CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-730

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-730

Drug Name: Xopenex (levalbuterol tartrate) HFA MDI

Indication(s): Treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age or older with reversible obstructive airways disease

Applicant: Sepracor Inc.

Date(s): Electronic NDA dated 05/11/2004.

Review Priority: Regular

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Keywords: Clinical Studies, NDA Review

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1 Executive Summary

1.1. Conclusions and Recommendations

In Study 051-353, levalbuterol 90 mcg MDI, manufactured by —— was significantly better than placebo for peak percent change in forced expiratory volume in one second (FEV_1) averaged over the 8 week double blind period and area under the FEV_1 percent change from visit predose curve averaged over the double-blind period in asthmatic adults and adolescents. In this study, racemic albuterol 180 mcg was significantly better than levalbuterol 90 mcg for these two endpoints.

In Study 051-355, both levalbuterol 90 mcg manufactured by —— and levalbuterol 90 mcg manufactured by 3M were significantly better than placebo for peak percent change in FEV_1 averaged over the 8 week double blind period and area under the FEV_1 percent change from visit predose curve averaged over the double-blind period in asthmatic adults and adolescents. Levalbuterol 90 mcg manufactured by 3M was significantly better than levalbuterol 90 mcg manufactured by —— for area under the FEV_1 percent change from visit predose curve averaged over the double-blind period. The 3M product was more similar to racemic albuterol than the —— product was.

In Study 051-354, levalbuterol 90 mcg manufactured by 3M was significantly better than placebo for peak percent change in FEV_1 averaged over the 4 week double blind period and area under the FEV_1 percent change from visit predose curve averaged over the double-blind period in asthmatic subjects 4-11 years of age.

In Studies 051-354 and 051-355, levalbuterol 90 mcg and racemic albuterol were not significantly different for these two endpoints.

The subjects in some of the studies used Spacers. The sponsor found that the use of spacers had an affect on the performance of racemic albuterol MDIs but not on the levalbuterol MDIs. It must be left to clinical judgment whether this information should be provided in the label.

1.2 Brief Overview of Clinical Studies

This review will mainly focus on the 3 phase III studies. One of which, a study with a 4 week treatment period, was in asthmatic children 4 to 11 years of age. The other two studies in asthmatic adults and adolescents had a 8 week treatment period. Two single dose, dose-ranging, exercise induced bronchospasm studies will also be discussed. This review will not discuss 3 cumulative dose studies which were mainly conduced for safety reasons. Two studies using CFC as a propellant and 2 studies using an earlier larger actuator will also not be discussed.

The sponsor used both a manufactured MDI and a 3M manufactured MDI in their studies. The sponsor wants to market the 3M manufactured MDI. One of the phase III studies used both the and 3M MDIs.

1.3 Statistical Issues and Findings

The sponsor supplied data and programs for these studies. This reviewer was able to duplicate the sponsor's results in the tables of this review from the programs and data provided.

2. Introduction

2.1 Overview

Levalbuterol is the (R)-stereoisomer of albuterol. Racemic albuterol is a mixture of the (R)- and (S)- stereoisomers. The sponsor states that results from in vitro studies of binding to human beta-adrenergic receptors demonstrated that levalbuterol has approximately 2-fold greater binding affinity than racemic albuterol and approximately 100-fold greater binding affinity than (S)-albuterol. Xopenex (levalbuterol HCL) Inhalation solution (NDA 20-837) was approved by the Agency in March 1999 for the treatment and prevention of bronchospasm in adults and adolescents. In January 2002, a pediatric supplement was approved for children 6 years of age and older. Xopenex HFA (levalbuterol tartrate) MDI, 45 mcg per actuation, was developed as an alternative dosing form. The sponsor plans to market the MDI manufactured by 3M. There were 3 Phase III studies in this submission (two adult and adolescent studies 051-353 and 051-355, and one pediatric study in children 4 to 11 years of age, Study 051-354). Study 051-353 used a MDI manufactured by whereas Study 051-354 used the 3M manufactured MDI. Study 051-355 used both the 3M and MDIs. Study 051-355 is thus both an efficacy and bridging study. Studies 051-308 and 051-312 used the 3M manufactured MDI.

There were 12 studies discussed in this submission. This review will only discuss two exercise induced bronchospasm (EIB) studies (051-308 in adults and adolescents and 051-312 in pediatric subjects) and the three Phase III studies. The studies that will not be reviewed are Studies 051-301 and 051-304 which used a CFC propellant, Studies 051-309, 051-310 and 051-311 which were cumulative dose studies done for safety reasons, and Studies 051-305 and 051-306 which used a larger actuator (orifice diameter mm) which effected device performance. The orifice diameters of the 3M and MDIs are . The EIB studies will be discussed for their dose ranging features.

This review will use the sponsor's table numbers. These table numbers do not necessarily correspond to the same variable but rather to the primary variable and important secondary variable. (The primary efficacy variable results of each study are given in Table 11.4.1.1-1 and the important secondary variable is given in Table 11.4.1.2-1.)

2.1.1 Study 051-308

This was a randomized, modified-blind, active-controlled, multicenter, parallel-treatment, 3x3 dose level crossover study of up to three weeks duration. Using an exercise challenge approach, the dose response of levalbuterol HFA MDI was evaluated in adolescent and adult subjects with asthma. All study medication was administered via a plastic spacer — to minimize dose-administration and eye-hand coordination errors. Throughout the study (i.e., in the clinic and at home), subjects were given open-label pirbuterol CFC MDI (0.2 mg/actuation) to use as needed as rescue medication for relief of asthma signs and symptoms. There was a five-day (± 2) washout between doses.

Subjects were using either a β-adrenergic agonist, and/or over-the-counter asthma medication for at least six months prior to Visit 1. Subjects had to demonstrate baseline $FEV_1 \geq 70\%$ of predicted at Visits 1-5 and a 20-50% decrease in FEV_1 following both baseline exercise challenges after placebo administration.

In-clinic dosing was performed by separate unblinded study personnel who were not responsible for any other study procedures (e.g., spirometry testing, completion of case report forms, review of diary card or medical events calendar). Dosing occurred in a separate room away from pulmonary function testing, and no other study personnel were present. Subjects were blinded to treatment by the use of blindfolds. [The subjects would not be blinded to the number of doses of study medication taken at the various on-treatment visits.] This modified-blinded procedure was used because masking devices were not available at the time study medication was packaged for this study.

Randomization occurred separately within each site using permuted blocks to maintain blinding of the Investigator and to balance enrollment across sites and treatment arms. At each site, Investigators assigned the lowest number to the first subject and proceeded in increasing sequential order within a block. An overall block size of 12 was used so that all possible sequence by treatment combinations were present. A subset block size of 6 was used within the overall block size to achieve balanced treatment arms.

Period I consisted of a screening visit followed by a four-day (±1 day) interval to ensure completion of safety laboratory analysis. The baseline period was initiated at Visit 2 after review of laboratory results. At this visit, subjects completed the first of two exercise challenge tests; the second challenge was conducted during the seven-day (±2 days) baseline period. Single-blind MDI placebo was administered prior to each of these two exercise challenge tests.

Subjects were randomized to either levalbuterol or racemic albuterol HFA MDI at the start of Period II. Those randomized to the levalbuterol arm completed one of six possible randomization sequences containing (A) levalbuterol 45 mcg (1 actuation of 45 mcg), (B) levalbuterol 90 mcg (2 actuations of 45 mcg), and (C) levalbuterol 180 mcg (4 actuations of 45 mcg). Subjects randomized to racemic albuterol completed one of six possible randomization sequences containing (A) racemic albuterol 90 mcg (1 actuation

of 90 mcg), (B) racemic albuterol 180 mcg (2 actuations of 90 mcg), and (C) racemic albuterol 360 mcg (4 actuations of 90 mcg). Subjects received each treatment, according to the randomization sequence, at Visits 3 to 5; each visit was separated by a five-day washout (±2 days). [Comparisons of dose levels is within patients whereas comparison of levalbuterol doses with racemic albuterol doses is a between patients comparison.]

The primary objective was to investigate, using an exercise challenge approach, the dose response of levalbuterol HFA MDI in adolescent and adult subjects with asthma. Secondary objectives of the study were:

- To investigate the relative potency of levalbuterol and racemic albuterol HFA MDI in the prevention of exercise-induced bronchoconstriction (EIB).
- To compare levalbuterol and racemic albuterol HFA MDI in the prevention of EIB at each dosing level.
- To characterize the exposure to (R)-albuterol in subjects treated with levalbuterol and the exposure to (R)- and (S)-albuterol in subjects given racemic albuterol HFA MDI at each dose level.
- To determine the safety and tolerability of levalbuterol and racemic albuterol HFA MDI in subjects with EIB.

The six possible levalbuterol and racemic albuterol sequences are shown below.

Levalbuterol			**Racemic Albuterol**		
A	B	C	A	B	C
B	C	A	B	C	A
C	A	B	C	A	B
C	B	A	C	B	A
A	C	B	A	C	B
B	A	C	B	A	C

The order of treatment sequences was randomized according to a William's Square design to balance treatment, period, sequence, and first order carryover effects. The 45 mcg, 90 mcg, and 180 mcg dose levels are equally spaced on the log scale (i.e., each successive dose is 2X the previous dose). Subjects randomized to the racemic albuterol arm received each of three dose levels (90 mcg, 180 mcg, and 360 mcg) in randomized order. These doses matched the (R)-albuterol doses of levalbuterol and were also equally spaced on a log scale (i.e., each successive dose was 2X the previous dose). The matching of (R)-albuterol doses and the equal spacing on the log-dose scale was, also, chosen to optimize the assessment of relative potency, a secondary endpoint.

At baseline, spirometry was performed at approximately 20 minutes postdose. Subjects were then challenged 30 minutes after administration of single-blind placebo. Following a two-minute warm up, subjects completed the exercise challenge on a treadmill at a sufficient intensity to achieve at least 80% of the maximum predicted heart rate. Spirometry was performed at 1, 5, 10, 15, 30, 45, and 60 minutes post-challenge. After 60 minutes, spirometry continued at 15-minute intervals until subjects returned to within 5% of predose values (for a maximum of six hours post-challenge). If FEV_1 values did not return to 5% of predose in six hours, the visit was concluded at the

Investigator's discretion. If rescue medication was administered during the first 60 minutes post-challenge, the visit was concluded and the challenge was re-scheduled within three to seven days at the Investigator's discretion. A final FEV_1 was measured prior to discharge. Subjects were to have a reduction in FEV_1 from pre- to post-challenge of at least 20%, but no more than 50%. Only subjects with FEV_1 reductions in the range were eligible. Subjects who did not meet this criterion were discontinued and could not be enrolled. At the Investigator's discretion, subjects who failed to qualify could be rescheduled for another assessment; if subjects did not meet the criterion after a second attempt they were discontinued.

Subjects received a second exercise challenge similar to the first. They had to satisfy the same criteria to be randomized into the study.

The primary efficacy variable was FEV_1, which was obtained at the following timepoints:

- Screening (Visit 1).
- Predose, 20 minutes after dosing with placebo MDI, and at approximately 1, 5, 10, 15, 30, 45, and 60 minutes post-challenge (Visit 2).
- Predose, 20 minutes after dosing with double-blind study medication, and at approximately 1, 5, 10, 15, 30, 45, and 60 minutes post-challenge at Visits 3, 4, and 5. (FEV_1 was also recorded after 60 minutes if subjects did not return to within 5% of predose FEV_1 values. These values were not used in the calculation of FEV_1 endpoints with the exception of the time-to-recovery analyses.)
- Final Evaluation (Visit 6/Early Termination)

FEV_1 was performed in triplicate at each of these timepoints; the highest of the three measurements was recorded in the CRF.

The primary efficacy parameter was the area under the percent decrease from visit postdose/pre-challenge FEV_1 curve (percent decrease from visit postdose/pre-challenge FEV_1 AUC [FEV_1 AUC(0-60 min)]). This parameter was calculated from the FEV_1 measurements obtained at each of the three treatment visits. [If the post challenge FEV_1 response was greater than the postdose/pre-challenge value, the percent decrease was set to zero in the AUC calculations.]

The sponsor stated that the detectable difference was based upon a two-tailed, α=0.05 level test, with 80% power, and 24 subjects per treatment arm (48 total subjects) completing the 1X and 4X doses. Assuming a within subject standard deviation of 700 L*minutes for percent decrease from visit postdose/pre-challenge FEV_1 AUC as reported in the literature, [Guidelines for Methacoline and Exercise Challenge Testing-1999. Am. J Respir Crit Care Med 161:309-329 (2000)], a difference between the 1X and 4X doses of 418 L*minutes could be detected for the primary efficacy parameter within each treatment. Assuming an attrition rate of approximately 15%, 30 randomized subjects per treatment arm (60 total subjects) were required to complete 24 subjects per treatment. [The sponsor did not say why these calculations are relevant to the primary analysis. The unit of measure of the primary analysis are %*hours not L*minutes.]

Efficacy parameters were analyzed to determine whether a dose response existed within a treatment arm. A mixed model was fitted that included data for the 1X and 4X doses within a treatment arm. Relative potency of levalbuterol to racemic albuterol was assessed using the parallel line assay.

2.1.2 Study 051-312

This study was similar to Study 051-308 with the following exceptions:

1. Subjects were between the ages of 6 to 11 years (inclusive).

2. The planned sample size of a minimum of 9 up to a maximum of 18 subjects per treatment arm (18 to 36 total subjects) was determined outside of statistical consideration.

3. Rather than using the modified blinding procedure of Study 051-308, blinding was accomplished by using a — masking device.

4. Only a descriptive comparison between dosing levels (1X, 2X, and 4X) within treatment and between treatments at corresponding dose levels (ie, 1X levalbuterol vs. 1X racemic albuterol, etc.) was planned, no statistical inferences were performed.

2.1.3 Study 051-353

This was a multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel group study of up to nine weeks in duration in asthmatic adults and adolescents. The study consisted of a screening visit (Visit 1) followed by a one-week single- blind placebo period. At Visit 2, eligible subjects were randomized to one of three treatment groups: 90 mcg levalbuterol, 180 mcg racemic albuterol, or placebo. Randomization occurred in a 2:1:1 ratio of levalbuterol to racemic albuterol to placebo. Randomization occurred separately within each site using permuted blocks of size 8. All study medication was administered as 2 actuations QID for 8 weeks.

The levalbuterol MDI in this study was manufactured by —

At each visit, subjects were supplied with three MDIs. Two of these MDIs were dispensed as study medication (one active and one dummy; one with a blue boot/actuator and one with a yellow boot/actuator). The third MDI was marked for use as rescue medication only. The plastic boot/actuator device for the levalbuterol HFA MDI was blue, and the Proventil (racemic albuterol) HFA MDI boot/actuator was yellow. Likewise, the matching levalbuterol HFA MDI placebo had a blue boot/actuator and the matching Proventil HFA MDI placebo had a yellow boot/actuator, so that these placebos were indistinguishable from their respective actives. Based on randomized treatment, the subject or subject's parent/legal guardian was given a supply of double-blind levalbuterol HFA MDI (45 mcg per actuation) or double-blind racemic albuterol CFC MDI (90 mcg per actuation) for use as needed as rescue medication for relief of asthma signs and symptoms. All rescue medication used, including the number of actuations and the date

and time of day used, was recorded on the study diary card. The subject administered two puffs (1 dose) from each MDI and always administered either the blue or yellow MDI first. The order of administration (blue or yellow first) was randomly assigned and this sequence was not related to the treatment assignment in other than a random way. The rescue medication (levalbuterol or racemic albuterol) was blinded by enclosing the entire device in a — masking device.

The patient population was male or female subjects ≥12 years of age with at least a 6-month history of non-life-threatening asthma, a baseline FEV_1 of ≥45% to ≤75% of predicted, and with a ≥12% reversibility of airflow obstruction within 15-30 minutes following inhalation of 180 mcg racemic albuterol.

If the subject experienced asthma symptoms at any time during serial spirometry, the Serial Spirometry Rescue Plan (as described in Appendix II of the Study Protocol) was required to be followed. [A spirometry maneuver was performed to determine the subject's FEV_1 and to further assess the need for rescue medication. If the subject showed >15% decrease from the baseline FEV_1 measurement, rescue medication was used and serial spirometry discontinued. If the subject did not show >15% decrease from the baseline FEV_1 measurement or if rescue medication was not appropriate, serial spirometry was continued.]

The following medications were allowed : short courses of oral corticosteroids, theophylline, low doses of inhaled corticosteroids, topical corticosteroids, nedocromil sodium or cromolyn sodium, leukotriene inhibitors, antihistamines, mucolytics, expectorants and decongestants, and immunotherapy.

At weeks 0 and 6, spirometry was performed immediately postdose, at approximate 15-minute intervals for the first 2 hours, then hourly until 8 hours postdose. At week 4, spirometry was performed immediately postdose, at approximate 15-minute intervals for the first 2 hours, then hourly until 4 hours postdose. At weeks 3 and 5 spirometry was performed predose, immediately postdose and at approximately 15 and 60 minutes.

The primary efficacy variable was forced expiratory volume in one second (FEV_1), and the primary endpoint was the peak percent change in FEV_1 from visit predose averaged over the 8-week double-blind period, calculated as the average of the peak percent change in FEV_1 values for Visits 2, 4, and 6 (i.e., Week 0[first dose], Week 4, and Week 8, respectively).

The primary analysis was performed using an analysis of covariance (ANCOVA) model with effects for treatment, investigator, and study baseline FEV_1 (predose FEV_1 at Visit 2). The primary statistical comparison was between 90 mcg levalbuterol and placebo using a 1-degree of freedom contrast. Secondary pairwise comparisons between levalbuterol and racemic albuterol and between racemic albuterol and placebo were performed using a 1-degree of freedom contrast, including only the treatment groups being compared.

A second important variable was area under the FEV_1 percent change from visit predose curve averaged over the double-blind period. To calculate area under the FEV_1 percent change from the visit predose, the area under the curve for FEV_1 versus time was first calculated from the FEV_1 measurements obtained during the serial spirometry days of Visits 2 and 6 using the linear trapezoid method with the following formula:

$$FEV_1\,AUC = \sum_{i=1}^{n} (c_i + c_{i-1})(t_i - t_{i-1})/2$$

where c_i was the FEV_1 measurement of the ith spirometry test, t_i was the actual time of collection corresponding to the ith FEV_1 measurement, and n was the number of non-missing postdose FEV_1 values collected. All AUC calculations began at the time of dosing (t_0) and continued until the 480th minute postdose. The subject's predose FEV_1 measurement was used as the FEV_1 measurement at the time of dosing (c_0).

The area under the FEV_1 percent change from visit predose curve was then calculated as:

$$\{AUC/c_i - (t_n - t_0)\}*100$$

for Visits 2 and 6, where c_i was the visit predose FEV_1 from Visit i. The area under the FEV_1 percent change from study baseline for Visit 2 and Visit 6 was calculated using the above formula with c_i equal to the study baseline FEV_1 (Visit 2 predose FEV_1) for both the Visit 2 and Visit 6 calculations. The area under the FEV_1 percent change from visit predose (and study baseline) curve averaged over the double-blind period was the average over the two visits (Visits 2 and 6).

The following practices were employed in the calculation of FEV_1 AUC:

- If a subject rescued during spirometry, then the last FEV_1 measurement prior to rescue medication use was carried forward to 480 minutes postdose.
- If a subject terminated the serial spirometry prior to 480 minutes postdose, then the last FEV_1 measurement was carried forward to 480 minutes postdose.
- If a subject's actual time of a given postdose spirometry test was missing and the corresponding FEV_1 value for that spirometry test was not missing, then the actual time of spirometry was set to the corresponding scheduled time interval added to the time of dosing. If the time point in question was the immediately postdose time point, then the actual time was set to 1 minute after the time of dosing.
- If a subject had FEV_1 measurements beyond the 480th minute, then the FEV_1 value for the 480th minute was interpolated between the next measurement beyond 480 minutes and the last measurement prior to 480 minutes. Subsequent FEV_1 values beyond 480 minutes were set to missing.
- If a subject's time of dosing was missing, it was assigned a time 1 minute prior to the immediately postdose time.
- If a subject's predose FEV_1 measurement was missing, no AUC was calculated for that subject at that visit.

The sample size calculation was based on a two-tailed, α=0.05 level test, with 90% power. A between subject standard deviation of approximately 21% in the maximum percent change from baseline was previously seen in the studies under Sepracor Protocols 051-301 and 051-304. Assuming that a treatment difference between levalbuterol and placebo of 10% is a clinically meaningful improvement and using an estimate of the between subject standard deviation of 21% for maximum percent change of FEV_1 from visit predose to end-of treatment, 100 evaluable subjects per treatment arm (300 total) were needed to achieve a power of at least 90%. To provide additional safety and product-use information for levalbuterol 90 mcg, an additional 100 subjects were randomized to the levalbuterol 90 mcg arm. A total of 200 subjects were to be randomized to levalbuterol 90 mcg, 100 to racemic albuterol 180 mcg, and 100 to placebo in a 2:1:1 randomization. Based on the standard deviation above, 90% power and the increased number of levalbuterol subjects, a difference of 8.4% between levalbuterol and placebo could be detected. Assuming a 20% attrition rate between randomization and study completion, at least 250 subjects for the levalbuterol 90 mcg arm and 125 subjects for each of the racemic albuterol and placebo arms needed to be randomized to complete the required number of subjects per treatment.

2.1.4 Study 051-355

This study was similar to Study 051-353 with the following exceptions:

1. In addition to the levalbuterol-B 90 mcg manufactured by — there was an additional treatment levalbuterol-A 90 mcg manufactured by 3M corporation.
2. Randomization occurred in a 2:1:1:1 ratio of levalbuterol –A (manufactured by 3M) to levalbuterol –B (manufactured by — , to racemic albuterol to placebo.
3. Randomization occurred separately within each site using permuted blocks of size 10.
4. Rescue medication for all subjects was Pirbuterol MDI.
5. Treatments were blinded using a — . device.
6. The planned sample size was 125 to levalbuterol-A arm and 63 to the other arms.

2.1.5 Study 051-354

This study was similar to Study 051-353 with the following exceptions:

1. The patient population was male or female subjects 4 to 11 years of age with at least a 6-month history of non-life-threatening asthma, a baseline FEV_1 of $\geq$45% to $\leq$ 80% of predicted.
2. The treatment period was only 4 weeks rather than 8 weeks.
3. Racemic albuterol (2.5 mg UDV inhalation solution) was used as rescue medication for all subjects during the run-in period, and for subjects who received double-blind placebo or racemic albuterol treatment. Levalbuterol (1.25 mg UDV inhalation solution) was used as rescue medication for subjects who received double-blind levalbuterol treatment.
4. Some subjects used spacers.
5. The planned sample size was 80 to the levalbuterol arm and 40 to the other arms.

2.2 Data Sources

Data for this submission was contained in \\Cdsesub1\n21730\n_000\2004-05-11.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study 051-308

There were 62 subjects (27 levalbuterol and 35 racemic albuterol) randomized into the trial. Twenty-six and 32 subjects in the respective treatment arms completed the study. The three racemic albuterol subjects who discontinued received only one dose whereas the levalbuterol subject who failed to complete received two different doses.

Five subjects, all from the same Investigator (27), were incorrectly randomized; one of these subjects was incorrectly randomized twice (subject 00270040 and 00270042). In each case, the subjects were assigned to racemic albuterol without regard to the randomization schedule. By chance, two subjects received the incorrect treatment (the subject who was mis-randomized twice received the incorrect treatment on two different occasions) and two of the five subjects received the correct treatment. The latter two subjects were considered randomization errors because the treatment arm was not selected randomly. The primary efficacy analysis excluded these five subjects, but they were included in the analysis of safety based upon the treatment they received.

Sepracor's Quality Assurance department detected significant non-compliant findings during an audit of Investigator 621. Based upon these findings, it was concluded that the efficacy data from this Investigator were not reliable and the site was excluded from the primary analysis population. Thus, all efficacy analyses were performed using the Correctly Randomized Population excluding Investigator 621.

The primary population of interest was the Correctly Randomized Population excluding Investigator 621, which consisted of all randomized subjects who received at least one dose of double-blind study medication to which they were correctly randomized; subjects who were incorrectly randomized, and subjects from site 621, were excluded.

The As-Treated population included all subjects randomized (correctly or incorrectly) and was summarized according to the actual treatment received. The primary efficacy endpoint, several secondary efficacy endpoints, and all safety analyses were analyzed using the As-Treated population. Selected efficacy analyses were performed utilizing the As-Treated population excluding Investigator 621. {This reviewer thinks it is acceptable to use an As-Treated population rather than an As-Randomized population in this small supportive Study.}

The treatment groups for the As-Treated population were comparable in demographic variables and baseline pulmonary function.

Table 11.1.1, of the sponsor, provides the number of subjects in the various populations.

Table 11.1-1: Number of Subjects in each Analysis Dataset by Treatment Group Study 051-308

Population	Levalbuterol	Racemic Albuterol	Single-Blind Only	Total
All Subjects Enrolled	27	35*	33	95
As-Treated				
Including Site 621	27	34*	0	61
Excluding Site 621	23	31	0	54
Correctly Randomized				
Including Site 621	27	30	0	57
Excluding Site 621	23	27	0	50

* One subject was mis-randomized to the racemic albuterol group twice. The subject was counted twice in the All Subjects Enrolled population and once in the As-Treated population.

NOTE: Seven subjects (four in the levalbuterol group and three in the racemic albuterol group) were excluded from Site 621.

NOTE: Five subjects were mis-randomized (one of these subjects was mis-randomized twice).

The percent decrease from visit postdose/pre-challenge FEV_1 AUC by treatment group and dose level is summarized in the sponsor's Table 11.4.1.1-1 for the Correctly Randomized Population excluding Investigator 621 (CR Population Excluding 621).

Table 11.4.1.1-1: Percent Decrease from Visit Postdose/Pre-challenge FEV_1 AUC (%*hrs) by Treatment and Dose Level (CR Excluding 621 Population) Study 051-308

	Levalbuterol			Racemic Albuterol		
Population	**45 mcg (1X)**	**90 mcg (2X)**	**180 mcg (4X)**	**90 mcg (1X)**	**180 mcg (2X)**	**360 mcg (4X)**
CR Excluding 621	23	23	22	25	27	25
Mean (SD)	267.089 (296.1)	169.146 (269.9)	174.320 (280.4)	191.777 (248.9)	153.134 (261.6)	109.440 (200.8)
LSMean (±) SE	264.580 ± 66.345		171.253 ± 66.814	184.217 ± 48.003		109.277 ± 47.821
Median	152.684	36.526	29.886	73.344	47.709	13.201
Min, Max	0.00, 1121.22	0.00, 915.81	0.00, 985.74	0.00, 948.53	0.00, 1136.65	0.00, 870.20
	LEV 45 mcg versus LEV 180 mcg		p=0.164	RAC 90 mcg versus RAC 360 mcg p=0.070		
	Relative Potency and 90% C.I.		0.491 (0.028, 2.836)			

NOTE: Percent decrease from visit postdose/pre-challenge FEV_1 AUC was calculated by first using the FEV_1 percent decrease from visit postdose/pre-challenge obtained during serial spirometry at Visits 3, 4, and 5 and applying the linear trapezoid method. If the post-challenge FEV_1 was greater than the postdose/pre-challenge FEV_1 the percent decrease was set to zero.

NOTE: Dose response relationship within each treatment group was assessed using a mixed effects model with sequence, dose (1X or 4X), period, and visit postdose/pre-challenge FEV_1 as fixed effects and subject as a random effect.

NOTE: Relative potency of levalbuterol and racemic albuterol was assessed using the parallel line assay method. A random coefficient model was fit with sequence, period, treatment group, and log (dose) as fixed effects and a random slope. The 90% confidence interval for the relative potency was constructed using Fieller s theorem.

The primary efficacy analysis, which compared the percent decrease from visit predose/pre-challenge FEV_1 AUC for the 1X and 4X levalbuterol doses, showed that 180 mcg levalbuterol provided greater bronchoprotection than 45 mcg levalbuterol. The LSMean percent decreases from visit postdose/pre-challenge FEV_1 AUC for the 1X and 4X doses were 264.580 %*hrs and 171.253 %*hrs, respectively. This is indicative of a dose response, although the difference between the 1X and 4X levalbuterol doses was not statistically significant for this endpoint. In addition, the 2X dose (mean= 169.146%*hrs)

provided more bronchoprotection than the 1X dose (267.089 %*hrs). A dose response for racemic albuterol was observed for the percent decrease from visit postdose/pre-challenge FEV_1 AUC; the difference between 90 mcg (LSMean percent decrease= 184.217 %*hrs) and 360 mcg (109.277 %*hrs) racemic albuterol was marginally significant (p=0.070).

As an exploratory analysis of the Correctly Randomized Population excluding Investigator 621, the potency of levalbuterol relative to racemic albuterol was assessed for the primary efficacy endpoint. The 90% confidence interval around the estimate of relative potency (0.491), based upon (R)-albuterol dose, was (0.028, 2.836). Because this range did not fall entirely within the two-fold limits of 0.5-2.0, [Division of Bioequivalence, Office of Generic Drugs, Food and Drug Administration Interim guidance for documentation of in-vivo bioequivalence of albuterol aerosols (metered dose inhalers). January 27, 1994. pp. 1-27.] the levalbuterol and racemic albuterol MDIs, when used with spacers, were not considered clinically comparable. Using the point estimate, a 100% higher dose of levalbuterol compared with racemic albuterol (standardized to (R)-albuterol dose) would be required to achieve equivalent efficacy. Similar results were observed in the As-Treated population; the point estimate of relative potency was 0.546 with a 90% confidence interval of (0.081, 2.210).

The maximum percent decrease from visit postdose/pre-challenge FEV_1 by treatment group and dose level is summarized in the sponsor's Table 11.4.1.2-1 for the Correctly Randomized Population excluding Investigator 621 (CR Population Excluding 621).

Table 11.4.1.2-1: Maximum Percent Decrease from Visit Postdose/Pre-challenge FEV_1 by Treatment and Dose Level (CR Excluding 621 Population) Study 051-308

		Levalbuterol			Racemic Albuterol	
Population	**45 mcg (1X)**	**90 mcg (2X)**	**180 mcg (4X)**	**90 mcg (1X)**	**180 mcg (2X)**	**360 mcg (4X)**
CR Excluding 621	23	23	22	25	27	25
Mean (SD)	9.75 (8.74)	5.95 (6.73)	5.57 (6.69)	7.64 (8.64)	5.73 (7.02)	3.90 (5.11)
LSMean (±)	9.45 ± 1.83		5.45 ± 1.85	7.54 ± 1.49		3.92 ± 1.48
Median	4.78	3.62	4.31	5.89	3.04	2.31
Min, Max	0.00, 27.1	0.00, 23.8	0.00, 25.3	0.00, 33.4	0.00, 27.2	0.00, 20.8
	LEV 45 mcg versus LEV 180 mcg		p=0. 055	RAC 90 mcg versus RAC 360 mcg p=0.026		
	Relative Potency and 90% C.I. 0.684 (0.211, 1.801)					

NOTE: Percent decrease from visit postdose/pre-challenge FEV_1 AUC was calculated by first using the FEV_1 percent decrease from visit postdose/pre-challenge obtained during serial spirometry at Visits 3, 4, and 5 and applying the linear trapezoid method. If The post-challenge FEV_1 was greater than the postdose/pre-challenge FEV_1 the percent decrease was set to zero.

NOTE: Dose response relationship within each treatment group was assessed using a mixed effects model with sequence, dose (1X or 4X), period, and visit postdose/pre-challenge FEV_1 as fixed effects and subject as a random effect.

NOTE: Relative potency of levalbuterol and racemic albuterol was assessed using the parallel line assay method. A random coefficient model was fit with sequence, period, treatment group, and log (dose) as fixed effects and a random slope. The 90% confidence interval for the relative potency was constructed using Fieller s theorem.

The key secondary efficacy endpoint, the maximum percent decrease from visit predose/pre-challenge FEV_1, demonstrated that the 4X dose of levalbuterol (LSMean maximum percent decrease= 5.45%) provided greater bronchoprotection than the 1X dose (9.45%); the difference between dose levels was nearly significant (p=0.055). In addition, the 2X dose of levalbuterol (mean= 5.95%) provided more bronchoprotection than the 1X dose (9.75%). A dose response for racemic albuterol was also observed; the

difference between the 1X (7.54%) and 4X doses of (3.92%) racemic albuterol was significant (p=0.026).

Median plasma concentration-time profiles and pharmacokinetic parameters showed that subjects treated with levalbuterol exhibited lower concentrations of (R)-albuterol across dose levels compared with subjects treated with equivalent amounts of (R)-albuterol from racemic albuterol. For (R)-albuterol, the median values of Cmax ranged from 1.83- to 2.62-fold higher, and AUC(0-last) ranged from 1.68- to 2.34-fold higher, across dose levels for subjects in the racemic albuterol group compared with levalbuterol.

3.1.2 Study 051-312

There were 33 (19 levalbuterol and 14 racemic albuterol) patients randomized into the study. [Two of these patients were given an invalid treatment sequence 2X, 2X, 2X and were re-randomized]. One additional patient received an invalid sequence 2X, 2X, 2X. The 2X, 2X, 2X data will not be used in this review. Of these 33 subjects, 28 (16 levalbuterol and 12 reacemic albuterol received all 3 doses of their assigned treatment. The primary population of interest was the Evaluable (EVAL) population, consisting of all randomized subjects who received at least one dose of double-blind study medication to which they were correctly randomized, subjects who were incorrectly randomized yet received a valid treatment sequence, and subjects who were re-randomized to treatment. All efficacy analyses were presented using the EVAL population.

There were some minor differences in demographics and screening pulmonary function. [All 4 blacks were in the racemic albuterol group.] The treatment groups were comparable, however, in their minimum % change from postdose/pre-challenge FEV_1 following the two exercise challenges at baseline.

The table 11.4.1.1-1 of the sponsor provides some descriptive statistics for the maximum percent decrease in FEV_1 from visit post-dose/pre-challenge for the Evaluable population. In this analysis, percent decrease was set to zero if the post-challenge value was greater than the postdose/pre-challenge value. The smaller the value, the better the protection.

Table 11.4.1.1-1: Maximum Percent Decrease in FEV_1 from Visit Postdose/Pre-Challenge (EVAL) Study 051-312

	Levalbuterol			Racemic Albuterol		
	45 mcg (1X) (n=16)	90 mcg (2X) (n=17)	180 mcg (4X) (n=17)	90 mcg (1X) (n=13)	180 mcg (2X) (n=13)	360 mcg (4X) (n=12)
Mean (SD)	3.81 (5.43)	7.57 (9.26)	5.24 (7.56)	4.53 (6.35)	2.69 (2.58)	3.72 (4.62)
95% CI[1]	0.92, 6.70	2.81, 12.33	1.35, 9.13	0.69, 8.37	1.13, 4.25	0.78, 6.65
Median	1.87	5.82	2.24	0.00	1.70	1.00
Min, Max	0.0, 20.6	0.0, 37.9	0.0, 23.6	0.0, 18.8	0.0, 7.9	0.0, 11.2

NOTE: The maximum percent decrease from visit postdose/pre-challenge was defined as the largest percent decrease observed during the spirometry throughout the 60-minute post-challenge interval. If the post-challenge FEV_1 was greater than the postdose/pre-challenge FEV_1 for all post-challenge time points, the maximum percent decrease was set to zero.

[1] 95%CI of the mean. Because the minimum value for any decrease was zero, when the lower bound of the confidence interval was less than zero, it was set to zero.

There was no dose response, a single actuation afforded nearly complete protection.

The table 11.4.1.2.1-1 of the sponsor provides some descriptive statistics for the AUC under the percent decrease in FEV_1 from visit post-dose/pre-challenge for the Evaluable population. In this analysis, percent decrease was set to zero if the post-challenge value was greater than the postdose/pre-challenge value. The smaller the value, the better the protection.

Table 11.4.1.2.1-1: Area Under the Percent Decrease from Visit Postdose/Pre-Challenge FEV_1 Curve (0-60 minutes) (EVAL) Study 051-312

	Levalbuterol			Racemic Ibuterol		
	45 mcg (1X) (n=16)	90 mcg (2X) (n=17)	180 mcg (4X) (n=17)	90 mcg (1X) (n=13)	180 mcg (2X) (n=13)	360 mcg (4X) (n=12)
Area Under the % Decrease from Visit PD/PC FEV_1 Curve (0-60 mins)						
Mean (SD)	84.78 (143.77)	187.08 (304.03)	119.48 (212.12)	66.98 (115.69)	51.62 (60.36)	74.09 (117.95)
95% CI[1]	8.17, 161.39	30.76, 343.40	10.42, 228.55	0.00, 136.89	15.14, 88.09	0, 149.03
Median	21.17	124.70	42.76	0.00	31.53	13.93
Min, Max	0.00, 423.35	0.00, 1285.21	0.00, 847.15	0.00, 360.53	0.00, 182.52	0.00, 388.45

NOTE: PD = postdose; PC = pre-challenge

NOTE: Area under the FEV_1 percent decrease from visit postdose/pre-challenge curve was calculated by first using the FEV_1 percent decrease from visit postdose/pre-challenge obtained during the serial spirometry days of Visits 3, 4, and 5 and applying the linear trapezoid method. If the post-challenge FEV_1 was greater than the postdose/pre-challenge FEV_1 the percent decrease was set to 0.

[1] 95% CI of the mean. Because the minimum value for any decrease was 0, when the lower bound of the confidence interval was <0, it was set to 0.

The bronchoprotection provided by racemic albuterol was slightly better than that provided by levalbuterol at each dose level. A dose response was not demonstrated for either treatment.

3.1.3 Study 051-353

There were 445 subjects (219 Levalbuterol 90 mcg, 119 racemic albuterol 180 mcg, and 107 placebo) randomized into this study. Of these 445 subjects, 56 (31 levalbuterol (14.2%), 13 racemic albuterol (10.9%), and 12 placebo (11.2%)) discontinued before completion. The two main reasons for withdrawals were AEs and voluntary withdrawals.

The treatment groups were comparable at baseline in demographic variables and baseline PFTs.

Table 11.4.1.1-1 of the sponsor presents the results of the analysis of peak percent change in FEV_1 from Visit predose averaged over the Double-Blind period and at Visits 2, 4 and 6 for the ITT population. Both the levalbuterol groups and the racemic albuterol groups were significantly different from placebo at Weeks 0, 4 and 8 and averaged over the 8 weeks. Racemic albuterol was significantly more effective than levalbuterol averaged over Visits 2, 4 and 6. The results at Visits 2 and 6 were nearly significant. The sponsor claims that this 3% advantage of racemic albuterol over levalbuterol was not clinically important.

Table 11.4.1.1-1: Peak Percent Change in FEV_1 from Visit Predose Averaged Over the Double-Blind Period and at Visits 2, 4, and 6 (ITT Population) Study 051-353

	Treatment Group		
	Levalbuterol 90 mcg	**Racemic Albuterol 180 mcg**	**Placebo**
Peak Percent Change in FEV_1 Averaged Over the Double-Blind Period[1]	**(n=219)**	**(n=119)**	**(n=107)**
LS Mean (SE)	25.63 (0.87)	28.98 (1.15)	13.94 (1.21)
Pairwise p-value vs. Placebo[2]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[2]	0.018		
Visit 2[3]			
LS Mean (SE)	30.94 (1.19)	34.75 (1.59)	19.67 (1.67)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[4]	0.052		
Visit 4[3]			
LS Mean (SE)	22.59 (1.05)	25.11 (1.38)	10.69 (1.46)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[4]	0.144		
Visit 6[3]			
LS Mean (SE)	22.25 (1.19)	25.66 (1.54)	10.70 (1.61)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[4]	0.077		

[1] Peak percent change in FEV_1 from visit predose averaged over the double-blind period was calculated by first taking the difference in peak FEV_1 recorded during the serial spirometry day (Visits 2, 4, and 6) and the visit predose FEV_1. This result was then divided by visit predose FEV_1 and multiplied by 100. The three peak percent change values were then averaged.
[2] Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV_1 as the covariate. The tests were performed using a one degree of freedom contrast.
[3] Peak percent change in FEV_1 from visit predose refers to the maximum FEV_1 recorded during the visit minus the FEV_1 observed at visit predose, divided by the visit predose FEV_1 and multiplied by 100.
[4] Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and visit predose FEV_1 as the covariate. The tests were performed using a one degree of freedom contrast.

The medical officer wanted to know whether the decreases at Visits 4 and 6 in the above table were due to tachyphylaxis. The answer is no. It is mainly due to an increase in pre-visit baseline, as demonstrated below. The table below, as an example, provides the results from the analysis of FEV_1 - Peak Percent Change from study baseline (Visit 2 pre-dose) at Visit 4. These LS means are more similar to those of Visit 2.

	Treatment Group		
	Levalbuterol 90 mcg	Racemic Albuterol 180 mcg	Placebo
Peak Percent Change in FEV1	(n=201)	(n=111)	(n=100)
Visit 4			
LS Mean (SE)	26.97 (1.38)	32.06 (1.82)	19.03 (1.92)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[4]	0.025		

The Visit 4 pre-dose mean FEV_1 of the 3 treatment groups were 2.30, 2.36, and 2.35 liters for Levalbuterol, Racemic albuterol and placebo, respectively. The study baseline

mean FEV_1 for these three groups were 2.20, 2.23, and 2.18 liters, respectively. The probable explanation for the increase in pre-dose baseline is regression to the mean. Patients regressed to their normal baseline from the baseline that entered them into the study.

Table 11.4.1.2-1 of the sponsor presents the results of the analysis of area under the FEV_1 percent change curve averaged over the visits 2 and 6.

Table 11.4.1.2-1: Area Under the FEV_1 Percent Change Curve Averaged Over the Double-Blind Period (ITT Population) Study 051-353

	Treatment Group		
Area Under the FEV_1 Percent Change Curve Averaged Over the Double-Blind Period Above Visit Predose (%-hr)[1]	**Levalbuterol 90 mcg (n=219)**	**Racemic Albuterol 180 mcg (n=119)**	**Placebo (n=107)**
LS Mean (SE)	109.57 (6.20)	130.17 (8.25)	59.86 (8.68)
Median	104.24	113.51	56.93
Min, Max	-217.66, 494.85	-87.71, 426.36	-206.56, 324.42
Pairwise p-value vs. Placebo[2]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[2]	0.043		
Above Study Baseline			
LS Mean (SE)	128.77 (8.50)	146.66 (11.31)	80.29 (11.91)
Median	98.30	119.61	57.78
Min, Max	-217.66, 821.58	-71.74, 603.95	-206.56, 566.54
Pairwise p-value vs. Placebo[2]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[2]	0.198		

[1] Area under the FEV_1 percent change curve averaged over the double-blind period was calculated by first applying the linear trapezoidal method to the FEV_1 percent change from baseline (visit predose or study baseline) obtained during Visits 2 and 6. These two AUC values were then averaged.
[2] Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV_1 as the covariate. The tests were performed using a one degree of freedom contrast.

Both the levalbuterol groups and the racemic albuterol groups were significantly different from placebo averaged over the 8 weeks. Racemic albuterol was significantly more effective than levalbuterol for AUC above visit predose averaged over visits 2 and 6.

The physician completed a global assessment at Visit 6 to evaluate the subject's asthma symptoms and their ability to manage the subject's asthma. After 8 weeks of treatment, asthma symptoms in 56.1%, 56.3%, and 36.5% of subjects in the 90 mcg levalbuterol, 180 mcg racemic albuterol, and placebo treatment groups, respectively, were slightly, moderately, or much better. Investigators also noted asthma management that was slightly, moderately, or much better in 52.4%, 52.2%, and 35.6% of subjects in the 90mcg levalbuterol, 180 mcg racemic albuterol, and placebo treatment groups, respectively. This somewhat supports the sponsor's conclusion that the differences seen between levalbuterol and racemic albuterol may not be clinically important.

3.1.4 Study 051-355

There were 303 subjects (122 Levalbuterol 90 mcg- Manufacture A, 62 Levalbuterol 90 mcg- Manufacture B, 60 racemic albuterol 180 mcg, and 59 placebo) randomized into this study. Of these 303 subjects, 39 (14 levalbuterol 90 mcg- Manufacture A (11.5%), 8

levalbuterol 90 mcg- Manufacture B (12.9%), 9 racemic albuterol (15.0%), and 8 placebo (13.6%)) discontinued before completion. Site A is 3M and Site B is [redacted]. The two main reasons for withdrawals were AEs and voluntary withdrawals.

The treatment groups were comparable at baseline in demographic variables and baseline PFTs.

Table 11.4.1.1-1 of the sponsor presents the results of the analysis of peak percent change in FEV_1 from Visit predose averaged over the Double-Blind period for the ITT population. Both the levalbuterol groups and the racemic albuterol groups were significantly different from placebo averaged over the 8 weeks. The 3M product was more similar to racemic albuterol than the [redacted] product was.

Table 11.4.1.1-1 Peak Percent Change in FEV_1 from Visit Pre-Dose Averaged Over the Double-Blind Period Study 051-355

Peak % Change in FEV_1 From Pre- Dose Over the DB Period[1]	Lev 90 mcg Mfg. A (n=122)	Lev 90 mcg Mfg. B (n=62)	Rac Albuterol 180 mcg (n=60)	Placebo (n=59)	P-value[2]
Mean (SD)	25.28 (11.54)	23.09 (12.72)	26.57 (13.62)	12.24 (7.94)	
LS Mean (SE)	25.33 (1.05)	23.01 (1.46)	26.14 (1.49)	12.45 (1.49)	
Median	23.12	20.51	22.65	12.17	
Min, Max	7.6, 78.9	1.5, 62.5	5.9, 77.5	-6.6, 32.8	
		Lev 90 mcg Mfg. A vs. Placebo			<0.001
		Lev 90 mcg Mfg. B vs. Placebo			<0.001
		Lev 90 mcg Mfg. A vs. Rac Albuterol			0.654
		Lev 90 mcg Mfg. B vs. Rac Albuterol			0.132
		Lev 90 mcg Mfg. A vs. Lev 90 mcg Mfg. B			0.194
		Racemic Albuterol vs. Placebo			<0.001

Note: DB = double-blind; Lev Mfg. A = Levalbuterol Manufacturing Site A; Lev Mfg. B = Levalbuterol Manufacturing Site B; Rac 180 mcg = Racemic albuterol 180 mcg.
[1] Calculated by first taking the difference in peak FEV_1 recorded during the serial spirometry day (Visits 2, 4, and 6) and the visit pre-dose FEV_1. This result was then divided by visit pre-dose FEV_1 and multiplied by 100. The three peak percent change values were then averaged.
[2] Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV_1 (Visit 2 pre-dose) as the covariate. The tests were performed using a one degree of freedom contrast.

Table 11.4.1.2-1 of the sponsor presents the results of the analysis of area under the FEV_1 percent change curve averaged over the visits 2 and 6. Both the levalbuterol groups and the racemic albuterol groups were significantly different from placebo averaged over the 8 weeks. The 3M product was significantly different from the [redacted] product. The 3M product was more similar to racemic albuterol than the [redacted] product was.

Table 11.4.1.2-1 Area Under the FEV_1 Percent Change from Visit Pre-Dose Curve Averaged Over the Double-Blind Period Study 051-355

Area Under the FEV_1 % Change From Visit Pre-Dose Curve Averaged Over the DB Period (%-hr) [1]	Lev 90 mcg Mfg. A (n=122)	Lev 90 mcg Mfg. B (n=62)	Rac Albuterol 180 mcg (n=60)	Placebo (n=59)	P-value[2]
Mean (SD)	105.76 (81.71)	80.94 (74.70)	98.38 (85.86)	28.65 (76.49)	
LS Mean (SE)	105.28 (7.29)	80.18 (10.13)	95.08 (10.39)	29.14 (10.39)	
Median	91.86	75.46	92.25	32.45	
Min, Max	-168.08, 445.62	-55.95, 251.30	-187.35, 355.97	-164.74, 255.00	
		Lev 90 mcg Mfg. A vs. Placebo			<0.001
		Lev 90 mcg Mfg. B vs. Placebo			<0.001
		Lev 90 mcg Mfg. A vs. Rac Albuterol			0.416
		Lev 90 mcg Mfg. B vs. Rac Albuterol			0.301
		Lev 90 mcg Mfg. A vs. Lev 90 mcg Mfg. B			0.044
		Racemic Albuterol vs. Placebo			<0.001

Note: DB = double-blind; Lev Mfg. A = Levalbuterol Manufacturing Site A; Lev Mfg. B = Levalbuterol Manufacturing Site B; Rac 180 mcg = Racemic albuterol 180 mcg.
[1] Calculated by first applying the linear trapezoidal method to the FEV_1 percent change from visit pre-dose obtained during Visits 2 and 6. These two AUC values were then averaged.
[2] Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV_1 (Visit 2 pre-dose) as the covariate. The tests were performed using a one degree of freedom contrast.

3.1.5 Study 051-354

There were 150 children (76 Levalbuterol 90 mcg, 39 racemic albuterol 180 mcg, and 35 placebo) randomized into this study. Of these 150 children, 16 (9 levalbuterol (11.8%), 3 racemic albuterol (7.7%), and 4 placebo (11.4%)) discontinued before completion. The two main reasons for withdrawals were AEs and voluntary withdrawals.

The treatment groups were comparable at baseline in demographic variables and baseline PFTs.

The sponsor analyzed the modified ITT population. The modified ITT population consisted of all ITT subjects minus subjects with spirometry performed by an unqualified study coordinator [Subjects 09530165 (levalbuterol) and 09530166 (levalbuterol)] and minus subjects who had at least one clinically implausible FEV_1 value that was greater than 200% of their predicted FEV_1, based on age, height, and race [Subjects 09520177 (racemic albuterol), 10000274 (placebo), and 10000293 (placebo)]. The sponsor included computer printout for the ITT analysis for the primary efficacy analysis in their study report which did not show any significant differences, the placebo group showed even the largest improvement. It is the implausible results of the last 3 patients that lead to the nonsignificant results. With so few patients in this study, such implausible results can greatly affect analysis results. The medical officer thought such exclusion is reasonable.

Table 11.4.1.1-1 of the sponsor presents the results of the analysis of peak percent change in FEV_1 from visit predose averaged over the Double-Blind period and at Visits 2, 4 and 6 for the Modified ITT population. Both the levalbuterol groups and the racemic albuterol groups were significantly different from placebo at Weeks 0, 2 and 4 and averaged over the 4 weeks.

Table 11.4.1.1-1: Peak Percent Change in FEV_1 from Visit Predose Averaged Over the Double-Blind Period and at Visits 2, 4, and 6 (Modified ITT Population) Study 051-354

	Treatment Group		
	Levalbuterol	Racemic Albuterol	
Peak Percent Change in FEV_1 Averaged Over the Double-Blind Period[1]	**90 mcg (n=74)**	**180 mcg (n=38)**	**Placebo (n=33)**
LS Mean (SE)	25.63 (1.34)	21.81 (1.83)	16.75 (1.94)
Median	24.07	20.92	13.70
Pairwise p-value vs. Placebo[2]	<0.001	0.057	
Pairwise p-value vs. Racemic Albuterol[2]	0.086		
Visit 2[3]			
LS Mean (SE)	33.14 (2.51)	29.56 (3.43)	17.77 (3.64)
Median	29.88	26.18	15.42
Pairwise p-value vs. Placebo[4]	<0.001	0.019	
Pairwise p-value vs. Racemic Albuterol[4]	0.390		
Visit 4[3]			
LS Mean (SE)	20.52 (1.92)	18.46 (2.62)	20.05 (2.71)
Median	17.03	16.63	10.66
Pairwise p-value vs. Placebo[4]	0.886	0.671	
Pairwise p-value vs. Racemic Albuterol[4]	0.519		
Visit 6[3]			
LS Mean (SE)	22.41 (1.53)	19.25 (2.02)	11.30 (2.19)
Median	18.18	17.57	8.55
Pairwise p-value vs. Placebo[4]	<0.001	0.009	
Pairwise p-value vs. Racemic Albuterol[4]	0.208		

[1] Peak percent change in FEV_1 from visit predose averaged over the double-blind period was calculated by first taking the difference in peak FEV_1 recorded during the serial spirometry day (Visits 2, 4, and 6) and the visit predose FEV_1. This result was then divided by visit predose FEV_1 and multiplied by 100. The 3 peak percent change values were then averaged.
[2] Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV_1 as the covariate. The tests were performed using a 1-degree-of-freedom contrast.
[3] Peak percent change in FEV_1 from visit predose refers to the maximum FEV_1 recorded during the visit minus the FEV_1 observed at visit predose, divided by the visit predose FEV_1 and multiplied by 100.
[4] Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and visit predose FEV_1 as the covariate. The tests were performed using a 1-degree-of-freedom contrast.

The decrease in peak percent increase at visits 4 and 6 are again mainly caused by an increase in pre-visit baseline over study baseline.

Table 11.4.1.2-1 of the sponsor presents the results of the analysis of area under the FEV_1 percent change curve averaged over the visits 2 and 6. Both treatment groups were significantly different from placebo.

Table 11.4.1.2-1: Area Under the FEV_1 Percent Change from Visit Predose Curve Averaged over the Double-Blind Period (Modified ITT Population) Study 051-354

	Treatment Group		
Area Under the FEV_1 Percent Change From Visit Predose Curve Averaged Over the Double-Blind Period (%-hr)[1]	**Levalbuterol 90 mcg (n=74)**	**Racemic Albuterol 180 mcg (n=38)**	**Placebo (n=33)**
LS Mean (SE)	90.33 (8.51)	84.35 (11.62)	42.73 (12.34)
Median	73.43	73.10	31.37
Pairwise p-value vs. Placebo[2]	0.001	0.010	
Pairwise p-value vs. Racemic Albuterol[2]	0.672		

Area under the FEV_1 percent change curve averaged over the double-blind period was calculated by first applying the linear trapezoidal method to the FEV_1 percent change from visit predose obtained during Visits 2 and 6. These 2 AUC values were then averaged.

[2] Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV_1 as the covariate. The tests were performed using a 1-degree-of-freedom contrast.

3.2. Evaluation of safety

The safety of this product mainly follows from the safety of albuterol and levalbuterol nebulized solution. Since the dose of (R)-albuterol (levalbuterol) 90 mcg is equal to the amount of (R)-albuterol in 180 mcg racemic albuterol and the PK indicates less absorption than from racemic albuterol, there should be no safety concerns. Additionally, there was no safety signals in these studies.

4. Findings in Special/ Subgroup Populations

4.1 Gender/age/race

Since the amount of (R)-albuterol in levalbuterol 90 mcg is equal to the (R)-albuterol in racemic Albuterol 180 mcg and the fact that (R)-albuterol is 100 times as potent as (S)-albuterol, the efficacy in these patient subgroups can be inferred from the known efficacy of racemic albuterol.

The sponsor in the ISE presented mean maximum percent change in FEV_1 from visit predose averaged over the double-blind period for the age subgroups (12-17, 18 to 65, >65 years), race subgroups (Caucasian, Black, Hispanic, other) and gender subgroups for Studies 051-353 and 051-355 individually and combined. There was no indication that levalbuterol was not effective in each of the various age, race or gender subgroups. Racemic albuterol was slightly more effective than levalbuterol in most of these subgroups.

4.2 Other special/subgroup populations

The sponsor in the ISE presented mean maximum percent change in FEV_1 from visit predose averaged over the double-blind period for the steroid use (users and nonusers) and baseline asthma severity (mild/moderate and severe) subgroups for Studies 051-353 and 051-355 individually and combined. There was no indication that levalbuterol was

not effective in each of these subgroups. Racemic albuterol was slightly more effective than levalbuterol in most of these subgroups.

The only other special subgroup of concern is those using spacers. Spacers increased the efficacy of racemic albuterol but not levalbuterol. It must be left to clinical judgment whether this should be reflected in the label.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

There were no statistical issues with the sponsor's analyses.

5.2 Conclusions and Recommendations

In Study 051-353, levalbuterol 90 mcg MDI, manufactured by ~ was significantly better than placebo for peak percent change in FEV_1 averaged over the 8 week double blind period and area under the FEV_1 percent change from visit predose curve averaged over the double-blind period in asthmatic adults and adolescents. In this study, racemic albuterol 180 mcg was significantly better than levalbuterol 90 mcg for these two endpoints.

In Study 051-355, both levalbuterol 90 mcg manufactured by ~ and levalbuterol 90 mcg manufactured by 3M were significantly better than placebo for peak percent change in FEV_1 averaged over the 8 week double blind period and area under the FEV_1 percent change from visit predose curve averaged over the double-blind period in asthmatic adults and adolescents. Levalbuterol 90 mcg manufactured by 3M was significantly better than levalbuterol 90 mcg manufactured by ~ , for area under the FEV_1 percent change from visit predose curve averaged over the double-blind period. The 3M product was more similar to racemic albuterol than the ~ product was.

In Study 051-354, levalbuterol 90 mcg manufactured by 3M was significantly better than placebo for peak percent change in FEV_1 averaged over the 4 week double blind period and area under the FEV_1 percent change from visit predose curve averaged over the double-blind period in asthmatic subjects 4-11 years of age.

In Studies 051-354 and 051-355, levalbuterol 90 mcg and racemic albuterol were not significantly different for these two endpoints.

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