nebulizer with a mouthpiece or face mask and a PARI DURA-NEB™ 3000 compressor three times daily (minimum 4 hours in between doses) for 3 weeks.

Dose selection for this age group was based on data from previous studies demonstrating that the peak change in FEV_1 produced by 0.31 mg and 0.63 mg of Lev IS was similar to 1.25 mg and 2.5 mg of racemic albuterol, respectively. In addition, an investigator-initiated study (051-SRC038) had administered Lev IS doses as high as 1.25 mg every 20 minutes for up to 6 doses in children ages 1-18 years of age with no significant adverse events reported.

Compliance was measured by the number of study drug ampules dispensed, returned, and lost.

Efficacy

The primary efficacy variable was the total score from the Pediatric Asthma Questionnaire (PAQ) which consisted of eight questions regarding difficulty breathing, cough, wheeze, activity limitation, level of activity limitation, overall symptom score, and nighttime asthma awakenings (see **Error! Reference source not found.**). Parents/legal guardians completed the PAQ on a daily basis. The daytime asthma questions were rated on a scale of 0 to 4, while the nighttime asthma questions were rated on a scale of 0 to 3 and 0 to 2; higher scores indicated greater symptom severity (maximum score=29). The primary efficacy endpoint was the mean change in the PAQ total score during the third week of treatment (Week 3) relative to the placebo run-in period (Week -1). The primary efficacy analysis was performed on the intent-to-treat (ITT) population, which included all subjects who received at least one dose of double-blind study medication, using an ANOVA model with effects for treatment, investigator, and weight group.

Figure 2. Pediatric Asthma Questionnaire (PAQ)

Daytime Asthma Questionnaire

A. How often did your child have trouble breathing today?

None of the time | A little of the time | Some of the time | Most of the time | All of the time

B. How often did your child cough today?

None of the time | A little of the time | Some of the time | Most of the time | All of the time

C. How often did your child wheeze today?

None of the time | A little of the time | Some of the time | Most of the time | All of the time

D. How often were your child's activities limited by his asthma today?

None of the time | A little of the time | Some of the time | Most of the time | All of the time

E. How much difficulty did your child have doing activities today due to his asthma (activities include any sort of physical activity, such as playing, running, or jumping)?

Not at all | A little | Some | A good deal | A lot

F. Overall, how much did your child's asthma bother him today?

Not at all | A little | Some | A good deal | A lot

Nighttime Asthma Questionnaire

G. How often did your child wake due to asthma symptoms last night (i.e., trouble breathing, coughing, wheezing, etc.)?

None of the time | Once | Twice | Three times or more

If answer to G was at least Once, answer the following:

H. If your child was awakened due to asthma symptoms last night, how long did it take him to go back to sleep?

Within the hour | More than 1 hour | Not able to go back to sleep

Source: Module 5.3.5.1, Study 051-032, Legacy CSR, Appendix IV, p727

Additional efficacy assessments included the following:

- Pediatric Asthma Caregiver Assessments (PACA) completed 3 days after each study visit
- Peak expiratory flow rate (PEFR), in-clinic and at home measurements obtained pre-dose and 30-45 minutes post-dose
- Rescue medication usage
- Number of uncontrolled asthma days[2]
- Number of asthma exacerbations[3]
- Functional Status II (R) Questionnaire and CHQ-PF50 General Health Perceptions Scale Questionnaire
- Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ)
- Global assessment by physician and parent/legal guardian at end of study

[2] Defined as days on which a subject used two or more nebules of rescue medication
[3] Defined as worsening of asthma symptoms or pulmonary function that required any of the following: emergency department visit, hospitalization, treatment with oral/parenteral corticosteroids, or unscheduled clinic visit to treat acute asthma symptoms.

Safety
Safety assessments included physical examinations, vital signs, clinical laboratory evaluations (hematology, chemistry, and urinalysis), 12-lead ECG, and adverse events.

5.3.2 Study 051-033

Protocol #	051-033
Title	A Safety, Tolerability, and Efficacy Study of Levalbuterol and Racemic Albuterol in Pediatric Subjects Birth to 48 Months Old with Reactive Airway Disease in an Acute Setting
Study dates	Study initiated: February 2, 2001 Study completed: July 27, 2002 Final study report: September 9, 2005
Sites	18 clinical study sites in the U.S.
IND	47,363
IRBs	• (b) (4) • Local IRBs

Amendments
There were three amendments to the protocol. Amendment #1, dated December 19, 2000, reduced the sample size from 210 to 130 randomized subjects and revised the timing and scope of clinical laboratory evaluations. Amendment #2, dated April 9, 2001, added PK samples for all subjects after the final dose at Visit 1. Amendment #3 dated December 7, 2001, removed all clinical laboratory and PK blood collections to facilitate enrollment and increased the sample size to 180 randomized subjects.

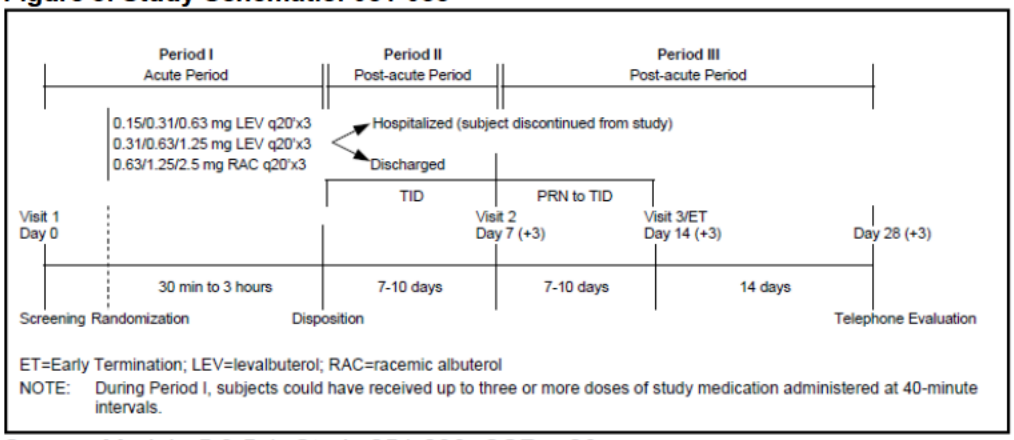
Objectives
The objectives of this study were to evaluate the efficacy (primary) and the safety/tolerability (secondary) and pharmacokinetics (secondary) of two doses of levalbuterol in pediatric subjects aged birth to 48 months.

Study Design
This was a multicenter, randomized, double-blind, active-controlled, parallel group trial in pediatric subjects from birth to 48 months of age presenting to the Emergency Department (ED) or physician's office with acute reactive airway disease. The study consisted of an acute period (Period I) and two post-acute periods (Periods II and III). Subjects who met enrollment criteria were randomized to one of three treatment groups: a) low dose Lev IS (0.15, 0.31, or 0.63 mg); b) high dose Lev IS (0.31, 0.63, or 1.25 mg); or c) racemic albuterol (0.63, 1.25, or 2.5 mg). Doses within each treatment group were stratified by weight: 2.5 to 5 kg, >5 to 10 kg, >10 kg. Initial presentation to the ED or physician's office was considered Visit 1 (Day 0) of Period I. After randomization, subjects received up to six doses of double-blind study medication via nebulization for

up to 3 hours[4]. Subjects who subsequently required hospitalization or did not meet discharge criteria[5] within 24 hours were discontinued from the study. After discharge from the ED/physician's office, subjects entered Period II of the study and were instructed to administer double-blind study medication TID for the next 7-10 days and to return to clinic for Visit 2 at that time. After Visit 2, subjects entered Period III and were instructed to administer double-blind study medication PRN to TID for an additional 7-10 days and to return to clinic for Visit 3. A follow-up safety evaluation was conducted by telephone 14 days after Visit 3. Rescue medication during Periods II and III consisted of blinded 1.25mg Lev IS for the levalbuterol treatment groups and blinded 2.5 mg racemic albuterol for the racemic albuterol treatment group. A study schematic and schedule of assessments are shown in Figure 3 and Table 7.

[4] Investigators were allowed to administer additional doses of blinded study medication to subjects who were not discharged after 3 hours.
[5] Based on diminished wheezing, good air exchange, no supraclavicular or intercostal retractions, O_2 saturation ≥95% on room air, minimum 25% improvement in Section III RSS total score, and investigator's clinical judgment.

Figure 3. Study Schematic: 051-033



ET=Early Termination; LEV=levalbuterol; RAC=racemic albuterol
NOTE: During Period I, subjects could have received up to three or more doses of study medication administered at 40-minute intervals.

Source: Module 5.3.5.1, Study 051-033, CSR, p26

Table 7. Schedule of Assessments: 051-033

	Period I		Period II	Period III	
	Visit 1	Visit 1	Visit 2	Visit 3	Telephone Evaluation
	Day 0	Day 0	Day 7 (+3)	Day 14 (+3)	Day 28 (+3)
Assessments	Screening/ Randomization	Discharge Period	Randomization Period	End of Randomization	Safety/ Relapse
Informed consent	X	X[1]			
Inclusion/exclusion	X	X			
Medical history	X				
Physical examination	X			X	
Holter monitoring	X	X			
Lead II ECGs			X	X	
Respiratory Status Scale	X	X[2]			
Vital signs	X	X[2]	X	X	
Oxygen saturation	X	X[2]			
RSV antigen		X			
Dispense Period I study medication	X	X			
Dispense Period II study medication		X[3]	X		
Assess adverse events	X	X	X	X	X
Assess relapse			X	X	X
Dispense diary card		X[3]	X		
Dispense medical events calendars		X[3]	X		
Dispense compressor/nebulizer		X[3]			
Review safety assessments	X	X	X	X	
Review diary card completion			X	X	
Assess concomitant medications	X	X	X	X	
Assess compliance			X	X	
Global assessments				X	

1 Prior to discharge, an outpatient informed consent was obtained.
2 Completed approximately 5-10 minutes after each dose until subject was hospitalized or discharged.
3 Only in subjects discharged to home.

Source: Module 5.3.5.1, Study 051-033, CSR, Table 9.1-1, p24

Study Population
A total of 117 subjects were randomized: 42 to low dose Lev IS, 40 to high dose Lev IS, and 35 to racemic albuterol.

Key Inclusion Criteria

1. Males or females from birth to 48 months of age (inclusive) at the time of informed consent
2. At least one previous episode of acute bronchospasm or previous history of reactive airway disease
3. Oxygen saturation ≥90% at room air or ≤2 L/min supplemental oxygen
4. Section III Respiratory Status Scale total score ≥5
5. Good health with the exception of acute reactive airway disease
6. For participation in Periods II/III, subjects must have required further dosing after completion of Period I (at the discretion of the investigator)

Key Exclusion Criteria

1. Prematurity (born at ≤32 weeks gestational age) or chronic lung disease of prematurity and/or required supplemental oxygen for ≥28 days after birth
2. Concurrently required use of supplemental oxygen
3. History of airway obstruction that required intubation, associated with hypercapnia, respiratory arrest, or hypoxic seizures within 12 months prior to Visit 1
4. Disallowed medication use or expected use during the trial
5. Clinically significant abnormalities that could interfere with metabolism or excretion of study drug
6. History of cystic fibrosis, bronchopulmonary dysplasia, bronchopulmonary aspergillosis or any form of allergic alveolitis
7. Clinically significant 12-lead ECG abnormality
8. History of cancer

For Period II only

9. Development of a clinically significant purulent respiratory tract infection
10. Scheduled for in-patient hospitalization, including elective surgery, during the course of the trial

Withdrawal Criteria
Subjects may have been discontinued for any of the following reasons:

- Life-threatening event precluding compliance with the protocol
- Withdrawal of consent
- Hospital admission
- Adverse event
- Intercurrent illness
- Protocol violation
- Use of disallowed medications
- Administrative reasons

Subjects who discontinued prematurely underwent all Visit 3/Early Termination procedures.

Prohibited Medications

A list of disallowed medications and the required washout periods, where applicable, is summarized in the following table.

Table 8. Disallowed Medications: Study 051-033

Medication	Wash-Out Period
During Period I	
Corticosteroids (parenteral and oral)	30 days[1]
During the first three hours of Period I[2]	
Corticosteroids (other than initial dose of prednisone)	
Adrenergic bronchodilators (other than study medication)	
Ipratropium bromide	
Leukotriene modifiers	
Antibiotics	
Aminoglycosides	
Mucolytics	
Magnesium	
During Period II	
Adrenergic bronchodilators (oral, nebulizer solution, dry powder inhaler, or metered dose inhaler)	
Astemizole	
Aminoglycosides (inhaled formulations)	
Mucolytics	
Nonprescription asthma medication	

1 Prior to Visit 1.

2 Medications were not permitted by any route of administration (i.e., aerosol, intravenous, subcutaneous, metered dose inhaler).

NOTE: Every effort was made to adhere to these guidelines, however, the health and safety of subjects was the prime consideration.

Source: Module 5.3.5.1, Study 051-033 CSR, Table 9.3.2-1, p29

Concomitant Medications

The following medications were allowed under specific conditions, such as if a stable dose had been established for a certain period of time prior to enrollment, and are summarized in the table below.

Table 9. Concomitant Medications: Study 051-033

Medication	Condition under which medication was allowed
Period I	
Corticosteroids (oral, IV, or IM)	administered to all enrolled subjects
Oxygen	for oxygen saturation <92% on room air
Periods II/III	
Oral corticosteroids	only 2 mg/kg x 5 days prescribed at discharge
Inhaled corticosteroids	stable dose 28 days prior to Visit 2

Medication	Condition under which medication was allowed
Ipratropium bromide	stable dose 5 days prior to Visit 1
Leukotriene inhibitor	stable dose 10 days prior to Visit 1
Nedocromil and cromolyn sodium	stable dose 5 days prior to Visit 1
Immunotherapy	stable dose 30 days prior to Visit 1
Antibiotics	Investigator's discretion
Expectorants, decongestants	Investigator's discretion
Antihistamines (except astemizole)	Investigator's discretion
Topical corticosteroids	Investigator's discretion
Other medications	Investigator's discretion
Source: Module 5.3.5.1, Study 051-033, Legacy CSR, p34	

Treatments/Dose Rationale

The study included three treatment groups:

- Low dose levalbuterol HCl: (R)-albuterol HCl Ampule Inhalation Solution, 0.15, 0.31, or 0.63 mg/3mL in 0.9% saline
- High dose levalbuterol HCl: (R)-albuterol HCl Ampule Inhalation Solution, 0.31, 0.63, or 1.25 mg/3 mL in 0.9% saline
- Racemic albuterol: (R,S)-albuterol HCl Ampule Inhalation Solution, 0.63, 1.25, or 2.5 mg/3 mL in 0.9% saline

Dose levels within each treatment group were stratified by weight: 2.5 to 5 kg, >5 to 10 kg, and >10 kg.

Rescue medication for use in Periods II and III consisted of blinded 1.25 mg Lev IS for both levalbuterol treatment groups and blinded 2.5 mg racemic albuterol for the racemic albuterol treatment group.

Study medication was administered using a PARI LC PLUS™ nebulizer with a mouthpiece or face mask and a PARI DURA-NEB™ 3000 compressor. During Period I, subjects received up to six doses of study medication in the ED or physician's office, with the first three doses delivered every 20 minutes for the first hour and the last three doses administered every 40 minutes thereafter. However, additional doses of blinded study medication could have been administered for up to 24 hours after enrollment at the discretion of the investigator until a final disposition was reached (i.e., discharge or hospitalization). The same blinded treatment was continued into Periods II and III at dosing frequencies of TID and PRN to TID, respectively.

Dose selection in this study was based on the generally accepted doses of racemic albuterol for acute asthma in this population since at the time there was no labeled dose for patients under 12 years of age. The most prevalent dose of racemic albuterol in children weighing more than 10kg was 2.5 mg, and therefore was the dose chosen for children in this weight category in this study. Comparable doses of racemic albuterol were then chosen for subjects in lower weight categories, and the levalbuterol doses were chosen based on the equivalent amount of (R)-albuterol in the comparable racemic albuterol doses.

Efficacy

The primary efficacy variable was the Respiratory Status Scale (RSS) total score shown in Figure 4. Respiratory Status Scale below. The RSS was completed by the healthcare provider predose and 5-10 minutes postdose for each administration of study medication during Period I. The scale was divided into three sections; however, the RSS total score was based solely on the sum of the Section III scores (maximum score=12). A lower RSS total score indicated improved respiratory status. The primary efficacy analysis was a comparison of the maximum decrease in RSS total score during Period I among treatment groups using an ANOVA model with effects for treatment, investigator, and weight group. A subject's maximum decrease in RSS total score was calculated as the minimum post-dose RSS total score minus the pre-dose RSS total score collected prior to the first dose administered in Visit 1.

Figure 4. Respiratory Status Scale (RSS)

Section I.

General Appearance:

☐ 0	☐ 1	☐ 2	☐ 3
Content / Happy Very Interactive No Crying	Mildly Irritable Somewhat Interactive Occasional Crying	Moderately Irritable Less Interactive Intermittent Crying	Extremely Irritable Not Interactive Constantly Crying

Section II.

Respiratory Rate (breaths/min)		**Heart Rate (beats/min)**		
Oxygen Saturation (%)		**With Supplemental Oxygen**	**YES** **NO**	**If yes:** **L/min**

Section III.

Grunting / Coughing:

☐ 0	☐ 1	☐ 2	☐ 3
None	Mild Occasional	Moderate Intermittent	Severe Constant

Wheezing:

☐ 0	☐ 1	☐ 2	☐ 3
None Inaudible Breath Sounds	Mild	Moderate Expiratory	Severe Inspiratory / Expiratory

Nasal Flaring:

☐ 0	☐ 1	☐ 2	☐ 3
None	Mild Occasional	Moderate Intermittent	Severe Constant

Air Exchange:

☐ 0	☐ 1	☐ 2	☐ 3
Excellent Equal, All Lobes	Good Diminished, Bases Only	Fair Diminished, Some Lobes (Other than bases)	Poor Diminished, All Lobes

Accessory Muscle Use:
(Supraclavicular or Intercostal Retractions)

☐ 0	☐ 1	☐ 2	☐ 3
None	Mild Just Visible	Moderate Evident	Severe Obvious

Source: Module 5.3.5.1, Study 051-033 CSR, Appendix V, p625

Secondary efficacy variables included:

- Individual RSS parameters
- Time to meet discharge criteria
- Time to maximum decrease in RSS total score
- Rate of hospitalization

Time to meet discharge criteria (or clinical decision to discharge) was calculated in minutes as the difference between the actual time subjects met discharge criteria and the start time of nebulization plus one minute. Discharge criteria were based on diminished wheezing (RSS scores for wheezing improved at least one unit); good air exchange (RSS scores for air exchange "0" or "1"), no supraclavicular or intercostal retractions (RSS score for accessory muscle use "0"); O_2 saturation ≥95% on room air; at least 25% in RSS total score. For hospitalized subjects, the time to discharge criteria was set to 24 hours and the subject was censored.

Exploratory efficacy variables included:

- Rate of relapse (return to ED/physician's office)
- Rate of respiratory exacerbations
- Rescue medication use
- Daytime and nighttime breathing symptoms assessed by the Children's Breathing Questionnaire
- Relief of bronchoconstriction as assessed by physician and caregiver global evaluations

Reviewer Comment: The clinical study report states that the RSS was developed because, at the time, there were no validated asthma symptom scales for children 0 to 48 months of age with acute asthma and because children of this age cannot reliably perform pulmonary function testing. However, the RSS is not a validated endpoint to quantitatively measure acute reactive airway disease activity either. Furthermore, the study design did not include a placebo control or a pre-specified non-inferiority margin to racemic albuterol, and thus was not adequately controlled for a clear test of efficacy.

Safety

Safety assessments included adverse events, vital signs, 12-lead ECG, serum potassium and glucose levels, clinical laboratory evaluations (hematology, chemistry, and urinalysis), and physical examinations.

5.3.3 Study 091-029

Protocol #	091-029
Title	A Cumulative Dose Safety and Tolerability Crossover Study of Arformoterol Tartrate Inhalation Solution and Levalbuterol Hydrochloride Inhalation Solution in Pediatric Subjects (Aged 2 to 11 Years of Age) with Asthma
Study dates	Study initiated: January 7, 2008 Study completed: December 2, 2008 Final study report: November 2, 2009

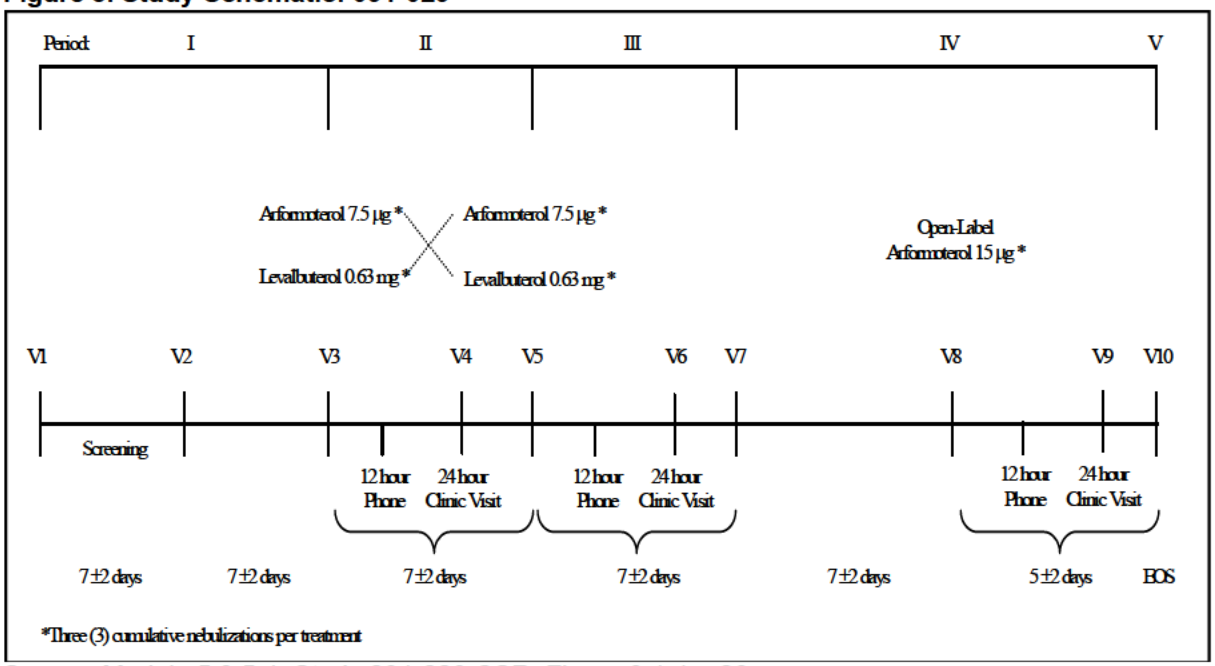
Sites	12 clinical study sites in the U.S.
IND	55,302
IRB (Site)	(b) (4)

Amendments
There were two protocol amendments. Amendment #1, dated October 18, 2007, reduced the number of lab collections and volume of blood drawn and added a minimum weight requirement and extra vital sign assessments between doses. Amendment #2, dated February 14, 2008, lowered the reversibility inclusion criteria from 15% to 12% and clarified timing of study assessments.

Objectives
The primary objective of this study was to compare the safety and tolerability of cumulative dosing with arformoterol tartrate inhalation solution versus levalbuterol HCl inhalation solution (3 cumulative nebulizations in one hour) in pediatric subjects with asthma. Secondary objectives were to characterize the pharmacokinetic profile of (R,R)-formoterol and to investigate the FEV_1 response in children 6 years of age and older.

Study Design
This was a randomized, double-blind, two-way crossover study evaluating three cumulative doses of arformoterol (7.5 mcg per nebulization) and levalbuterol IS (0.63 mg per nebulization) administered over a 1-hour period, followed by a single open-label treatment day with three cumulative doses of arformoterol 15 mcg per nebulization in subjects 2 to 11 years of age with asthma. The study was divided into five periods as shown in Figure 5. Study Schematic: 091-029 Period I (Visits 1 and 2) consisted of a screening visit and a 7-day washout period during which LABAs were withheld. Subjects received either Lev IS 0.63 mg or Lev HFA 45 mcg/actuation as needed for rescue medication for the duration of the study. Period II (Visits 3 and 4) and Period III (Visits 5 and 6) consisted of the blinded active treatment days during which subjects received three cumulative doses of either arformoterol 7.5 mcg per nebulization or Lev IS 0.63 mcg per nebulization. Period IV (Visits 7-9) consisted of the open-label arformoterol (15 mcg per nebulization) treatment day. On each treatment day, the study medication was administered every 30 minutes over 1 hour (at 0, 30, and 60 minutes). Following each treatment, subjects were monitored for 6 hours after dosing, and then followed at 12 and 24 hours by phone and in clinic, respectively. The three treatment days were separated by a 7-day washout period and safety review for each subject. Period V (Visit 10) occurred 5 days after arformoterol open-label treatment and consisted of the final clinical study evaluation.

Figure 5. Study Schematic: 091-029



Source: Module 5.3.5.4, Study 091-029 CSR, Figure 9.1-1, p26

Table 10. Schedule of Assessments: Study 091-029

Period	I		II			III			IV				V
Clinic Visit	1	2	3		4	5		6	7	8		9	10
Day	-14	-7	1	1	2	8	8	9	15	22	22	23	27
Assessments*	Screening Visit	Washout	Treatment I	Phone Evaluation	Evaluation Visit	Treatment II	Phone Evaluation	Evaluation Visit	Continuation Washout	Treatment III	Phone Evaluation	Evaluation Visit	Final Safety Visit EOS
Informed Consent	X												
Inclusion/Exclusion Criteria	X	X	X										
Continuation Criteria									X				
Medical History	X												
Physical Examination	X												X
Dispense/Return Rescue Meds	X	X	X			X			X	X			X
Administer Study Medication[a]			X			X				X			
ECGs	X[b]		X[b]			X[b]				X[b]			X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X		X[c]		X	X[c]		X	X	X[c]		X	X
Spirometry	X[d]												X
Serial Spirometry			X[e]			X[e]				X[e]			
Clinical Laboratory Evaluation	X												X
Serum K+, Glucose	X		X[f]			X[f]				X[f]			X
Serial PK			X[g]			X[g]				X[g]			
Serum Pregnancy Test	X[h]												X[h]
Urine Drug Screening	X												
Dispense/Review MEC and Diaries	X	X	X		X	X		X	X	X		X	X
Assess Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

EOS=End of Study
*At Visits 3, 5, and 8, the timing of the procedures was relative to the start of nebulization (dosing was performed at T=0, T=30, and T=60, where 0 was the start of the first nebulization.
a Nebulization was completed to sputter within 6 to 8 minutes. If nebulization was not complete at 10 minutes, it was stopped in order to do the 10 minute spirometry assessment and a note was made in the source documents.
b ECG was performed at predose and 2 hours post last cumulative dose at Visits 3, 5, and 8.
c Vital signs were taken predose, 15, 30, and 60 minutes post the first two cumulative doses, and every 30 minutes post final dose for 5 hours. Vital signs were taken prior to spirometry when the timing of these procedures coincided.
d All children 6 and older were required to perform spirometry and reversibility testing. Children 5 or younger who could adequately perform spirometry were also required to demonstrate ≥12% FEV_1 reversibility within 15-30 minutes after 2 puffs of levalbuterol MDI.
e Serial spirometry was performed predose, 10 and 25 minutes after each of the three cumulative doses, and at 2, 4, and 6 hours after the first dose (10 total). Serial spirometry was performed in all subjects ≥6 years of age and for all other subjects able to adequately perform FEV_1.
f Blood samples for potassium and glucose were collected predose, 2 and 6 hours post the first cumulative dose.
g PK samples were collected predose, 25 minutes post each of the first two cumulative doses, and at 2 and 6 hours post the first cumulative dose (5 samples per visit).
h Female subjects 8 years of age and older, inclusive.
Source: Module 5.3.5.4, Study 091-029 CSR, Table 9.1-1, p24

Study Population
A total of 53 subjects were enrolled in the study. Randomization was stratified by age group (2-5 years and 6-11 years); fourteen of the subjects were in the 2-5 year old age group.

Key Inclusion Criteria

1. Male and female subjects between the ages of 2 to 11 years, inclusive, at the time of consent and weight ≥15 kg
2. Negative serum pregnancy test at Visit 1 for females ≥8 years of age
3. Physician-diagnosed asthma of at least 2 years duration for children ≥6 years of age and for at least 1 year duration for children ≤5 years of age
4. Baseline FEV_1 of 65-85% predicted for subjects ≥6 years of age (and for subjects ≤5 years of age who could perform spirometry)
5. Demonstration of ≥12% reversibility of airflow obstruction within 15-30 minutes following inhalation of levalbuterol 0.63 mg inhalation solution in subjects ≥6 years of age (and any subjects ≤5 years of age who could perform spirometry)
6. Stable asthma with use of a β-adrenergic agonist, and/or asthma anti-inflammatory medication, and/or over-the-counter asthma medication for at least 6 months prior to Visit 1
7. Good health with the exception of reversible airways disease
8. Physical examination that was not suggestive of a pulmonary condition other than asthma

Key Exclusion Criteria

1. Expected to require any disallowed medications
2. Pregnancy or lactation
3. Inability to take first daily dose of study medication and/or to start study visits before 9 AM
4. History of hospitalization of asthma within 1 year prior to Visit 1 or scheduled for in-patient hospitalization, including elective surgery, during the course of the trial
5. History of life-threatening asthma defined as asthma episodes requiring intubations, associated with hypercapnia, respiratory arrest, or hypoxic seizures

6. Unstable asthma, change in asthma therapy, or visit to the ED/hospital for worsening asthma within 6 weeks
7. History of cigarette smoking or use of any tobacco products
8. Clinically significant abnormalities that may interfere with metabolism/excretion of study drug
9. Hyperthyroidism, diabetes, hypertension, cardiac disease, or seizure disorders
10. History of cancer
11. Bronchopulmonary aspergillosis or any form of allergic alveolitis
12. Clinically significant upper or lower respiratory tract infection in the 6 weeks prior to Visit 1 or during the study
13. Clinically significant laboratory or 12-lead ECG abnormality
14. Weight less than 15kg

Withdrawal Criteria

Subjects may have been discontinued from the study for any of the following reasons:

- Adverse event
- Protocol violation
- Voluntary withdrawal
- Lost to follow-up
- No longer met entry criteria
- Other

Subjects who prematurely discontinued from the study were not replaced, and, regardless of cause, were required to be seen for a final early termination evaluation.

Prohibited Medications

The following medications were disallowed for the duration of the study and must have been withheld for the specified time period prior to Visit 1.

Table 11. Disallowed Medications: Study 091-029

Medication Disallowed for Study Duration	Required Withholding Interval Prior to Visit 1
Systemic corticosteroids (oral and parenteral)	≥30 days and study duration
Adrenergic Bronchodilators (oral, nebulizer solution, dry powder inhaler, or metered dose inhaler)[a]	>7 days and study duration
Inhaled, short acting	≥10 hours and study duration
Nebulized, short acting	≥10 hours and study duration
Inhaled, long acting	≥2 weeks and study duration
Oral qid or tid preparations	≥24 hours and study duration
Oral bid preparations	>36 hours and study duration
Nonprescription Asthma Medications	≥48 hours and study duration
Ipratropium Bromide and Tiotropium Bromide	≥48 hours and study duration
Theophylline	study duration

Abbreviations: bid = twice daily; tid = three times daily; qid = four times daily
a Exceptions: The provided rescue medication was allowed to be used as needed but was to be withheld prior to study visits according to the schedule listed above.

Source: Module 5.3.5.4, Study 091-029 CSR, Table 9.4.7.1-1, p33

Treatments/Dosing Rationale
Subjects received three cumulative doses of each of the following blinded treatments according to their randomization sequence:

- Arformoterol tartrate inhalation solution 7.5 mcg, supplied as 15 mcg/2 mL
- Levalbuterol HCl inhalation solution 0.63 mg, supplied as 0.63 mg/3 mL

Subjects who tolerated both treatments received three cumulative doses of open-label arformoterol tartrate inhalation solution 15 mcg (15 mcg/2 mL).

Rescue medication consisted of Lev IS 0.63 mg or Lev HFA 45 mcg/actuation, as determined by the physician based on the subject's ability to use an MDI.

Both study and rescue medications were administered via a PARI LC® SPRINT nebulizer with a mouthpiece or face mask and a TREK® S compressor.

The dose of Lev IS was based on the approved dose for patients 6 years of age and older with reversible obstructive airway disease.

Concomitant Medications
The following medications were allowed under specific conditions, such as if a stable dose had been established for a certain period of time prior to enrollment, and are summarized in the table below.

Table 12. Concomitant Medications: Study 091-029

Medication	Condition under which medication was allowed
Adrenergic bronchodilators	rescue medication provided by the investigator; withheld ≥10 hours before spirometry at Visits 3, 5, and 8
Inhaled corticosteroid (low-moderate dose)	stable dose 4 weeks prior to Visit 1; withheld ≥10 hours prior to study visits
Leukotriene inhibitor	stable dose 4 weeks prior to Visit 1; withheld 12 hours prior to spirometry
Nedocromil and cromolyn sodium	stable dose 10 days prior to Visit 1
Immunotherapy	stable dose 60 days prior to Visit 1
Antibiotics	Investigator's discretion
Mucolytics, expectorants	Investigator's discretion
Antihistamines	Investigator's discretion; withheld 48 hours prior to study visits
Topical corticosteroids	as needed
Other medications	stable dose 60 days prior to Visit 1
Source: Module 5.3.5.4, Study 091-029, Legacy CSR, p34	

Efficacy
Pulmonary function testing was performed on subjects 6 years of age and older (and on subjects ≤5 years of age who could perform spirometry) in triplicate in accordance with American Thoracic Society (ATS) guidelines. The highest FEV_1 and PEFR from each

set of at least three acceptable measurements were recorded in the CRF. For eligible subjects, serial testing was performed at Visits 3, 5, and 8 prior to the first dose and 10 and 25 minutes after each of the three cumulative doses, then again at 2, 4, and 6 hours after the first cumulative dose. Change and percent change in FEV_1 and PEFR from visit predose to each postdose time point were secondary endpoints.

Safety
Safety assessments included adverse events, clinical laboratory measurements, potassium and glucose levels, vital signs, heart rate monitoring, 12-lead ECG, and physical examinations. The primary safety analyses assessed differences between the cumulative dosing of arformoterol and Lev IS with respect to change from visit predose to each postdose measurement in heart rate, blood pressure, potassium, and glucose.

5.3.4 Study 051-359

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. 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, based on FDA feedback. 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

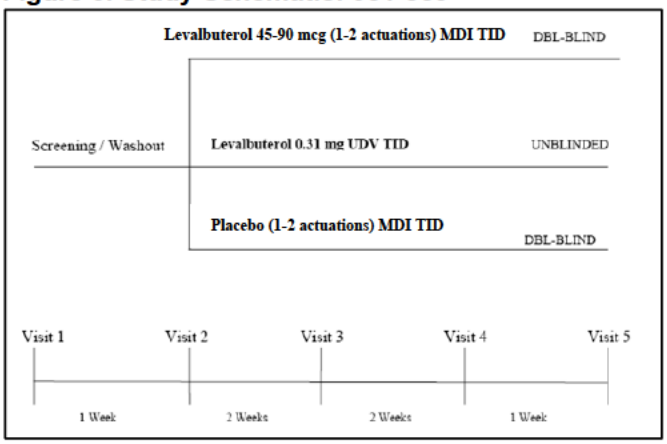
of abnormal lab values that was inadvertently removed in the previously amended protocol. Amendment #4, dated February 11, 2010, removed the minimum number of patients required to perform PEF due to difficulty with recruitment, and clarified target enrollment numbers (30 patients aged 0 to 11 months and no more than 30 subjects aged 12 to 23 months).

Objectives
The objectives were to examine the safety, tolerability, and efficacy of levalbuterol HFA MDI 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: Lev HFA 45-90 mcg (1-2 actuations) MDI, Lev IS 0.31 mg, or placebo 1-2 actuations MDI. All study treatments were administered three times daily for 4 weeks. The 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. The MDI treatment arms were double-blind while the Lev 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.

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 28-day 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 6. Study Schematic: 051-359



Source: 5.3.5.4, Study 051-359 CSR, Figure 1, p18

Table 13. Schedule of Assessments: Study 051-359

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 Lev HFA MDI, 64 to Lev IS, and 68 to placebo MDI. Of the 64 patients within the Lev IS treatment group, 9 patients were under 12 months of age, 22 patients were between 12 and 23 months of age, and 41 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 14. Disallowed Medications: Study 051-359

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/Dose Rationale
The study included three treatment groups:

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

The 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 MDI treatment arms were double-blind, the Lev IS treatment arm was open-label with the same 0.31 mg dose administered regardless of age.

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

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 Lev HFA MDI 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 PACA, a questionnaire consisting of five domains that was completed by parents/legal guardians daily (see Table 15. Pediatric Asthma Caregiver Assessments (PACA) below). The maximum score was 19, with higher scores indicating greater symptom severity. The primary endpoint was the change in mean daily composite 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 Lev IS treatment arm was unblinded, the only relevant comparison was between the blinded Lev HFA MDI and placebo MDI treatment groups.

Table 15. 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 (see **Error! Reference source not found.**) 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.

5.3.5 Study 051-SRC038

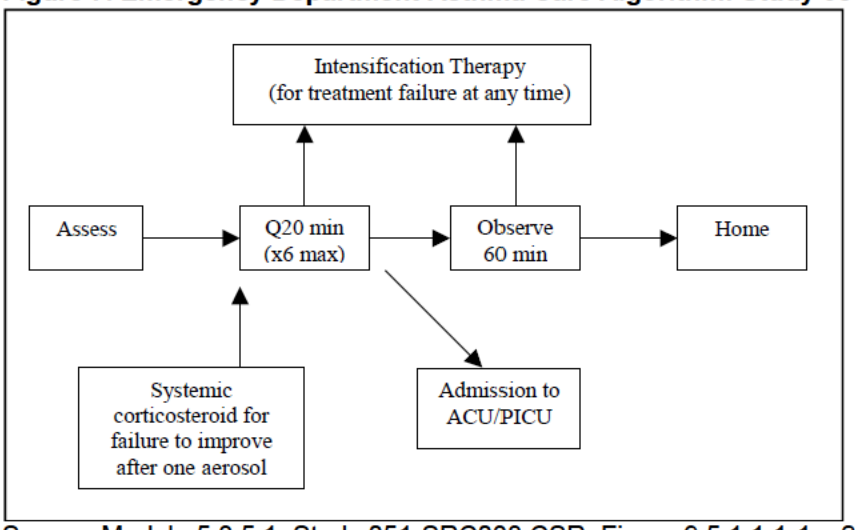
Protocol #	051-SRC038
Title	Comparison of Single Isomer and Racemic Albuterol in Reducing Hospital Admissions and Decreasing Length of Stay for Childhood Status Asthmaticus
Study dates	Study initiated: April 17, 2000 Study completed: January 19, 2001 Final study report: June 3, 2002
Site	PI: Dr. Carolyn M. Kercsmar Rainbow Babies & Children's Hospital Cleveland, OH
IND	(b) (4)
IRB	(b) (4)

Amendments
There were no amendments to the protocol.

Objectives
The primary objective of this study was to determine the effect of Lev IS compared with racemic albuterol for the treatment of acute asthma in children as determined by hospital admission rates and overall hospital length of stay. Secondary objectives included the evaluation of number of aerosols required before discharge or admission, number of subjects with length of stay <24 hours, number of subjects requiring intensification of therapy, and safety of treatment with Lev IS or racemic albuterol.

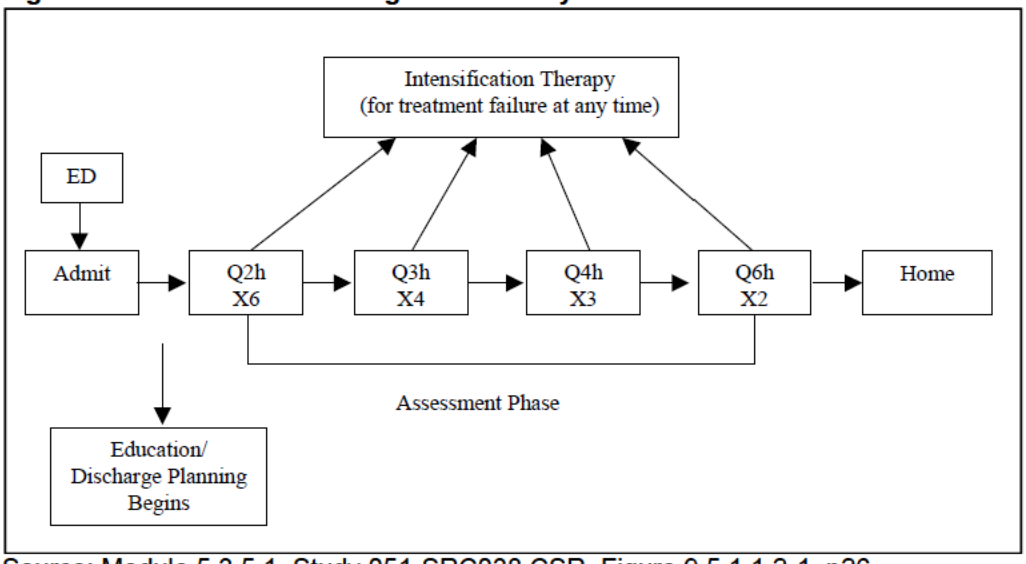
Study Design
This was an investigator-initiated, single-center, randomized, double-blind, active-control study in pediatric subjects who presented to the ED with an acute asthma exacerbation. The Sponsor was not involved in the conduct of this study, but provided a grant and blinded study medication. Upon completion of the study, the Investigator provided the Sponsor with the datasets for analysis and preparation of the clinical study report. Upon presentation to the ED, eligible subjects were randomized to receive either Lev IS 1.25 mg or racemic albuterol 2.5 mg. Subjects received blinded study drug and underwent reassessment every 20 minutes for a maximum of 6 treatment doses in the ED over two hours. Subjects who worsened during any assessment interval received intensification therapy (ipratropium, blinded study drug, and subcutaneous epinephrine). The treatment algorithm is shown in Figure 7 below. If a subject failed to meet discharge criteria after receiving six doses of study drug, he/she was admitted to the Asthma Care Unit (ACU) and continued to receive blinded study drug as per the treatment algorithm in Figure 8. Subjects completed the study upon discharge from the ED/ACU, maintaining discharge criteria for at least 6 hours without treatment, or upon transfer to the pediatric intensive care unit (PICU).

Figure 7. Emergency Department Asthma Care Algorithm: Study 051-SRC038



Source: Module 5.3.5.1, Study 051-SRC038 CSR, Figure 9.5.1.1.1-1, p25

Figure 8. Asthma Care Path Algorithm: Study 051-SRC038



Source: Module 5.3.5.1, Study 051-SRC038 CSR, Figure 9.5.1.1.2-1, p26

Table 16. Schedule of Assessments: Study 051-SRC038

Procedures	Presentation to ED	ED Care Path[c]	Asthma Care Path[d]	Early Termination/ End of Study
Informed consent	X			
Inclusion/Exclusion criteria	X			
Asthma history	X			
Current chronic medication use	X			
Vital signs[a]	X	X	X[b]	X
Study drug administration		X	X	
Concurrent medications		X	X	X
Adverse events		X	X	X

a Heart rate, respiration rate, oxygen saturation by pulse oximeter (SpO_2).
b Blood pressure was assessed every 6 hours.
c ED Care Path: subjects were assessed every 20 minutes for 2 hours; repeat inhalation treatment with study drug occurred any time subject failed to meet discharge criteria, for a total of six treatments. Discharge criteria required a "good" rating on all chest assessment measures (air exchange, degree of wheezing, and accessory muscle use) and maintenance of room air oxygen saturation readings by pulse oximetry of ≥94 %.
d Asthma Care Path: Phase I: assessment every 2 hours up to 6; Phase II: assessment every 3 hours x 4; Phase III: assessment every 4 hours x 3; Phase IV: assessment every 6 hours x 2; subjects advanced to the next phase when discharge criteria were met or 12 hours had elapsed without deterioration.

Source: Module 5.3.5.1, Study 051-SRC038 CSR, Table 9.5.1.1-1, p24

Study Population

A total of 483 patients were enrolled in the study; randomization was stratified by age (<6 years, ≥6 years). Of the patients under 6 years of age, 111 were randomized to Lev IS and 102 to racemic albuterol.

Key Inclusion Criteria

1. Male or female between 2 and 17 years of age
2. History of physician-diagnosed asthma or reactive airway disease and presenting to the pediatric ED at Rainbow Babies & Children's Hospital for treatment of acute asthma

Key Exclusion Criteria

1. Chronic disease such as cystic fibrosis, cyanotic or uncorrected congenital heart disease, active bronchopulmonary dysplasia, or chronic obstructive pulmonary disease
2. Pregnancy
3. Sensitivity to racemic albuterol

Withdrawal Criteria

Subjects were withdrawn from the study for any of the following reasons:

- Protocol violation
- Administrative reasons
- Investigator decision
- Withdrawal of consent
- Admission to PICU, ward, or other facility

Treatments/Dosing Rationale
The study included two treatment groups:

- Levalbuterol 1.25 mg: levalbuterol HCl Inhalation Solution, 0.042% (w/v), 1.25 mg levalbuterol/3 mL in 0.9% saline
- Racemic albuterol 2.5 mg: Albuterol SO4 Inhalation Solution, 0.083% (w/v), 2.5 mg albuterol/3 mL in 0.9% saline

Up to six doses were administered in the ED with additional doses administered to subjects admitted to the ACU. Study drug was administered using high-density small volume nebulizer devices ((b) (4)) via facemask (< 6 years of age) or mouthpiece (≥6 years of age).

Additional treatments administered during intensification therapy consisted of the following:

- Ipratropium bromide 500 mcg (0.5 mg/2.5 mL) inhalation solution
- Subcutaneous epinephrine 0.01mL/kg (1:1000 injection ampules), max dose 0.5 mg
- Double dose of blinded study drug (2.5 mg Lev IS or 5 mg racemic albuterol)
- Supplemental oxygen
- Corticosteroids (oral prednisone 2 mg/kg or IV methylprednisolone 1 mg/kg)

Efficacy
Primary efficacy variables were hospital admission rates and total length of stay (LOS). Secondary efficacy variables included ED length of stay, Asthma Care Path length of stay, number of aerosols required before discharge criteria were met, number of subjects with LOS <24 hours in each group, number of subjects requiring intensification therapy, requirement for supplemental oxygen, concurrent medication in the ED, and rates of acute visits or readmissions to the hospital for worsening asthma. Although patients were stratified by age, the study did not prespecify or power for separate analyses of patients less than 6 years of age.

Safety
Safety assessments included vital signs (heart rate, respiratory rate, and oxygen saturation) and unexpected adverse events. Because asthma-related events were expected, these were not captured during the study.

Reviewer Comment:
Despite enrolling the highest number of patients, Study 051-SRC038 provides no meaningful efficacy or safety information, and thus is not relevant to this review.

6 Review of Efficacy

Efficacy Summary

The Applicant submitted two Phase 3 pediatric studies (051-032 and 051-033) to evaluate the efficacy of levalbuterol inhalation solution for the treatment and prevention of bronchospasm in patients less than 6 years of age with reversible obstructive airway disease. In Study 051-032, subjects received one of four double-blind medications three times daily for 3 weeks: levalbuterol inhalation solution 0.31 mg or 0.63 mg, racemic albuterol, or placebo. The primary efficacy endpoint was the mean change in Pediatric Asthma Questionnaire (PAQ) total score from run-in to its mean during Week 3 compared to placebo. In Study 051-033, subjects received one of three double-blind medications for treatment of an acute asthma exacerbation: low dose or high dose levalbuterol inhalation solution or racemic albuterol. The primary efficacy endpoint was the maximum decrease in the Respiratory Status Scale (RSS) total score from pre-dose to each post-dose measurement during the acute exacerbation treatment period.

Both studies failed to demonstrate a statistically significant benefit of levalbuterol inhalation solution for the prevention or treatment of asthma or reactive airway disease in this age group. In Study 051-032, the levalbuterol inhalation solution treatment groups experienced the greatest numerical decrease in PAQ total score over the 3 week treatment period; however, the overall difference between treatment groups was not statistically significant. Furthermore, this numerical advantage disappears when the analysis is adjusted for the higher baseline PAQ scores in the levalbuterol inhalation solution treatment groups. Study 051-033 evaluated a non-validated respiratory symptom score as its primary endpoint and did not include a placebo control or a pre-specified non-inferiority margin to the active control, racemic albuterol. Even if these design flaws are dismissed, levalbuterol inhalation solution performed worse than an equivalent racemic albuterol dose, and the low dose of levalbuterol outperformed the high dose.

Although the Applicant included a third study, 051-SRC038, which compared levalbuterol with racemic albuterol in children 2 to 17 years of age experiencing an acute asthma exacerbation, this study did not prespecify nor power for separate efficacy analyses of patients less than 6 years of age.

The Applicant submitted this supplement to comply with PREA regulations, but based on the results from these studies, is not seeking to expand the indication to patients less than 6 years of age. It is of note, however, that while the submitted studies failed to meet their primary endpoints, 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 Inhalation Solution. Currently, the FDA-approved indication in the product labeling (Section 1) is "Xopenex (levalbuterol HCl) Inhalation Solution is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 6 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

This efficacy review focuses on two of the five studies included in this submission, Study 051-032 and Study 051-033. The remaining studies were not included in the efficacy review for the following reasons: Study 091-029 did not consistently assess efficacy in patients <6 years of age, Study 051-359 evaluated Lev IS treatment in an open-label fashion, and Study 051-SRC038 did not prespecify or power for separate analyses of patients <6 years of age, which were the minority of patients enrolled in that study. See Section 5.3 for full descriptions of the study design and conduct.

6.1.2 Demographics

Table 17. Subject Demographics of ITT Population: Studies 051-032 and 051-033 summarizes the demographic data for the ITT subject population in Studies 051-032 and 051-033. Overall, the demographics and baseline characteristics of subjects were similar across treatment groups in both studies. There were, however, more males than females overall and within each treatment group

Table 17. Subject Demographics of ITT Population: Studies 051-032 and 051-033

Study	Variable	Lev IS 0.31 mg	Lev IS 0.63 mg	RA	PBO	Total
051-032	ITT population	58	51	52	50	211
	Age (Years)					
	Mean (SD)	3.4 (1.2)	3.3 (1.1)	3.4 (1.1)	3.7 (1.0)	3.5 (1.1)
	Median	3.0	3.0	3.5	4.0	3.0
	Sex – n(%)					
	Female	17 (29.3)	16 (31.4)	19 (36.5)	22 (44.0)	74 (35.1)
	Race – n(%)					
	White	34 (58.6)	29 (56.9)	31 (59.6)	35 (70.0)	129 (61.1)
	Black	12 (20.7)	12 (23.5)	9 (17.3)	5 (10.0)	41 (19.4)
	Asian	1 (1.7)	1 (2.0)	1 (1.9)	1 (2.0)	4 (1.9)
	Hispanic	5 (8.6)	6 (11.8)	9 (17.3)	5 (10.0)	25 (11.8)

	Other	6 (10.3)	3 (5.9)	2 (3.8)	1 (2.0)	12 (5.7)
Study	**Variable**	**LD Lev IS**	**HD Lev IS**	**RA**		**Total**
051-033	ITT population	42	40	35		117
	Age (months)					
	Mean (SD)	20.3 (13.9)	19.5 (13.3)	19.1 (21.4)		19.7 (13.2)
	0-1 months – n(%)	1 (2.4)	2 (5.0)	0		3 (2.6)
	2-12 months – n(%)	15 (35.7)	12 (30.0)	13 (37.1)		40 (34.2)
	13-24 months – n(%)	10 (23.8)	12 (30.0)	11 (31.4)		33 (28.3)
	25-48 months – n(%)	16 (38.1)	14 (35.0)	11 (31.4)		41 (35.0)
	Sex – n(%)					
	Female	10 (23.8)	15 (37.5)	10 (28.6)		35 (29.9)
	Race – n(%)					
	White	17 (40.5)	17 (42.5)	13 (37.1)		47 (40.2)
	Black	12 (28.6)	11 (27.5)	15 (42.9)		38 (32.5)
	Asian	2 (4.8)	1 (2.5)	0		3 (2.6)
	Hispanic	9 (21.4)	8 (20.0)	6 (17.1)		23 (19.7)
	Other	2 (4.8)	3 (7.5)	1 (2.9)		6 (5.1)

Abbreviations: Lev IS=levalbuterol HCl inhalation solution, LD=low dose, HD=high dose, RA=racemic albuterol, PBO=placebo, ITT=intent-to-treat, SD=standard deviation
*Seven subjects (4 Lev IS, 3 RA) received the wrong dose of study medication for their weight. All but one received a lower dose. Analyses were performed based on the randomized dose.
Sources: Module 5.3.5.1, Study 051-032 CSR, Table 11.2-1, p76; Study 051-033 CSR, Table 11.2-1, p69

6.1.3 Subject Disposition

The majority of screening and randomization failures were from failure to meet entry criteria or lack of sufficient asthma symptoms. The table below displays the disposition for randomized ITT subjects in Studies 051-032 and 051-033. In both studies, the overall number of early discontinuations across treatment groups in was similar; however, there were numerically more subjects in the Lev IS treatment groups who discontinued due to an adverse event. This imbalance is explored further in Section 7.3.3.

Table 18. Disposition of Subjects: Studies 051-032 and 051-033

Study 051-032	Lev IS 0.31 mg	Lev IS 0.63 mg	RA	PBO	Total
Screened/Enrolled					408
Randomization Failures					197
ITT population	58	51	52	50	211
Completed Study	49 (84.5)	41 (80.4)	44 (84.6)	42 (84.0)	176 (83.4)
Early Discontinuation	9 (15.5)	10 (19.6)	8 (15.4)	8 (16.0)	35 (16.6)
Adverse event	5 (8.6)	8 (15.7)	3 (5.8)	2 (4.0)	18 (8.5)
Voluntary withdrawal	0	1 (2.0)	3 (5.8)	0	4 (1.9)
Protocol violation	1 (1.7)	0	2 (3.8)	2 (4.0)	5 (2.4)
Lost to follow-up	0	1 (2.0)	0	0	1 (<1)
Treatment failure	0	0	0	2 (4.0)	2 (<1)
Did not meet entry criteria	1 (1.7)	0	0	0	1 (<1)

Other	2 (3.4)	0	0	2 (4.0)	4 (1.9)

Study 051-033	LD Lev IS	HD Lev IS	RA	Total
Screened/Enrolled				129
Randomization Failures				12
ITT population	42	40	35	117
Completed Study	31 (73.8)	32 (80.0)	24 (68.6)	87 (74.4)
Early Discontinuation	11 (26.2)	8 (20.0)	11 (31.4)	30 (25.6)
Adverse event	2 (4.8)	3 (7.5)	1 (2.9)	6 (5.1)
Voluntary withdrawal	1 (2.4)	0	2 (5.7)	3 (2.6)
Protocol violation	3 (7.1)	2 (5.0)	3 (8.6)	8 (6.8)
Lost to follow-up	4 (9.5)	2 (5.0)	2 (5.7)	8 (6.8)
Treatment failure	0	1 (2.5)	2 (5.7)	3 (2.6)
Did not meet entry criteria	0	0	1 (2.9)	1 (<1)
Other	1 (2.4)	0	0	1 (<1)

Sources: Module 5.3.5.1, Study 051-032 CSR, Figure 10.1-1, p72; Study 051-033 CSR, Figure 10.1-1, p65

6.1.4 Analysis of Primary Endpoint(s)

Study 051-032

The primary endpoint in Study 051-032 was the mean change in PAQ total score from placebo run-in (Week -1) to its mean during Week 3. PAQ was assessed daily by parents/legal guardians and consisted of eight questions regarding difficulty breathing, cough, wheeze, activity limitation, level of activity limitation, overall symptom score, and nighttime asthma awakenings (refer to Section 5.3, **Error! Reference source not found.**). The six daytime asthma questions were rated on a scale of 0 to 4, while the two nighttime asthma questions were rated on a scale of 0 to 3 and 0 to 2; higher scores indicated greater symptom severity (maximum score=29). The primary efficacy analysis was performed on the ITT population (although essentially a "per protocol" population since patients with major protocol deviations and disallowed medication use were removed) using an ANOVA model with independent effects for treatment, investigator, and weight group. The overall F-test was used to first determine whether there was a difference among treatment groups. If this overall test was statistically significant at the 0.05 level of significance, then pairwise tests were performed comparing each active treatment arm to placebo. If a particular Lev IS arm differed significantly from placebo, then a pairwise test of that arm versus racemic albuterol was performed.

Results of the primary efficacy analysis are shown in Table 19. Although the Lev IS treatment groups experienced the greatest numerical decrease in PAQ total score over the 3 week treatment period, the overall difference between treatment groups was not statistically significant (p=0.76). However, this numerical advantage for the Lev IS treatment groups disappears when the analysis is adjusted for baseline PAQ score,

which was higher in the Lev IS groups. For further details see the original Biometrics Review from supplement 011 completed by Dr. James Gebert on February 21, 2003.

Table 19. PAQ Total Score Results: Study 051-032

	Treatment Group			
	Levalbuterol 0.31 mg (n=58)	Levalbuterol 0.63 mg (n=51)	Racemic Albuterol (n=52)	Placebo (n=50)
Mean Baseline PAQ Total Score for All Enrolled Subjects (Week –1 to Week 0)	6.81 (4.04)	7.31 (4.37)	6.31 (4.13)	6.28 (4.68)
Mean Change in PAQ Total Score				
	(n=49)	(n=41)	(n=44)	(n=45)
Mean Baseline PAQ Total Scores for the ITT Population	6.67 (3.78)	7.35 (4.01)	6.15 (4.12)	5.98 (4.24)
Mean Change(SD)	-3.50 (3.10)	-3.28 (4.33)	-2.93 (4.06)	-2.66 (2.85)
Median	-3.61	-3.00	-2.22	-2.71
Min, Max	-12.1, 5.6	-12.3, 8.0	-17.2, 6.5	-9.0, 3.8

Source: Medical Officer Review of NDA 20-837, Supplement 011 by Howard Birenbaum, MD (February 25, 2003)

Study 051-033

The primary endpoint for Study 051-033 was the maximum decrease in RSS total score during Period I, from initial pre-dose at screening and each post-dose measurement. The RSS total score was based solely on the sum of the Section III scores comprised of grunting/coughing, nasal flaring, wheezing, air exchange, and accessory muscle use (refer to Section 5.3, Figure 4). A lower RSS total score indicated improved respiratory status (maximum score=12). As noted in Section 5.3, the RSS is not a validated endpoint to quantitatively measure acute reactive airway disease activity, and the study design did not include a placebo control or a pre-specified non-inferiority margin to the presumably effective active control, racemic albuterol. The statistical methodology was the same as in Study 051-032, but as noted in the Biometrics Review of this submission by Dr. Robert Abugov, this study was improperly designed due to its comparison of Lev IS to an equivalent racemic albuterol mixture using a test for superiority rather than non-inferiority. Therefore, Dr. Abugov revised the primary efficacy analysis in his statistical review to evaluate the superiority of HD Lev IS to LD Lev IS for maximum change from baseline in RSS total score.

The baseline RSS total scores were similar between both Lev IS treatment groups with means and medians of 7.0. The baseline RSS total score was slightly higher in the racemic albuterol group with a mean and median of 7.7 and 8.0, respectively. The results for the primary efficacy analysis, as performed by Dr. Abugov, are shown in Table 20 (note a higher decrease indicates greater benefit). The improvements in RSS

total score from baseline were statistically significantly less for HD Lev IS compared to LD Lev IS.

Table 20. Maximum Decrease from Baseline RSS Total Score: Study 051-033

Maximum Decrease RSS (N)			Difference Between Treatments (P-Value)		
LL	**HL**	**RA**	**HL - LL**	**HL - RA**	**LL - RA**
5.3 (42)	4.1 (40)	5.3 (35)	1.1 (0.0127)	1.2 (0.0102)	0.1 (0.8467)

Source: Biometrics Review by Dr. Robert Abugov

6.1.5 Analysis of Secondary Endpoints(s)

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 endpoints and the Applicant's decision to seek no further indication based on the results of these studies.

6.1.7 Subpopulations

Because neither study showed effectiveness for Lev IS, differences by gender, race, age, or geographic region were not examined for this review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant evaluated Lev IS doses of 0.31 mg and 0.63 mg in Study 051-032 as well as high and low Lev IS doses for weight in Study 051-033. Although neither study demonstrated effectiveness for any Lev IS dose, the higher dose groups consistently performed more poorly than the lower dose groups. Whether this is due to a differential tachyphylaxis effect after chronic dosing in Study 051-032 or perhaps a potentially a harmful effect from Lev IS, as will be discussed in Section 7, is unclear.

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 due to known tolerance or tachyphylaxis to the bronchodilator effects that occurs with long term, scheduled use. In Study 051-032, the mean baseline change in PEF (measured 30-45 minutes postdose at weekly clinic visits) diminished over the course of 3 weeks in the Lev 0.63 mg treatment group, but not the Lev 0.31 mg or racemic albuterol treatment groups (data not shown).

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

This sNDA submission contains adequate data to update the product label regarding use in patients less than 6 years of age. The majority of safety data in this age group is based on three of the five studies included in this submission: 051-032 (3-week chronic dosing trial in patients 2 to 5 years), 051-033 (acute exacerbation trial with 2-week follow up period in patients birth to 48 months), and 051-359 (4-week chronic dosing trial in patients birth to 47 months).

No deaths were reported in any study, and nonfatal serious adverse events (SAEs) were rare overall. Although there is no apparent imbalance among treatment groups, the SAEs that did occur primarily involved hospitalization for asthma or other respiratory illnesses such as pneumonia. Data from the three primary safety studies revealed a small but consistent pattern of increased asthma exacerbations, asthma-related treatment-emergent adverse events, and treatment discontinuations due to asthma in patients receiving levalbuterol inhalation solution compared to placebo or racemic albuterol. This safety information will be added to the product label. Additionally, even though a decrease in β_2-agonist associated side effects is an often touted safety benefit of levalbuterol use, there was no substantial difference in the occurrence of hypokalemia, cardiovascular effects, or hyperglycemia among treatment groups.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical trials used to evaluate safety are described in Table 3 in Section 5.1 and primarily include studies 051-032, 051-033, and 051-359. For studies 091-029 and 051-SRC038, which enrolled pediatric subjects up to 11 and 17 years of age, respectively, only the subset of subjects under 6 years of age were included in this safety review; however, these two studies contributed very little evaluable safety data given the short duration and small size of Study 091-029 and limited amount of safety data captured in Study 051-SRC038. It is also worth noting that one study site (#0183), which enrolled 25 subjects (~20% of all subjects) in Study 051-033 did not report any adverse events.

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 each study. Serious adverse events (SAEs) were collected through 30 days after the last dose and followed until resolution or lost to follow up. The coding dictionary used to categorize AEs differed by study and included COSTART for Studies 051-032 and 051-033, MedDRA version 11.1 for Study 091-029, and MedDRA version 16.0 for Study 051-359. Treatment emergent adverse events (TEAEs) were defined as AEs that occurred or worsened on or after the first dose of study medication. For Study 091-029, TEAEs were assigned to the last treatment received on or before the start date of the event; if the AE start date was missing, the AE was assigned to all treatments for which the subject received at least one dose. Study 051-SRC038 collected AEs from a checklist containing the items nausea, vomiting, tremor, rash, or other. Only unexpected AEs were collected. Events related to the underlying condition of asthma were considered normal and expected, and thus not captured as AEs.

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

Due to the varying design and duration of studies submitted, pooling of data across studies was not appropriate; instead, safety findings are discussed separately for individual studies.

7.2 Adequacy of Safety Assessments

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

Table 21 shows the overall exposure to levalbuterol inhalation solution by age group, sex, and race, while Table 22 shows the overall exposure by dose, duration of exposure, and completion rates across the five studies. Although Study 051-033 grouped subjects according to low or high dose Lev IS treatment, this safety review will present exposure and safety data from this study according to the actual randomized dose. The total exposure was adequate to evaluate the safety of levalbuterol inhalation solution in patients under 6 years of age for the purposes of updating the label. Note that over a third of Lev IS exposure occurred in Study 051-SRC038, which provides no meaningful safety data.

Table 21. Demographics of Overall Exposure

Category	Study				
	051-032	051-033	091-029	051-359	051-SRC038
ITT population	211	117	14[a]	196	213[a]
Age (Years)					
Mean (SD)	3.5 (1.1)	1.6 (1.1)	4.4 (0.8)	2.4 (1.0)	3.42 (1.3)
Age Group					
0 to < 2 years – n(%)	0	76	0	68	26
≥ 2 to < 4 years – n(%)	106	41	2	128	114

Category	Study				
	051-032	051-033	091-029	051-359	051-SRC038
≥ 4 to < 6 years – n(%)	105	0	12	0	73
Sex – n(%)					
Female	74 (35.1)	35 (29.9)	7 (50.0)	88 (44.9)	72 (33.8)
Race[a] – n(%)					
White	129 (61.1)	47 (40.2)	7 (50.0)	121 (61.7)	37 (17.4)
Black	41 (19.4)	38 (32.5)	7 (50.0)	65 (33.2)	174 (81.7)
Asian	4 (1.9)	3 (2.6)	--	1 (0.5)	--
American Indian/Alaska Native	--	--	--	1 (0.5)	--
Hispanic[b]	25 (11.8)	23 (19.7)	--	56 (28.6)	--
Other	12 (5.7)	6 (5.1)	0	0	2 (<1)
Multiple	--	--	--	7 (3.6)	--

[a]Only includes ITT population under 6 years of age
[b]Not all race categories included in each study
[c]Studies 051-032 and 051-033 reported Hispanic as a race category while Study 051-359 reported Hispanic as an ethnicity category
Sources: Module 5.3.5.1, Study 051-032 Legacy CSR, Table 11.2-1, p76; Study 051-033 CSR, Table 11.2-1, p69; Study 051-SRC038 CSR, Table 11.2-1, p40; and Module 5.3.5.4, Study 051-359 CSR, Table 5, p47; Study 091-029 CSR, Table 11.2-1, p62

Table 22. Extent of Exposure

Study	Lev IS 0.15 mg	Lev IS 0.31 mg	Lev IS 0.63 mg	Lev IS 1.25 mg	Lev HFA	RA	PBO
051-032							
ITT	--	58	51	--	--	52	50
Completed (%)	--	49 (84)	41 (80)	--	--	44 (85)	42 (84)
Mean exposure in days (SD)	--	20.1 (4.9)	20.5 (6.7)	--	--	20 (4.3)	20.2 (3.5)
051-033							
ITT	2	18	39	23	--	35	--
Completed (%)	1 (50)	16 (67)	33 (85)	17 (74)	--	24 (69)	--
Mean exposure in days (SD)	9.0 (9.9)	12.8 (5.7)	14.1 (5.1)	12.3 (5.8)	--	13.1 (6.1)	--
091-029							
ITT[a]	--	--	14	--	--	--	--
Completed (%)	--	--	13 (93)	--	--	--	--
051-359							
ITT	--	63	--	--	65	--	68
Completed (%)	--	53 (84)	--	--	60 (92.3)	--	62 (91.2)
Mean exposure in days (SD)	--	26.6 (6.9)	--	--	28.2 (4.2)	--	28.1 (4.5)
051-SRC038							
ITT[a]	--	--	--	111	--	102	--
Mean number of aerosol treatments (range)	--	--	--	3.62 (1-6)	--	4.09 (1-7)	--
Total Number of ITT Subjects per Treatment Group	**2**	**139**	**104**	**134**	**65**	**189**	**118**

Abbreviations: Lev IS=levalbuterol HCl inhalation solution, Lev HFA=levalbuterol tartrate HFA MDI, RA=racemic albuterol, PBO=placebo, ITT=intent-to-treat, SD=standard deviation
[a]Only includes ITT population < 6 years of age
Sources: Module 5.3.5.1, Study 051-032 Legacy CSR, 12.1-1, p115; Study 051-033 "DEMOG" dataset; Study 051-SRC038 CSR, p59; and Module 5.3.5.4, Study 051-359 CSR, 17, p75; Study 091-029 CSR, Table 10.1-2, p60

7.2.2 Explorations for Dose Response

Across the five studies, Lev IS doses ranging from 0.15 mg to 1.25 mg were evaluated; however, the majority of evaluable safety data is derived from treatment administration with 0.31 mg and 0.63 mg doses. Following chronic dosing, there was no appreciable dose response in terms of efficacy or safety.

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 Lev IS 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 inhalation solution were submitted by the Applicant in support of the original NDA for the use of levalbuterol inhalation solution 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 to potential to cause paradoxical bronchospasm, particularly with continued or scheduled use. The Sponsor assessed for protocol-defined asthma exacerbations as a secondary endpoint in Study 051-032 and for β_2-agonist related TEAEs, treatment failures, and asthma-related TEAEs in Study 051-359; 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 in any of the five studies reviewed in this supplemental NDA.

7.3.2 Nonfatal Serious Adverse Events

The number of nonfatal serious adverse events (SAEs) was low overall, and no SAEs were reported in Studies 091-029 and 051-SRC038. However, the majority of SAEs involved hospitalization for asthma exacerbations or other respiratory illnesses such as pneumonia.

Table 23. Nonfatal Serious Adverse Events

	Lev IS 0.31 mg		Lev IS 0.63 mg		Lev IS 1.25 mg		Lev HFA		RA		PBO	
	Subj	Event	Subj	Event	Subj	Event	Subj	Event	Subj	Event	Subj	Event
Overall, n(%)**	5 (3.6)	6	1 (1.1)	1	3 (13.0)	3	1 (1.5)	3	4 (4.6)	5	2 (1.7)	2
Study 051-032 (n)	58		51		--		--		52		50	
Asthma	0	0	0	0	--	--	--	--	2*	2	1*	1
Infection	0	0	0	0	--	--	--	--	0	0	1	1
Pneumonia	1*	1	0	0	--	--	--	--	1*	0	0	0
Study 051-033 (n)	18		39		23		--		35		--	
Asthma	0	0	0	0	2*	2	--	--	0	0	--	--
Convulsion	0	0	0	0	1	1	--	--	0	0	--	--
Cough increased	0	0	0	0	0	0	--	--	1	1	--	--
Hypoxia	1	1	1	1	0	0	--	--	0	0	--	--
Pneumonia	0	0	0	0	0	0	--	--	1	1	--	--
Study 051-359 (n)	63		--		--		65		--		68	
Asthma	2	2	--	--	--	--	0	0	--	--	0	0
Hypoxia	0	0	--	--	--	--	1	1	--	--	0	0
Metapneumovirus	0	0	--	--	--	--	1	1	--	--	0	0
Pneumonia	1	1	--	--	--	--	0	0	--	--	0	0
Status asthmaticus	0	0	--	--	--	--	1	1	--	--	0	0
UTI	1	1	--	--	--	--	0	0	--	--	0	0

Abbreviations: Lev IS=levalbuterol HCl inhalation solution, Lev HFA=levalbuterol tartrate HFA MDI, RA=racemic albuterol, PBO=placebo, Subj=number of subjects
* One event occurred during follow-up period
**Percentage calculations based on total number of ITT subjects per treatment group from Studies 051-032, 051-033, and 051-359
Sources: Reviewer analyses of "AE" (Studies 051-032 and 051-033) and "ADAE" (Study 051-359) datasets; Module 5.3.5.1, Study 051-032 CSR Appendix 16.2.29; Study 051-033 CSR, Appendix 16.2.24; Module 5.3.5.4, Study 051-359 CSR, Table 22, p81

A brief narrative for each nonfatal SAE, organized by study and active treatment, is provided below:

Study 051-032

Subject 0771110 (Lev IS 0.31 mg): This was a 2-year-old male with history of SAR and twin brother to Subject 0771109 (below). On Day 20, he developed an upper respiratory infection, which was treated with Augmentin and oral corticosteroids. He was discontinued from the study due to disallowed medication use (oral corticosteroids). The subject was hospitalized (b) (4) days after the last dose of study medication for treatment of pneumonia.

Subject 0771109 (RA 1.25 mg): This was a 2-year-old male with history of sinopulmonary infections and SAR. On Day 20, he developed otitis media, sinusitis, and an upper respiratory infection, which were treated with Augmentin and prednisone; study medication was discontinued due to disallowed medication use (prednisone). The

subject was hospitalized (b) (4) days after the last dose of study medication for treatment of pneumonia (and concurrent sinusitis).

Subject 1652163 (RA 2.5 mg): This was a 3-year-old male with history of eczema, SAR, and PAR. He experienced wheeze and cough of moderate severity on Day 4 of double-blind study treatment, and received four doses of rescue medication on that day. On Day (b) (4), he presented to the ED for persistent symptoms and was hospitalized for treatment with albuterol, ipratropium, oral corticosteroids, and oxygen. He was subsequently transferred to another hospital on the following day for continuing treatment and was discharged on Day (b) (4). Study medication was discontinued due to this event.

Subject 1732074 (RA 2.5 mg): This was a 3-year-old male with history of eczema, food allergy, SAR, and PAR. (b) (4) days after completing the double-blind treatment period, he experienced an asthma exacerbation of moderate severity resulting in hospitalization.

Study 051-033

Subject 03313152 (HD Lev IS, 1.25 mg): This was a 23-month-old male weighing 12.8 kg upon presentation to the ED for an asthma exacerbation. He had a history of reactive airway disease and "respiratory issues" since birth, but had not received controller medications (albuterol nebulizer and Pulmicort) for the past 3 days. He was afebrile with a respiratory rate of 32 breaths/minute, O2 saturation of 92% on room air, and RSS score of 5. He received three nebulized doses of 1.25 mg Lev IS and oral prednisone while in the ED before planned discharge. However, before leaving the ED, his condition worsened (O2 sat 85%, decreased air entry, and increased wheeze); therefore, he was subsequently admitted to the hospital and was treated with continuous albuterol nebulization, atrovent, and prednisone. This event was assigned to Period I, and the subject was discontinued from the study due to this event. The event was considered resolved (b) (4) days later.

Subject 00274082 (RA 1.25 mg): This was a 2-month-old male weighing 7.1 kg upon presentation to the ED for an asthma exacerbation. He had a history of asthma treated with PRN albuterol. (b) (4) days prior to presentation, he was evaluated for cough and wheeze and noted to have bronchiolitis and a red tympanic membrane for which he was started on albuterol, Pediazole, and a 5-day course of Prelone before being sent home. In the ED, his RSS score was 6, and he received four doses of RA 1.25 mg before discharge home. During the follow-up period, he received protocol-specified oral corticosteroids. (b) (4) days after discharge, he presented to the ED with irritability, shortness of breath, cough, congestion, low-grade fever, tachypnea, and tachycardia. A chest x-ray revealed pneumonia, and he was subsequently hospitalized for treatment with IV cefotaxime, Solu-Medrol, albuterol, and supplemental oxygen. Sputum culture returned positive for H. influenzae and Staphylococcus. He was discharged (b) (4) days later, and discontinued from the study due to this event.

Subject 01783129 (HD Lev IS, 1.25 mg): This was a 29-month-old-male (11.5 kg) with a history of asthma, IgG subclass and IgA deficiency, and RSV who presented to the ED for an asthma exacerbation. He had a familial history of febrile seizures and epilepsy. Upon arrival his RSS score was 5, and he received one nebulized dose of 1.25 mg Lev IS before discharge. He continued to take oral prednisone and study medication during the follow-up period. (b) (4) days after presentation to the ED, he experienced a fever and decreased oral intake followed by tonic-clonic seizures. He was hospitalized for a hypoglycemic seizure (last dose of study medication (b) (4) days prior). After an extensive evaluation, the etiology was felt to be iatrogenic adrenal suppression from oral and inhaled glucocorticoid. The subject was discontinued from the study due to this event.

Subject 02592025 (HD Lev IS, 0.63 mg): This was a 6-month-old female (weight 8.2 kg) with a history of gastroesophageal reflux and bronchiolitis who presented to the ED with an acute asthma exacerbation. She received 4 doses of study medication prior to discharge. After (b) (4) days of treatment with blinded study medication during Period II, she was hospitalized for hypoxia and respiratory distress secondary to bronchiolitis. She was discontinued from the study due to this event.

Subject 02592027 (LD Lev IS 0.31 mg): This was a 9-month-old male (weight 9.8 kg) with a history of recurrent otitis media who presented to the ED with an acute asthma exacerbation. He reported having had one asthma exacerbation within the past 30 days. He received two doses of study medication in the ED prior to discharge. The (b) (4) (Period II), he received three doses of study medication and one dose of rescue medication for wheeze and cough without improvement. He was hospitalized for observation of respiratory distress, apnea, and hypoxia and was treated with albuterol, amoxicillin, and erythromycin. He was discharged (b) days later and discontinued from the study due to this event.

Subject 02593145 (HD Lev IS 1.25 mg): This was a 35-month-old male (weight 15.5 kg) who presented to the ED with an acute asthma exacerbation. He was received four doses of study medication prior to discharge and continued to receive blinded study medication TID to PRN in Periods II and III. Six days after completing the study, he experienced sudden onset of wheezing, cough, tachypnea and retractions. He presented to the ED and was subsequently

Study 051-359

Subject 0032/S013 (Lev IS 0.31 mg): 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) (4), 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 (Lev IS 0.31 mg): 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) (4), 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 (b) days later, and these events led to discontinuation from the study.

Subject 0065/S001 (Lev IS 0.31 mg): This was a 37-month-old female with history of recurrent otitis media, recurrent UTI, GERD, and asthma. On Day (b) (4), she developed an E.coli UTI of moderate intensity that was treated with Bactrim. On Day (b) (4), she presented to the ED with persistent fever and ill appearance; a clean-catch urine culture revealed E.coli resistant to Bactrim. She was hospitalized for treatment of her UTI, and discharged (b) (4) days later once afebrile. She received her last dose of study medication on Day (b) (4) and completed the study.

Subject 0060/S041 (Lev 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) (4) 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.

7.3.3 Dropouts and/or Discontinuations

The number of subjects who discontinued study medication early due to an adverse event are displayed in the table below. None of the subjects under 6 years of age in Studies 091-029 and 051-SRC038 discontinued study medication due to an adverse event; thus these studies are not included in the table below. Also, note that the Lev HFA treatment group from Study 051-359 is not displayed in the table due to space considerations. However, this study is reviewed in detail under NDA 21-730, supplement 36.

A reviewer analysis of the Applicant's datasets did not reveal any additional adverse dropouts. Although the numbers are small, there appears to be more adverse drop-outs in the Lev IS treatment groups across studies when compared to the control groups.

Furthermore, the adverse events leading to discontinuation in the Lev IS treatment groups more often involve asthma-related events.

Table 24. Subject Discontinuations due to AEs by Study and Treatment Group

	Lev IS 0.15 mg	Lev IS 0.31 mg	Lev IS 0.63 mg	Lev IS 1.25mg	RA	PBO	Total
Study 051-032 – n	--	58	51	--	52	50	211
Adverse dropouts, n(%)	--	5 (8.6)	8(15.7)	--	3 (5.8)	2 (4.0)	18 (8.5)
Asthma	--	4	6	--	2	2	14
Laryngitis	--	0	1	--	0	0	1
Otitis media	--	1	0	--	1	0	2
Sinusitis	--	1	2	--	1	0	4
Viral Infection	--	0	2	--	1	1	4
Vomiting	--	0	1	--	1	0	2
Study 051-033 – n	2	18	39	23	35	--	117
Adverse dropouts, n(%)	0	2 (11.1)	1 (2.6)	2 (8.7)	1 (2.9)	--	6 (5.1)
Asthma	0	1	0	1	0	--	2
Cough increased	0	0	0	0	1	--	1
Convulsion	0	0	0	1	0	--	1
Gastritis	0	0	0	0	1	--	1
Hypoxia	0	1	1	0	0	--	2
Pneumonia	0	0	0	0	1	--	1
Study 051-359 – n[a]	--	63	--	--	--	68	131
Adverse dropouts, n(%)	--	3 (4.8)	--	--	--	2 (2.9)	5 (3.8)
Asthma	--	2	--	--	--	0	2
Pneumonia	--	2	--	--	--	1	3
Pyrexia	--	1	--	--	--	0	1
Urticaria	--	0	--	--	--	1	1
Vomiting	--	1	--	--	--	0	1

Abbreviations: Lev IS=levalbuterol HCl inhalation solution, RA=racemic albuterol, PBO=placebo
Some subjects reported more than one AE leading to discontinuation
[a]Levalbuterol HFA treatment group not included
Sources: Reviewer analyses of "TERM" and "AE" datasets (Studies 051-032 and 051-033) and "ADSL" and "ADAE" datasets for Study 051-359; Module 5.3.5.1, Study 051-032 CSR, Figure 10.1-1, p72; Module 5.3.5.4, Study 051-359 CSR, Table 24, p83

7.3.4 Significant Adverse Events

The number of severe AEs was relatively low and balanced across treatment groups; however, an increased number of asthma-related adverse events was noted in the Lev IS treatment groups (see Section 7.3.5). Nearly all severe AEs were also reported as SAEs and described above in Section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

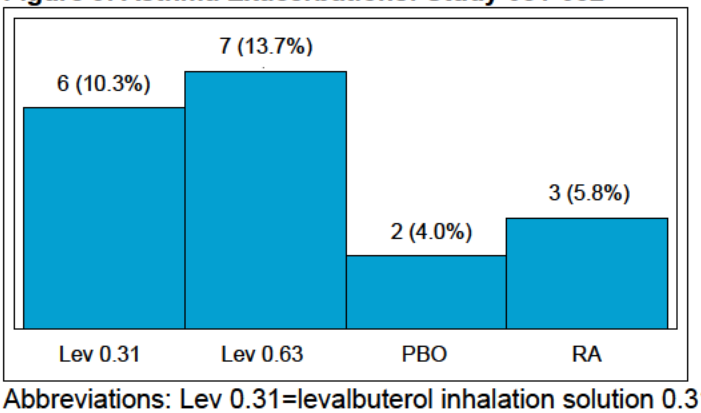
In the original review of Study 051-032, the medical officer noted that more patients treated with Lev IS at either dose discontinued from the study due to an AE or

experienced a protocol-defined asthma exacerbation. While the numbers were small and not statistically significant (though not powered for such), the trend was felt to be concerning. Because the Sponsor withdrew the supplement prior to receiving a Not Approvable Action, this information could not be used to update the product label. In light of this history, the clinical review of this submission focuses on evaluating the potential safety signal of asthma-related AEs, particularly those leading to hospitalization or discontinuation, in patients under 6 years of age.

This section presents the frequency of asthma exacerbations from Study 051-032 and combined asthma-related TEAEs from Studies 051-032, 051-033, and 051-359. There were no asthma or respiratory-related TEAEs reported in Study 091-029, and these AEs were not captured in Study 051-SRC038.

In Study 051-032, an asthma exacerbation was defined as worsening of asthma symptoms or pulmonary function that required any of the following: emergency department visit, hospitalization, treatment with oral/parenteral corticosteroids, or unscheduled clinic visit to treat acute asthma symptoms. This definition appears reasonable and should have captured clinically significant acute exacerbations. 4 additional subjects (one from each treatment group) experienced asthma exacerbations Figure 9 displays the discrepancy in asthma exacerbation frequency during the double-blind treatment period between the Lev IS and control subjects. Four additional subjects (one per treatment group) experienced an asthma exacerbation during the follow-up period after completing study drug dosing. If all asthma-related TEAEs from this study are considered, there was one additional AE of increased cough in a racemic-albuterol treated patient.

Figure 9. Asthma Exacerbations: Study 051-032



Abbreviations: Lev 0.31=levalbuterol inhalation solution 0.31 mg, Lev 0.63=levalbuterol inhalation solution 0.63 mg, PBO=placebo, RA=racemic albuterol
Numbers above each column indicate number and percentage of subjects
Source: Reviewer generated table from JMP using "AE" dataset

Looking at the additional safety data from Studies 051-033 and 051-359, the trend of increased asthma exacerbations or TEAEs continues.

Table 25. Asthma Exacerbations and Treatment Discontinuations: Study 051-033

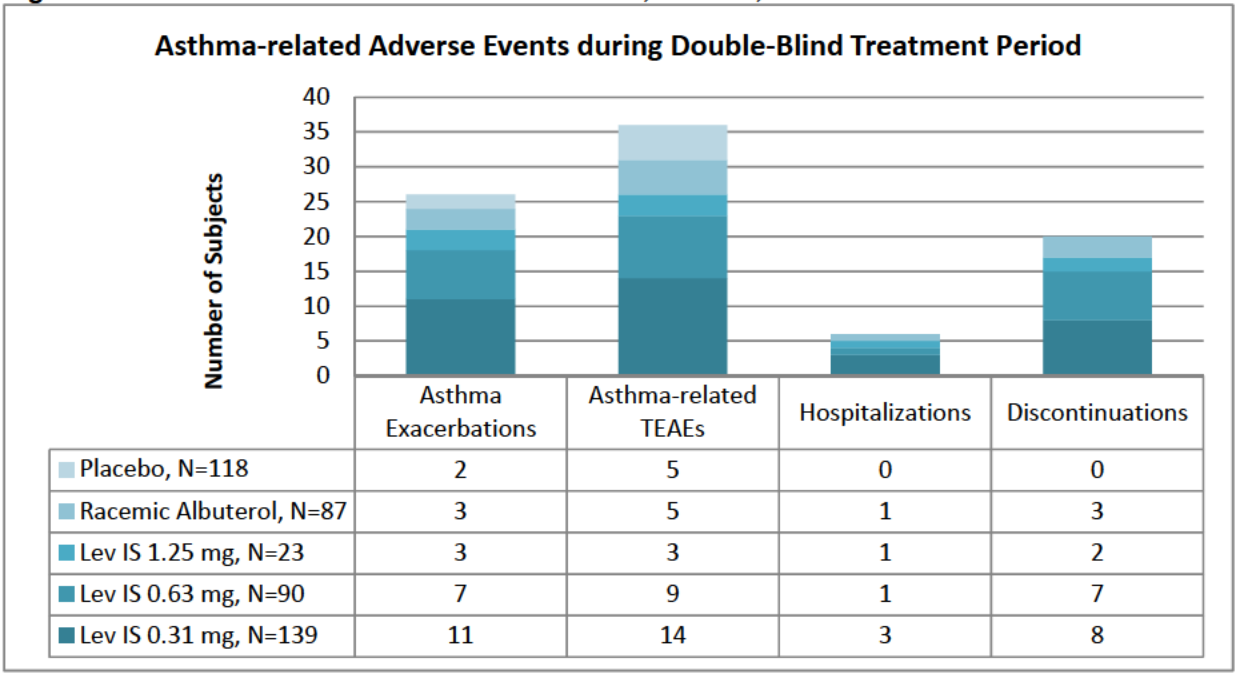
Study 051-033	Xopenex (LD) N=42	Xopenex (HD) N=40	RAC N=35
Asthma exacerbations, n(%) Periods II/III	1 (2.4)	2 (5)	0
Treatment discontinuations due to asthma-related AEs, n(%) Period I Periods II/III	0 2 (4.8)	1 (2.5) 1 (2.5)	0 0
Source: Reviewer analysis of "AE" and "DEMOG" datasets			

Table 26. Asthma-related TEAEs and Treatment Discontinuations: Study 051-359

Study 051-359	PBO N=68		Lev HFA N=65		Lev IS N=63	
	Subject n(%)	Event n	Subject n(%)	Event n	Subject n(%)	Event n
Asthma-related TEAEs*, n(%)	3 (4.4)	3	8 (12.3)	10	6 (9.5)	6
Treatment discontinuations due to asthma, n(%)	0	0	1 (1.5)	1	2 (3.2)	2
*Includes the following PTs: asthma, cough, hypoxia, status asthmaticus, tachypnea Source: Reviewer analysis of "ADAE" and "ADSL" datasets						

Despite the small numbers in any individual study, there was a consistent pattern of increased asthma-related TEAEs in Lev IS treatment groups across studies. In combining data from the three studies in Figure 10, the safety signal becomes more apparent. Since fewer patients received treatment with the higher Lev IS doses, it is difficult to determine if this is a dose-related adverse reaction.

Figure 10. Asthma-related TEAEs: Studies 051-032, 051-033, 051-359



	Asthma Exacerbations	Asthma-related TEAEs	Hospitalizations	Discontinuations
Placebo, N=118	2	5	0	0
Racemic Albuterol, N=87	3	5	1	3
Lev IS 1.25 mg, N=23	3	3	1	2
Lev IS 0.63 mg, N=90	7	9	1	7
Lev IS 0.31 mg, N=139	11	14	3	8

Source: Reviewer generated graph/table using "AE", "DEMOG", "ADAE", and "ADSL" datasets

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common AEs reported across studies and treatment groups were vomiting, viral infection/upper respiratory tract infection, fever/pyrexia, and asthma. The higher frequency of vomiting in Study 051-033 was primarily due to emesis after oral corticosteroid administration. Overall, the type and frequency of common adverse events generally appears similar to those observed in the clinical trials of Lev IS in patients ≥6 years of age, although interestingly there were fewer reports of tremor and tachycardia than one would expect. Table 27 displays TEAEs that occurred in at least 2 patients within a treatment group in Studies 051-032, 051-033, and 051-359. Due to space considerations, the Lev IS 0.15 mg and Lev HFA treatment groups have been omitted from the table. Only two patients were randomized to treatment with Lev IS 0.15 mg in Study 051-033, and only one patient reported a TEAE of viral infection.

Table 27. Common TEAEs by Study and Treatment

System Organ Class[a] / Preferred Term	Study 051-032				Study 051-033[b]				Study 051-359[c]	
	Lev 0.31 N=58	Lev 0.63 N=51	RA N=52	PBO N=50	Lev 0.31 N=18	Lev 0.63 N=39	Lev 1.25 N=23	RA N=35	Lev 0.31 N=63	PBO N=68
Overall – any TEAE, n(%)	31 (53.4)	31 (60.8)	28 (53.8)	26 (52.0)	6 (33.3)	22 (56.4)	12 (52.1)	9 (25.7)	29 (46.0)	28 (41.2)
Gastrointestinal Disorders										
Abdominal Pain	1 (1.7)	0	0	2 (4.0)	0	0	0	0	0	0
Diarrhea	0	3 (5.9)	1 (1.9)	0	1 (5.6)	3 (7.7)	1 (4.3)	2 (5.7)	2 (3.2)	3 (4.4)

System Organ Class[a] / Preferred Term	Study 051-032				Study 051-033[b]				Study 051-359[c]	
	Lev 0.31 N=58	Lev 0.63 N=51	RA N=52	PBO N=50	Lev 0.31 N=18	Lev 0.63 N=39	Lev 1.25 N=23	RA N=35	Lev 0.31 N=63	PBO N=68
Vomiting	0	4 (7.8)	3 (5.8)	2 (4.0)	3 (16.7)	10 (25.6)	3 (13.0)	2 (5.7)	2 (3.2)	2 (2.9)
General Disorders and Administration Site Conditions										
Fever/Pyrexia[d]	11 (19.0)	8 (15.7)	5 (9.6)	9 (18.0)	3 (16.7)	4 (10.3)	3 (13.0)	0	7 (11.1)	6 (8.8)
Pain	2 (3.4)	1 (2.0)	0	2 (4.0)	0	0	0	1 (2.9)	0	0
Infections and Infestations										
Conjunctivitis	2 (3.4)	0	1 (1.9)	2 (4.0)	0	1 (2.6)	3 (13.0)	0	2 (3.2)	0
Flu Syndrome/Influenza[d]	1 (1.7)	0	0	2 (4.0)	0	0	0	0	0	1 (1.5)
Otitis media	3 (5.2)	0	4 (7.7)	3 (6.0)	0	2 (5.1)	1 (4.3)	0	8 (12.7)	5 (7.4)
Pneumonia	0	0	0	0	0	0	0	1 (2.9)	2 (3.2)	1 (1.5)
Tonsillitis	0	0	0	0	0	0	0	0	0	3 (4.4)
Viral Infection / Upper respiratory tract infection[d]	6 (10.3)	12 (23.5)	9 (17.3)	5 (10.0)	0	1 (2.6)	1 (4.3)	1 (2.9)	5 (7.9)	4 (5.9)
Injury, poisoning and procedural complications										
Accidental Injury	2 (3.4)	3 (5.9)	1 (1.9)	3 (6.0)	0	2 (5.1)	1 (4.3)	1 (2.9)	0	0
Nervous System Disorders										
Headache	1 (1.7)	4 (7.8)	1 (1.9)	4 (8.0)	0	0	0	0	0	0
Insomnia	1 (1.7)	0	0	0	0	2 (5.1)	0	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders										
Asthma	6 (10.3)	7 (13.7)	3 (5.8)	2 (4.0)	1 (5.6)	0	3 (13.0)	0	4 (6.3)	0
Cough	0	0	1 (1.9)	0	0	0	0	1 (2.9)	2 (3.2)	3 (4.4)
Pharyngitis/Nasopharyngitis[d]	4 (6.9)	2 (3.9)	1 (1.9)	1 (2.0)	0	0	0	0	1 (1.6)	3 (4.4)
Rhinitis/Rhinorrhea[d]	7 (12.1)	1 (2.0)	0	3 (6.0)	1 (5.6)	0	3 (13.0)	0	0	2 (2.9)
Sinusitis	1 (1.7)	2 (3.9)	3 (5.8)	0	0	0	0	0	0	0
Skin and Subcutaneous Tissue Disorders										
Rash	0	1 (2.0)	2 (3.8)	2 (4.0)	2 (11.1)	4 (10.3)	1 (4.3)	0	0	0

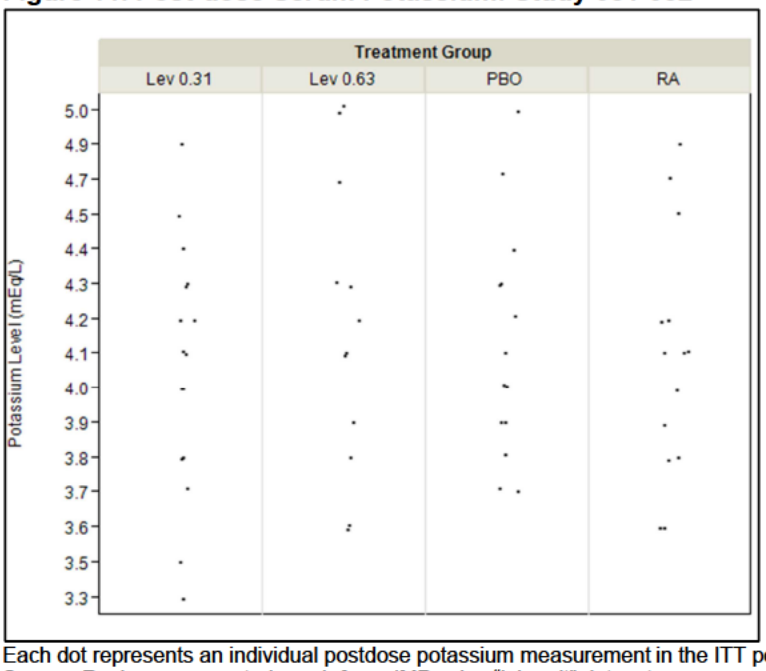
Abbreviations: Lev=levalbuterol HCl Inhalation Solution, RA=racemic albuterol, PBO=placebo
[a]Preferred Terms listed under corresponding MedDRA SOC rather han COSTART Body System for Studies 051-032 and 051-033
[b]Levalbuterol 0.15 mg treatment group (n=2) omitted; 1 patient reported a TEAE of viral infection
[c]Levalbuterol treatment group was open-label and placebo was blinded MDI; levalbuterol HFA treatment group omitted.
[d]Similar COSTART and MedDRA Preferred Terms combined
Sources: Reviewer analyses of "AE" (Studies 051-032 and 051-033) and "ADAE" (Study 051-359) datasets; Module 5.3.5.1, Study 051-032 CSR, Table 12.2 2.-1, p118; Module 5.3 5.4, Study 051-359 CSR, Table 19, p77

7.4.2 Laboratory Findings

As with other β-adrenergic agonists, Lev IS 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.

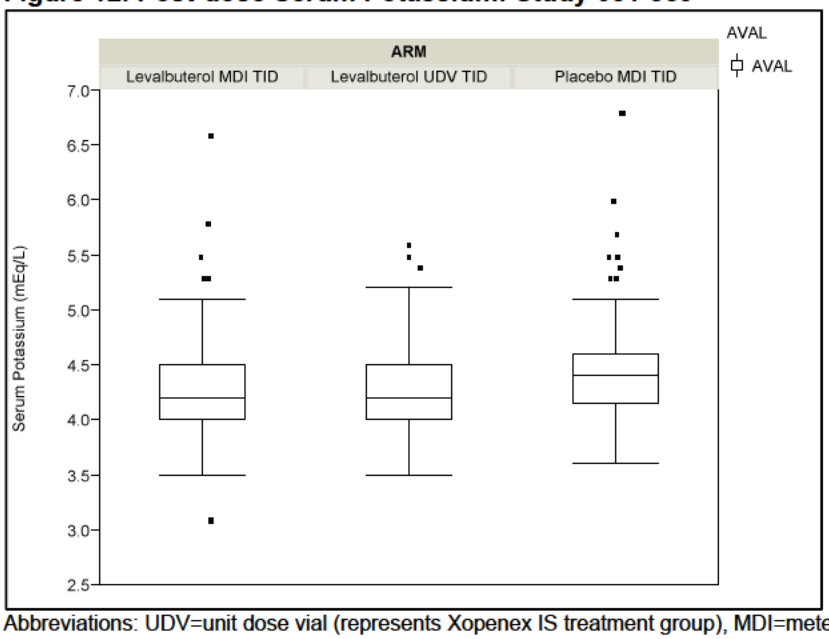
Serum potassium and glucose levels obtained postdose in Studies 051-032 and 051-359 are shown below. There was no apparent clinically significant difference in average potassium or glucose levels among treatment groups observed in these studies. The lab results from Studies 051-033 and 091-029 were consistent with these findings; no labs were obtained for Study 051-SRC038.

Figure 11. Post-dose Serum Potassium: Study 051-032



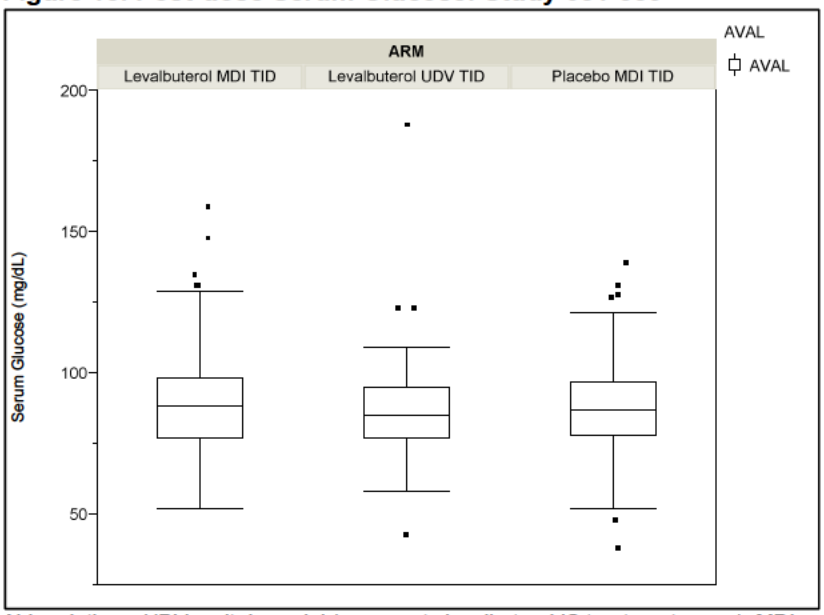
Each dot represents an individual postdose potassium measurement in the ITT population from Visit 4 or 5.
Source: Reviewer generated graph from JMP using "labreslt" dataset.

Figure 12. Post-dose Serum Potassium: Study 051-359



Abbreviations: UDV=unit dose vial (represents Xopenex 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 13. Post-dose Serum Glucose: Study 051-359



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. Arterial pressure may increase as well if the decrease in systemic vascular resistance does not offset the increase in cardiac output.

The figures below display heart rate and blood pressure measurements immediately post-dose in Studies 051-032 and 051-359. Although these figures represent absolute values rather than change from baseline, there was no apparent clinically significant difference in the vital sign measurements among treatment groups. Moreover, the often purported safety advantage that Xopenex causes fewer cardiovascular side effects compared with racemic albuterol was not observed in these trials. Vital sign assessments from Studies 051-033 and 091-029 were consistent with these findings.

Figure 14. Heart Rate 20 minutes Post-dose: Study 051-032

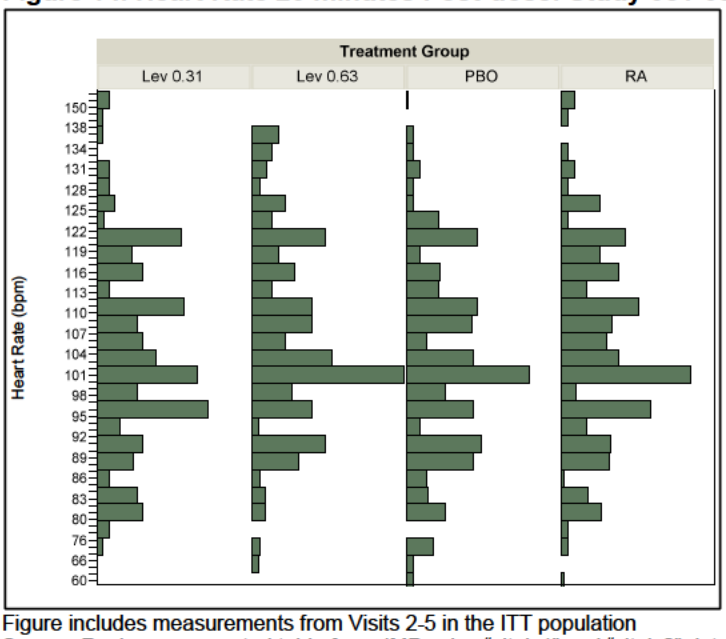
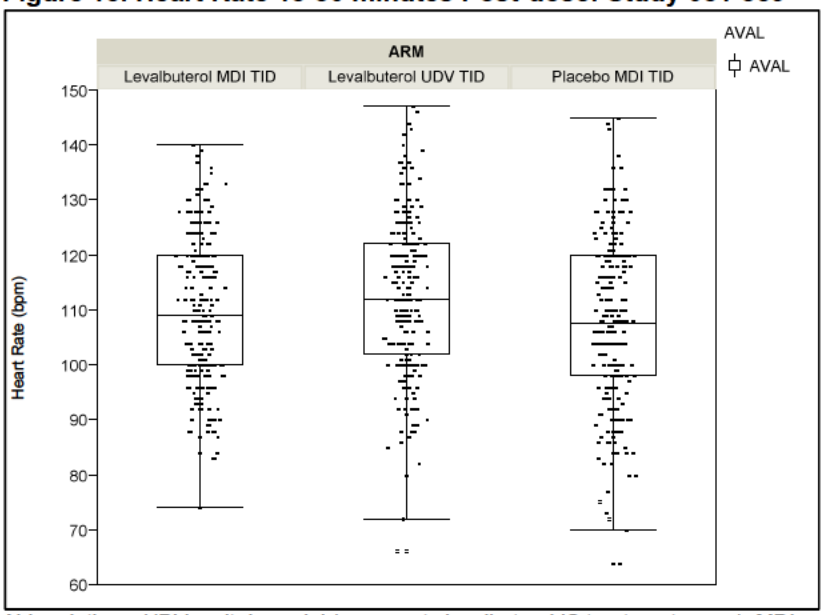


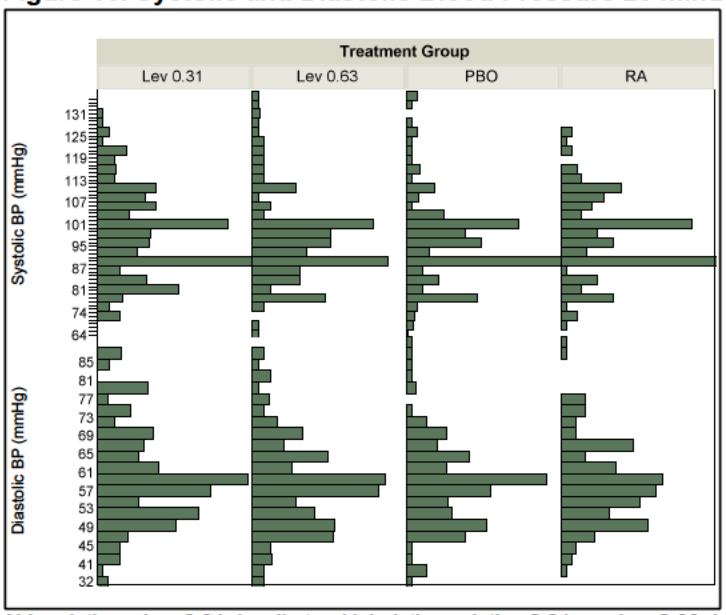
Figure includes measurements from Visits 2-5 in the ITT population
Source: Reviewer generated table from JMP using "vitals1" and "vitals2" datasets.

Figure 15. Heart Rate 15-30 minutes Post-dose: Study 051-359



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 overlying individual data points of heart rate measurements 15 and 30 minutes 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 740 observations.
Source: Reviewer generated table in JMP using "ADVS" dataset

Figure 16. Systolic and Diastolic Blood Pressure 20 minutes Post-dose: Study 051-032



Abbreviations: Lev 0.31=levalbuterol inhalation solution 0.31 mg, Lev 0.63=levalbuterol inhalation solution 0.63 mg, PBO=placebo, RA=racemic a buterol
Histogram includes a total of 771 blood pressure measurements from Visits 2-5 in the ITT population.
Source: Reviewer generated figure in JMP using "vitals1" and "vitals2" datasets

7.4.4 Electrocardiograms (ECGs)

B-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. All studies except 051-SRC038 included serial ECGs as part of the safety assessment, and none of the patients experienced a clinically significant ECG abnormalities such as arrhythmias or QTc prolongation.

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 hydrochloride is a small molecular entity with no known immunogenic potential.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The majority of safety data is this submission comes from the 0.31 mg and 0.63 mg Lev IS doses. Although there was no clear dose dependence for adverse events, the

smaller number of patients receiving higher Lev IS doses may have blunted any apparent dose response.

7.5.2 Time Dependency for Adverse Events

As mentioned previously regarding tachyphylaxis and paradoxical bronchospasm, the risk for experiencing an asthma-related TEAE was higher for subjects enrolled in chronic dosing studies of 3-4 weeks duration. Although only 12 subjects less than 6 years of age were treated in Study 091-029, there were few adverse events reported following cumulative dosing with Lev IS over the course of 1 hour.

7.5.3 Drug-Demographic Interactions

There were no apparent drug-demographic interactions based on 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 levalbuterol hydrochloride during pregnancy and lactation has not been evaluated.

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 levalbuterol hydrochloride.

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 IS 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 an Periodic Adverse Experience Report on May 22, 2014 covering the reporting period of March 25, 2013 through March 24, 2014. Of the 12 individual SAE case reports, none were for patients under 6 years of age.

8 Postmarket Experience

The Applicant estimated the commercial usage of Xopenex IS from January 2006 to September 2013 in patients below 6 years of age to approach 50% based on number of prescriptions dispensed and surveys from panel doctors. From market introduction (1999) through October 4, 2013, a total of 809 postmarketing events were spontaneously reported for Xopenex IS in this age group: 174 events in patients aged 0 to <1 year, 123 events in patients aged 1 to <2 years, 302 events in patients aged 2 to <4 years, and 210 events in patients aged 4 to <6 years. The most frequently reported events were cough (41 events), psychomotor hyperactivity (35 events), drug ineffective (27 events), rash (24 events), tremor (23 events), increased heart rate (22 events), urticaria (22 events), and vomiting (21 events). There was one case reported of sudden death in a 3-month old male with a possible viral illness with reactive airway disease who received two administrations of Xopenex IS 0.63 mg. The cause of death was listed as sudden infant death syndrome associated with bronchiolitis. Accidental overdose was reported in two patients 2 to <4 years of age and 1 patient 4 to <6 years of age; none were considered serious adverse events. The potential asthma-related postmarketing spontaneous reports in the US for pediatric patients <6 years of age from marketing (1999) through October 4, 2013, are listed in the table below.

System Organ Class Preferred Term MedDRA version 16.0	Age Category (n=events)			
	0 to <1 years	1 to <2 years	2 to <4 years	4 to <6 years
Investigations				
Breath sounds abnormal	0	0	1	0
Oxygen decreased	1	3	1	0
Peak expiratory flow rate decreased	0	0	0	1
Pulmonary function test decreased	0	0	0	1

System Organ Class Preferred Term MedDRA version 16.0	Age Category (n=events)			
	0 to <1 years	1 to <2 years	2 to <4 years	4 to <6 years
Respiratory rate increased	0	1	0	0
Respiratory, thoracic, and mediastinal disorders				
Apnea	1	0	0	0
Asthma	2	5	6	7
Bronchial hyperactivity	0	1	0	1
Bronchospasm	1	0	3	2
Bronchospasm paradoxical	0	0	1	0
Cough	6	3	18	14
Dyspnea	5	0	5	3
Hyperventilation	0	1	0	1
Hypoventilation	0	1	0	0
Lung disorder	0	0	1	0
Painful respiration	0	0	1	0
Respiratory arrest	0	0	1	0
Respiratory disorder	0	0	1	0
Respiratory distress	1	0	2	0
Stridor	1	1	1	0
Tachypnea	0	0	0	1
Wheezing	6	1	2	2
Source: Module 2.7.4, Summary of Clinical Safety, Table 28, p72				

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 IS after >10 years of commercial availability suggests that the safety profile in pediatric patients below 6 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 6 years, the relatively small number of events does not support inclusion of (b) (4) language for this age group in the Pediatric Use section of the label.

9 Appendices

9.1 Literature Review/References

A PubMed search using the terms “levalbuterol AND pediatric” retrieved 38 articles, none of which change the risk-benefit assessment any further. Although older publications suggested an advantage for levalbuterol, newer trials have failed to confirm either a safety or efficacy advantage over racemic albuterol.

9.2 Labeling Recommendations

At the time of this review, labeling discussions between the Applicant and the Agency were ongoing. Major labeling recommendations include updating Section 8.4 with efficacy and safety data for pediatric patients <6 years of age, specifically with information regarding the increased number of asthma-related adverse reactions in the Xopenex treatment groups. The Office of Prescription Drug Promotion (OPDP) and the Division of Medical Policy Programs (DMPP) 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 Inhalation Solution is already approved for the treatment or prevention of bronchospasm in adults, adolescents, and children 6 years of age and older with reversible obstructive airway disease, and the Applicant is not seeking to expand the indication.

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

/s/

STACY J CHIN
12/19/2014

ANTHONY G DURMOWICZ
12/20/2014