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Statistical Review

CLINICAL STUDY

NDA / Sequence Number:	NDA 020837 / Seq 0045
Drug Name:	Xopenex® (levalbuterol hydrochloride)
Proposed Indication:	Treatment and prevention of bronchospasm in patients with reversible obstructive airway disease (b) (4)
Applicant:	Sunovion
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1 EXECUTIVE SUMMARY

Sunovion has submitted a supplemental NDA to evaluate the safety and efficacy of Xopenex IS (levalbuterol hydrochloride inhalation solution) for the treatment and prevention of bronchospasm in patients with reversible obstructive airway disease in patients less than six years of age. This product was approved for this indication in adults on March 25, 1999 and in children 6 to 11 years of age on January 30, 2002. As required by the Pediatric Research Equity Act (PREA), the current submission evaluates efficacy and safety of Xopenex IS in children less than 6 years of age.

Based on the results from two phase 3 studies, 051-32 and 051-33, this submission fails to demonstrate statistically significant benefits of Xopenex IS for the treatment or prevention of bronchospasm in children less than six years of age with reversible obstructive airway disease.

In study 051-32, Xopenex IS did not improve bronchospasms relative to placebo for the Pediatric Asthma Questionnaire during the third week after commencement of treatment. In study 051-33, for the primary endpoint, a non-validated respiratory symptom score, Xopenex IS was worse than an equivalent levalbuterol dose administered as racemic albuterol, and high levalbuterol dose Xopenex IS was worse than low levalbuterol dose Xopenex IS.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Xopenex IS is a solution containing levalbuterol, a long acting beta2-adrenergic receptor agonist. This supplemental NDA evaluates use of Xopenex IS for a pediatric indication, i.e. for the treatment and prevention of bronchospasm in patients with reversible obstructive airway disease in patients less than six years of age.

2.1.2 History of Drug Development

Xopenex IS, for the treatment or prevention of bronchospasm in adults and adolescents 12 years of age and older with reversible obstructive airway disease, was introduced to the Agency under IND 74,674, and was approved for use in adults under NDA 20-837 on March 25, 1999. Based on supplemental NDA 20-837 (S-006), the Agency approved its use in children 6 to 11 years of age on January 30, 2002. However, the approval letter for this supplement noted that a requirement for evaluation of efficacy in patients less than six years of age had not yet been completed, and granted a deferral for submission until July 31, 2003. [redacted] James Gebert, PhD, completed a Biometrics review of study 051-32 on February 21, 2003, and concluded that study 051-32 "does not provide evidence of efficacy in the pediatric population aged 2 to 5 years." Between 2003 and 2008 there were numerous communications between the Agency and the applicant regarding the pediatric studies for Xopenex IS, however no further efficacy supplements were submitted.

On November 14, 2012, the Agency informed the applicant that, unless pediatric studies were completed by April 5, 2013, or a deferral extension was requested by January 5, 2013, the applicant would be considered non-compliant. On December 21, 2012, the applicant proposed to submit data from three Xopenex IS studies, 051-032, 051-033, and 051-SRC038 to meet PREA requirements and, on March 5, 2013 requested a meeting for further discussion. In preliminary meeting comments communicated to the applicant on May 31, the Division stated that the proposal was acceptable. The applicant withdrew the meeting request and, with the intention of meeting PREA requirements, provided the current submission on March 28, 2014.

2.2 Data Sources

Data for all three studies was provided by the applicant and is currently located at:

\\cdesub1\evsprod\NDA020837\0045\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The efficacy data and analysis quality were adequate in this submission. Information requests sent to the applicant resolved issues concerning data formats which were missing in the original submission.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The current submission provides results from two randomized, double-blind, placebo-controlled, parallel arm studies to evaluate the efficacy of Xopenex IS for treatment and prevention of bronchospasm in pediatric patients with asthma (Table 1). Study 051-032 (32) randomized 211 asthma patients two to five years of age in a 1:1:1:1 ratio to 0.31 mg levalbuterol (L31) three times daily (tid), 0.63 mg levalbuterol (L63) tid, racemic albuterol (RA), or placebo (P). The RA arm was administered as 1.25 mg tid for patients < 33 lb and 2.5 mg tid for patients weighing ≥ 33 lb. Study 051-033 (33) recruited and randomized 117 patients from birth to less than 48 weeks of age at the emergency department or physician's office with a diagnosis of acute reactive airway disease, in a 1:1:1 ratio to low dose levalbuterol (LL), high dose levalbuterol (HL), or RA. LL was defined as 0.15, 0.31, or 0.63 mg among patients 2.5 kg to 5 kg, >5 kg to 10 kg, and >10 kg, respectively and HL was defined as 0.31, 0.63, or 1.25 mg among patients 2.5 kg to 5 kg, >5 kg to 10 kg, and >10 kg, respectively. RA was administered as 0.63, 1.25, or 2.5 mg among patients 2.5 kg to 5 kg, >5 kg to 10 kg, and >10 kg, respectively.

In studies 32 and 33, treatment was administered using a standard jet nebulizer with facemask or mouthpiece connected to an air compressor.

Table 1. Phase 3 Studies in Current Submission

Study	Design	Population	Endpoints
051-032 (32)	L31 L63 RA P Parallel arm DB P run in W -1 P to W3	Asthma 2 to 5 years old N=211 1:1:1:1 strat: weight	Primary: during Week 3 ΔPAQ Key Secondary: during Week 3 ΔIPAQS symptom scores Caregiver asthma symptom assessments ΔPEF Rescue medication usage Uncontrolled asthma days Asthma exacerbations Child Health Status questionnaires PACQLQ Global evaluations
051-033 (33)	LL HL RA Parallel arm DB P run in W -1 P to W3	Asthma 0 to <4 years old RSS Section III ≥ 5 N=117 1:1:1 strat: weight group	Primary: Maximum decrease RSS Key Secondary: Δindividual RSS items Time to meet discharge criteria Time to maximum decrease in RSS Rate of hospitalization

Source: Reviewer
DB double blind, W -1 week -1, W3 week 3, PAQ Pediatric Asthma Questionnaire, IPAQS individual scores from PAQ, PEF peak expiratory flow rate, PACQLQ Pediatric Asthma Caregiver's Quality of Life Questionnaire, RSS Respiratory Status Scale

Study 32 was placebo-controlled for three weeks, with a one-week run-in period using a single-blind placebo. During the run-in period, rescue medication consisted of a double-blind 1.25 mg nebulized levalbuterol and, during the treatment period, rescue medication was double-blind 1.25 mg nebulized levalbuterol for patients randomized to levalbuterol, and double-blind 2.5 mg nebulized racemic albuterol for those randomized to racemic albuterol or placebo.

The primary endpoint in study 32 was mean change in pediatric asthma questionnaire (PAQ) total score from run in (week -1) to its mean during week 3. PAQ was assessed daily by each parent or legal guardian.

In study 33, patients newborn to four years of age diagnosed with acute reactive airway disease were recruited at an emergency department (ED) or physician's office; those meeting the enrollment criteria were randomized to LL, HL, or RA. In the three hours following randomization, each patient was administered up to six doses of their assigned study medication. Patients who were hospitalized following randomized treatment in the emergency room or physician's office in the next week were discontinued from the study.

Study 33 was divided into three phases: period one, from enrollment to discharge from the ED or physician's office, period two, from termination of period one to seven to ten days after termination of period one, and period three for seven to ten days following period 2, during which patients could discontinue randomized study medication at the discretion of the investigator. After randomization, patients continuing after discharge from the ED or physician's office were prescribed randomized medication tid and returned to the clinic for weekly assessments until the final visit at the end of the third week (week 3). After initial release from the emergency center, rescue medication consisted of blinded 1.25 mg levalbuterol for patients randomized to the levalbuterol and blinded 2.5 mg racemic albuterol unit dose vial for patients randomized to racemic albuterol.

The primary endpoint for study 33 was the maximum decrease during period one of respiratory status scale (RSS, see Appendix), from initial pre-dose at screening and each post-dose measurement. However, there does not seem to be any literature validating this endpoint as a quantitative measure of acute reactive airway disease.

According to the applicant, the primary objective of study 33 was to "investigate the efficacy of two dose levels of levalbuterol compared with one dose level of racemic albuterol." Considering that the doses of the active ingredient, levalbuterol, were the same in HL and RA, the appropriate statistical test would have been for non-inferiority of HL to RA. However, a non-inferiority margin was not pre-specified, and therefore study 33, by design, could not be used to demonstrate non-inferiority of HL to RA. For the present review, I will assume that low dose (LL) is as good as or superior to placebo, and will then conclude that dose HL is effective for the non-validated endpoint, RSS, if HL is superior to LL. As a secondary endpoint, HL will be compared to RA, with statistically significant differences possibly raising concerns regarding proper HL dosage.

In study 32, the first patient was randomized to treatment November 28, 2000 and the last patient was randomized to treatment on November 30, 2001. In study 33, the first patient was randomized to treatment February 2, 2001 and the last patient was randomized to treatment on July 27, 2002. Both studies were conducted at multiple sites in the United States.

The submission provides a third study, 051-SRC038, intended to compare levalbuterol with racemic albuterol in children 2 to 17 years of age that was conducted at a single hospital, (b) (4) Primary response variables in this investigator initiated study were hospital admission rates and time until discharge. However, more than half of the enrolled patients were over six years old, and the study did not prespecify or power for separate analyses of patients less than six years old. Therefore this study will not be further addressed in this review.

3.2.2 Statistical Methodologies

Primary efficacy analyses in both studies used 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, for study 32, pairwise tests in study were performed comparing each active treatment arm to control (placebo in study 32, racemic albuterol in study 33). In study 32, if a particular levalbuterol arm differed significantly from placebo, then a pairwise test of that arm versus racemic albuterol was performed.

Given the design difficulties in study 33, the primary efficacy analysis in the current review will evaluate superiority of HL to LL for maximum change from baseline RSS. As a secondary endpoint, HL will be compared for superiority to the putative equivalent levalbuterol dose in RA.

Additional analyses for the primary efficacy endpoints included investigator by treatment and weight group by treatment interactions. If either interaction was statistically significant, appropriate exploratory analyses were performed.

Efficacy analyses in both studies were conducted on what the applicant termed the 'intent-to-treat population,' consisting of all randomized patients receiving at least one dose of double-blind study medication. However, in both studies, patients with major protocol deviations or who used disallowed medications were removed from the analyses. The populations analyzed by the applicant were therefore effectively 'per-protocol' rather than intention-to-treat. The analyses provided in this review consider an intent-to-treat population consisting of all randomized and treated patients – the results are similar to those from the applicant's per-protocol analyses.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were no obvious differences between treatment groups for demographic and baseline characteristics (Table 2 and Table 3).

Table 2. Demographic and Baseline Characteristics, Study 32

Characteristic	Treatment Group			
	L31 (n=58)	**L63 (n=51)**	**RA (n=52)**	**Placebo (n=50)**
Age				
Mean (SD)	3.4 (1.2)	3.3 (1.1)	3.4 (1.1)	3.7 (1.0)
Median	3.0	3.0	3.5	4.0
Min, Max	2, 5	2, 5	2, 5	2, 5
Gender				
Male	41 (70.7%)	35 (68.6%)	33 (63.5%)	28 (56.0%)
Female	17 (29.3%)	16 (31.4%)	19 (36.5%)	22 (44.0%)
Race				
Caucasian	34 (58.6%)	29 (56.9%)	31 (59.6%)	35 (70.0%)
Black	12 (20.7%)	12 (23.5%)	9 (17.3%)	8 (16.0%)
Asian	1 (1.7%)	1 (2.0%)	1 (1.9%)	1 (2.0%)
Hispanic	5 (8.6%)	6 (11.8%)	9 (17.3%)	5 (10.0%)
Other	6 (10.3%)	3 (5.9%)	2 (3.8%)	1 (2.0%)
Height (cm)				
Mean (SD)	103.02 (10.57)	100.73 (8.09)	101.02 (9.09)	103.35 (9.34)
Median	103.07	101.60	100.40	102.40
Min, Max	85.3, 121.9	83.7, 118.0	81.3, 121.9	83.8, 125.6
Weight (kg)				
Mean (SD)	18.16 (4.71)	17.91 (4.40)	17.27 (3.96)	17.87 (4.64)
Median	17.28	17.24	16.33	17.40
Min, Max	11.2, 34.0	11.1, 29.9	11.1, 31.5	11.8, 35.8

From CSR Table 11.2-1 page 76

Table 3. Demographic and Baseline Characteristics, Study 33

Characteristic		Treatment Group		
		LL (N=42)	HL (N=40)	RA (N=35)
Age (months)	Mean (SD)	20.3 (13.9)	19.5 (13.3)	19.1 (21.4)
	Min, Max	0, 47	0, 45	2, 46
Age category N (%)	0-1 month	1 (2.4)	2 (5.0)	0
	2-12 months	15 (35.7)	12 (30.0)	13 (37.1)
	13-24 months	10 (23.8)	12 (30.0)	11 (31.4)
	25-48 months	16 (38.1)	14 (35.0)	11 (31.4)
Gender N (%)	Male	32 (76.2)	25 (62.5)	25 (71.4)
	Female	10 (23.8)	15 (37.5)	10 (28.6)
Race N (%)	Caucasian	17 (40.5)	17 (42.5)	13 (37.1)
	Black	12 (28.6)	11 (27.5)	15 (42.9)
	Asian	2 (4.8)	1 (2.5)	0
	Hispanic	9 (21.4)	8 (20.0)	6 (17.1)
	Other	2 (4.8)	3 (7.5)	1 (2.9)
Height (cm)	N	34	34	32
	Mean (SD)	80.25 (13.86)	78.27 (14.75)	79.82 (14.57)
	Min, Max	53.3, 103.1	50.8, 99.1	43.2, 106.7
Weight (kg)	N	42	40	35
	Mean (SD)	11.38 (3.19)	11.47 (3.79)	11.79 (3.22)
	Min, Max	4.8, 18.0	4.1, 20.9	4.5, 19.1
Weight category N (%)	2.5-5 kg	2 (4.8)	2 (5.0)	1 (2.9)
	>5-10 kg	16 (38.1)	15 (37.5)	13 (37.1)
	>10 kg	24 (57.1)	23 (57.5)	21 (60.0)
RSV N (%)	Negative	31 (73.8)	30 (75.0)	30 (85.7)
	Positive	3 (7.1)	2 (5.0)	1 (2.9)
RSS Total Score (predose at Visit 1)	N	42	40	35
	Mean (SD)	7.0 (1.3)	7.0 (2.1)	7.7 (2.4)
	Median	7.0	7.0	8.0
	Min, Man	5, 9	4, 15	5, 13

From CSR Table 11.2-1 page 69

In both studies, patterns of patient disposition did not appear to favor or disfavor use of levalbuterol (Table 4 and Table 5).

Table 4. Patient Disposition, Study 32

	L31	**L63**	**RA**	**P**
Randomized	58 (100%)	51 (100%)	52 (100%)	50 (100%)
Completed Study	49 (85%)	41 (80%)	44 (85%)	42 (84%)
Terminated Early	9 (15%)	10 (20%)	8 (15%)	8 (16%)
Adverse Event	5 (9%)	8 (16%)	3 (6%)	2 (4%)
Protocol Violation	1 (2%)	0 (0%)	2 (4%)	2 (4%)
Voluntary Withdrawal	0 (0%)	1 (2%)	3 (6%)	0 (0%)
Lost to Follow-up	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Treatment Failure	0 (0%)	0 (0%)	0 (0%)	2 (4%)
Failed Entry Criteria	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	2 (0%)	0 (0%)	0 (0%)	2 (4%)

From CSR Table 14.1.3, page 172.

Table 5. Patient Disposition, Study 33

	LL	**HL**	**RA**
Randomized	42 (100%)	40 (100%)	35 (100%)
Completed Study	31 (74%)	32 (80%)	24 (69%)
Terminated Early	11 (26%)	8 (20%)	11 (31%)
Adverse Event	2 (5%)	3 (8%)	1 (3%)
Protocol Violation	3 (7%)	2 (5%)	3 (9%)
Voluntary Withdrawal	1 (2%)	0 (0%)	2 (6%)
Lost to Follow-up	4 (10%)	2 (5%)	2 (6%)
Treatment Failure	0 (0%)	1 (3%)	2 (6%)
Failed Entry Criteria	0 (0%)	0 (0%)	1 (3%)
Other	1 (2%)	0 (0%)	0 (0%)

From CSR Table 14.1.3, page 161.

3.2.4 Results and Conclusions

3.2.4.1 Study 32

The Biometrics review for study 32 was completed on February 21, 2003. The statistical reviewer, James Gebert, Ph.D., concluded that study 32 "does not provide evidence of efficacy in the pediatric population aged 2 to 5 years." We take his conclusion for granted, without further review here.

3.2.4.2 Study 33

As already noted, study 33 was improperly designed, proposing comparison of levalbuterol to an equivalent levalbuterol dose in a racemic mixture using a test for superiority rather than non-inferiority. Further, the primary endpoint, RSS, was not validated.

Results from study 33 fail to demonstrate that high dose levalbuterol is superior to low dose levalbuterol. In particular, improvements from baseline RSS were statistically significantly less for high HL compared to LL (Table 6). Further, HL provided significantly less benefit than RA. The applicant stated that the differences were 'not considered to be clinically meaningful.' However, that characterization is meaningless, because minimal clinically important differences for endpoint RSS are not known.

Table 6. Maximum Decrease from Baseline RSS, Study 33.

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: reviewer program fda_maxrss.sas
Higher decrease indicates greater benefit.

3.3 Evaluation of Safety

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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

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

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study 33 was improperly designed for examination of efficacy. There were no other outstanding statistical issues in the current submission.

5.2 Collective Evidence

Neither study in this submission provides any evidence of efficacy.

5.3 Conclusions and Recommendations

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

In study 051-32, Xopenex IS did not improve bronchospasms relative to placebo for the Pediatric Asthma Questionnaire during the third week after commencement of treatment. In study 051-33, for the primary endpoint, a non-validated respiratory symptom score, Xopenex IS was worse than an equivalent levalbuterol dose administered as racemic albuterol, and high levalbuterol dose Xopenex IS was worse than low levalbuterol dose Xopenex IS.

5.4 Labeling Recommendations

The applicant has not proposed any changes to the clinical studies section of the current Xopenex IS label. Modifications to the pediatric section of the label proposed by the applicant clearly state that Xopenex is not indicated for patients less than six years of age.

6 Appendix: RSS Total Score

RSS Total Score is Sum of:

Grunting/Coughing:	0 = None, 1 = Mild Occasional, 2 = Moderate Intermittent, 3 = Severe Constant
Nasal Flaring:	0 = None, 1 = Mild Occasional, 2 = Moderate Intermittent, 3 = Severe Constant
Wheezing:	0 = None, 1 = Mild Expiratory, 2 = Moderate Inspiratory/Expiratory, 3 = Severe Inaudible Breath Sounds
Air Exchange:	0 = Excellent Equal, All Lobes, 1 = Good Diminished, Bases Only, 2 = Fair Diminished, Some Lobes (other than bases), 3 = Poor Diminished, All Lobes
Accessory Muscle Use:	0 = None, 1 = Mild Just Visible, 2 = Moderate Evident, 3 = Severe Obvious

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/s/

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12/12/2014

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