CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-730

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-730
Proprietary Drug Name:	XOPENEX HFA MDI INHALATION AEROSOL
Generic Name:	Levalbuterol
Indication:	Treatment or prevention of bronchospasm
Dosage Form:	MDI
Strength:	45 μg
Route of Administration:	Oral Inhalation
Applicant:	Sepracor, Inc.
Clinical Division:	DPADP (HFD-570)
Submission Dates:	May 11, 2004; November 23, 2004; Feb 22, 2005
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.

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1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-730 submitted on May 11, 2004. We found this NDA acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's labeling recommendations. Please convey labeling recommendations and comment to sponsor as appropriate.

1.2 Phase IV Commitments

None

1.3 Comments (not to be submitted to sponsor)

- A dose-response relationship for efficacy (maximum percent decrease in FEV_1) was not observed in the range of 45- to 180 μg for Xopenex HFA in asthmatic subjects 6 to 11 years of age. The degree of bronchoprotection did not appear to improve much beyond what was observed after administration of the 45 μg. Since plasma concentrations increased nearly proportionately to the dose of inhaled drug and a concentration-response relationship for side effects was observed, this reviewer recommends that the efficacy of the 45 μg dose be further investigated in pediatric patients.
- A large portion (65%) of subjects receiving levalbuterol treatment had measurable S-albuterol concentrations despite the sponsor's claim that there is not in vivo interconversion of R-albuterol to S-albuterol.
- Dose-related increases in QTc-F interval were observed for both levalbuterol and racemic albuterol; the greatest increases in QTc-F were observed after 16x the dose (x=45 μg) (levalbuterol mean, SD: 10 (12.4) ms, racemic albuterol mean, SD: 14.5 ms (13.7)). The LS mean changes in QTc-F were not significantly different between the treatment groups. Mean QTc changes from baseline higher than 5 msec were observed at doses higher than those proposed in the label.

1.4 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Xopenex® HFA MDI inhalation aerosol contains R-albuterol (Levalbuterol), a β-agonist that inhibits the release of inflammatory mediators from mast cells and other proinflammatory cells in the airways. Xopenex is indicated for the treatment or prevention of bronchospasm. The proposed dose in adults and children 4 years of age and older is 2 inhalations (90 μg) repeated every 4 to 6 hours. Levalbuterol HCl Inhalation Solution (Xopenex® UDV) is currently marketed for the treatment or prevention of bronchospasm in subjects 6 years of age and older with reversible obstructive airway disease.

This NDA includes data from twelve completed studies, and one ongoing safety study conducted in pediatric and adult/adolescent subjects utilizing single or multiple doses ranging from 22.5- to 180 μg of levalbuterol. However, three large (N=898), adequate and well controlled, Phase III studies (Studies 051-353, 051-354 and 051-355) are the foundation for understanding both the safety and efficacy of the levalbuterol HFA. These studies were randomized, double-blind, multiple-dose, placebo- and active-controlled (racemic albuterol [Proventil® HFA]) clinical trials in subjects with asthma.

The clinical pharmacology of Xopenex was assessed in 11 studies. Two of these studies (051-304 and 051-305) were not reviewed because they utilized the CFC formulation and are not relevant to the NDA. The clinical pharmacology program was designed to explore the key PK and PD effects of (R)-albuterol, with respect to both safety and efficacy, following administration of Levalbuterol HFA MDI versus Proventil® HFA MDI. The PK studies included a relative BA, dose-response and cumulative dosing

studies in adult and pediatric subjects, and population PK and PD analysis. Since systemic absorption of inhaled drugs is the result of pulmonary and gastrointestinal absorption, and because there is uncertainty about the site of absorption along the respiratory tract/airways, plasma concentrations cannot be correlated to efficacy (FEV_1). Therefore, the PK/PD relationship with respect to efficacy was not reviewed. A summary to the PK findings is described below.

Relative Exposure Analysis

In general, the systemic exposure (Cmax, AUC_{0-4hr}) of R-albuterol was 10 % to 30 % lower following administration of Xopenex HFA MDI (45- to 720 µg) compare to that from the Proventil HFA formulation (90- to 1440 µg). The use of spacers ( ) increased the exposure of R-albuterol in both products: in the adolescents/adults studies the increase in systemic exposure when Proventil plus spacer were used was more pronounced (50% higher for the 180 µg dose) compared to that after Xopenex HFA (40% higher for the 90 µg). However, in the pediatric studies the increase in exposure when spacer was used was more pronounced for Xopenex HFA (44% higher for the 90 µg) compared to that for Proventil (34% higher for the 180 µg dose). The systemic exposure (Cmax and AUC_{0-4hr}) of levalbuterol manufactured at was similar to that of levalbuterol manufactured at 3M (the point estimates and 90% CI were 103 (85-124) and 104 (84-130) for the AUC_{0-4hr} and Cmax respectively). The relative small higher systemic exposure (Cmax) observed for levalbuterol manufactured at is not clinically relevant (smaller Cmax values obtained for the commercial production site (3M) may favor the safety of the product). A large portion (65%) of subjects receiving levalbuterol treatment had measurable S-albuterol concentrations despite the sponsor's claim that there is not in vivo interconversion of R-albuterol to S-albuterol.

Dose- Response with Respect to Efficacy

Adolescents and Adults

Based on the primary endpoint (percent decrease from visit postdose/pre-challenge FEV_1 AUC), there was a trend for dose-response with increasing doses (45-, 90, and 180 µg) of levalbuterol in asthmatic adolescent and adults following multiple administration of the treatments; however, the difference between the 45 µg and 180 µg dose levels was not statistically significant for this endpoint. A trend for dose response for racemic albuterol was observed; the difference between 90 µg and 360 µg racemic albuterol was marginally significant. The LS mean maximum percent decreases from visit postdose/pre-challenge FEV_1 (a secondary endpoint) for the 1X and 4X doses were 9.45 and 5.45, respectively. The difference between the 1X and 4X doses was nearly significant (p=0.055). In addition, the 2X dose of levalbuterol (mean maximum percent decrease= 5.95) was more bronchoprotective than the 1X dose (9.75). The 180-µg dose appeared not to have any additional efficacy over the 90 µg dose.

Children 6 to 11 years of age

A dose-response relationship for FEV_1 was not observed in the range of 45- to 180 µg for levalbuterol or in the range of 90- to 360 µg for racemic albuterol in asthmatic subjects 6 to 11 years of age. The median maximum percent decreases from visit postdose/pre-challenge in FEV_1 were 1.87%, 5.82%, and 2.24% for the 45 µg, 90 µg, and 180 µg doses of levalbuterol, respectively, and were 0.00%, 1.70%, and 1.00% for the comparable doses of racemic albuterol, respectively. The degree of bronchoprotection did not appear to improve much beyond that which was observed after administration of the 1X doses. Since plasma concentrations increased nearly proportionately to the dose of drug inhaled and a concentration-response relationship for side effects (see below) was observed, this reviewer recommends that the efficacy of the 45 µg QID dose regimen be further investigated in pediatric patients.

Dose- Response with Respect to Safety

The changes in mean heart rate, systolic blood pressure, and glucose levels in adolescent/adults generally increased with increasing mean concentrations of (R)-albuterol within each treatment group (levalbuterol 1x (45 μg), 2x, 4x, 8x and 16x the dose, or racemic albuterol 1x (90 μg), 2x, 4x, 8x and 16x the dose). The changes in mean diastolic blood pressure and potassium levels generally decreased with increasing mean concentrations of (R)-albuterol within each treatment group. Similar concentrations of (R)-albuterol had comparable effects on each of these safety endpoints, independent of the source of (R)-albuterol (i.e., from either the levalbuterol or racemic albuterol products) and the use of spacer. The results from pediatric subjects were in agreement with observations in adults and adolescents that measures of drug safety were comparable to Proventil HFA, and were related to (R)-albuterol concentrations.

Dose-related increases in QTc-F interval were observed for both levalbuterol and racemic albuterol; the greatest increases in QTc-F were observed after 16X (levalbuterol Mean, SD: 10 (12.4) ms, racemic albuterol Mean, SD: 14.5 ms (13.7)). The LS mean changes in QTc-F were not significantly different between the treatment groups, as indicated by the 95% confidence intervals that included zero. Mean QTc changes observed with levalbuterol were not higher than those observed for the currently marketed Proventil (racemic albuterol) product. Mean QTc changes from baseline higher than 5 msec were observed at doses higher than those proposed in the label.

Pharmacokinetics in Special Populations

Based on population PK analysis, body weight (kg) was found to be a significant predictor of both the apparent clearance (Cl/F) and apparent central volume of distribution (Vc/F) of (R)-albuterol in adults and pediatric subjects. Once body weight was incorporated in the population PK model, age, body surface area, creatinine clearance, gender, and race did not affect the PK of R-Albuterol. Exposures were relatively similar over the range of ages studied, from approximately 4 to 81 years of age. Therefore, no dose adjustment is necessary in these subgroups.

Reviewer

Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel O. Fadiran Ph.D., Team leader

cc:

NDA 21-730	:	Division File
HFD-870:		Malinowski, Hunt
HFD-570:		Fadiran, Green, Seymour, Suarez-Sharp

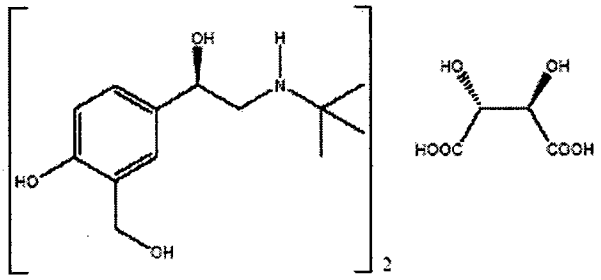
2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

The drug substance (R)-α[1]-[[(1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol L-tartrate (2:1 salt), more commonly known as levalbuterol tartrate, is a β2-adrenergic receptor agonist. Levalbuterol is the pharmacologically active R-enantiomer of racemic albuterol.

Structural formula:



Molecular formula: $(C_{13}H_{21}NO_3)_2 \cdot C_4H_6O_6$

Molecular weight: 628.71

The drug substance is a — , white to light-yellow solid —

FORMULATION

Xopenex HFA is a pressurized metered-dose inhaler containing a suspension of micronized levalbuterol tartrate in ethanol, oleic acid and propellant HFA-134a. It is designed to deliver 45 µg levalbuterol (as free base) per actuation and a minimum of 200 actuations per canister; one dose consists of two actuations. The composition for the proposed commercial drug product is listed below in Table 1. The batch sizes used during clinical development ranged from — to — units. The commercial batch size will be approximately — units.

Table 1. Xopenex inhalation aerosol unit-dose composition

Name of Ingredient	Function	Amount per actuation	Amount per canister
Levalbuterol tartrate	Active ingredient		
Oleic acid NF			
Dehydrated alcohol USP			
HFA-134a	Propellant		
Total quantity		60.00 mg	15.00 g

* equivalent to — µg of levalbuterol free base (ex-valve), to deliver 45 µg levalbuterol free base/59 µg of levalbuterol tartrate (ex-actuator)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?
Mechanism of Action:

Levalbuterol tartrate is a relatively selective β_2-adrenergic receptor agonist. Activation of β_2-adrenergic receptors on airway smooth muscle leads to the 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 the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Increased cyclic AMP concentrations are also associated with the inhibition of the release of inflammatory mediators from mast cells and other proinflammatory cells in the airways.

INDICATION (as per proposed label)

XOPENEX HFA Inhalation Aerosol is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed route of administration is by oral inhalation.

DOSAGE AND ADMINISTRATION (as per proposed label)

For adults and children 4 years of age and older is 2 inhalations (90 μg) repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations is not routinely recommended

2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

The primary efficacy endpoint was the maximum percent change from visit predose in FEV_1 averaged over the eight-week double-blind period. The key secondary efficacy endpoints were the area under the FEV_1 percent change curve from visit predose and from study baseline curves averaged over the double-blind period. The primary safety endpoints were the changes in heart rate, blood pressure, potassium, and glucose from visit predose following each cumulative dose.

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

FEV_1 is a well established and validated clinical endpoint of efficacy in asthma and bronchospasm. This endpoint was calculated as the average of the peak percent change in FEV_1 values at Visits 2, 4, and 6. Peak percent change at each week was calculated as the maximum FEV_1 recorded during the given serial spirometry day minus the FEV_1 observed at visit predose, divided by the visit predose FEV_1 and multiplied by 100. The primary efficacy analysis was performed on the average of the peak percent change over the double-blind period.

Although FEV_1 is a well established and validated clinical endpoint of efficacy in asthma, it does not, by itself, fully describe the level of overall asthma control. Therefore, key secondary endpoints reflecting asthma control, including PEF (peak expiratory flow), symptom scores, and quality of life, were measured. Since systemic absorption of inhaled drugs is the result of pulmonary and gastrointestinal absorption, and because there is uncertainty about the site of absorption along the respiratory tract/airways, plasma concentrations cannot be correlated to efficacy (FEV_1).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

(R)-albuterol and (S)-albuterol were analyzed in plasma using an LC/MS/MS. The LC/MS/MS method was validated over the plasma concentration range of 2.00 pg/mL to 4000 pg/mL using a 2 mL sample volume. Precision, as measured by CV (%), was generally $\leq 20\%$. Accuracy was generally within 20%.

2.2.4 Exposure Response

2.2.4.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

ADULTS

There was a trend for dose-response (percent decrease from visit postdose/pre-challenge FEV_1 AUC) with increasing doses of levalbuterol in asthmatic adolescent and adults following multiple administration of the treatments (Figure 1), however, the difference between the 45 µg and 180 µg dose levels was not statistically significant for this endpoint. A trend for dose response for racemic albuterol was observed; the difference between 90 µg and 360 µg racemic albuterol was marginally significant.

The LS Mean maximum percent decreases from visit postdose/pre-challenge FEV_1 (a secondary endpoint) for the 1X and 4X doses were 9.45 and 5.45, respectively. The difference between the 1X and 4X doses was nearly significant (p=0.055). In addition, the 2X dose of levalbuterol (mean maximum percent decrease= 5.95) was more bronchoprotective than the 1X dose (9.75) (Table 2). The 180-µg dose appeared not to have any additional efficacy over the 90-µg dose. A dose response for racemic albuterol also was observed; the difference between 90 µg and 360 µg racemic albuterol was significant (Table 2). The use of levalbuterol 90 µg in the adolescent and adult Phase III clinical trials is supported by the results of the phase II dose-response studies.

These results come from Study 051-308, 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 60 (30/treatment arm) adolescent and adult subjects with asthma. All study medication was administered via a plastic spacer ( ). Treatments: levalbuterol HFA MDI (1, 2, and 4 actuations of 45 µg /actuation) or racemic albuterol HFA MDI (1, 2, and 4 actuations of 90 µg /actuation).

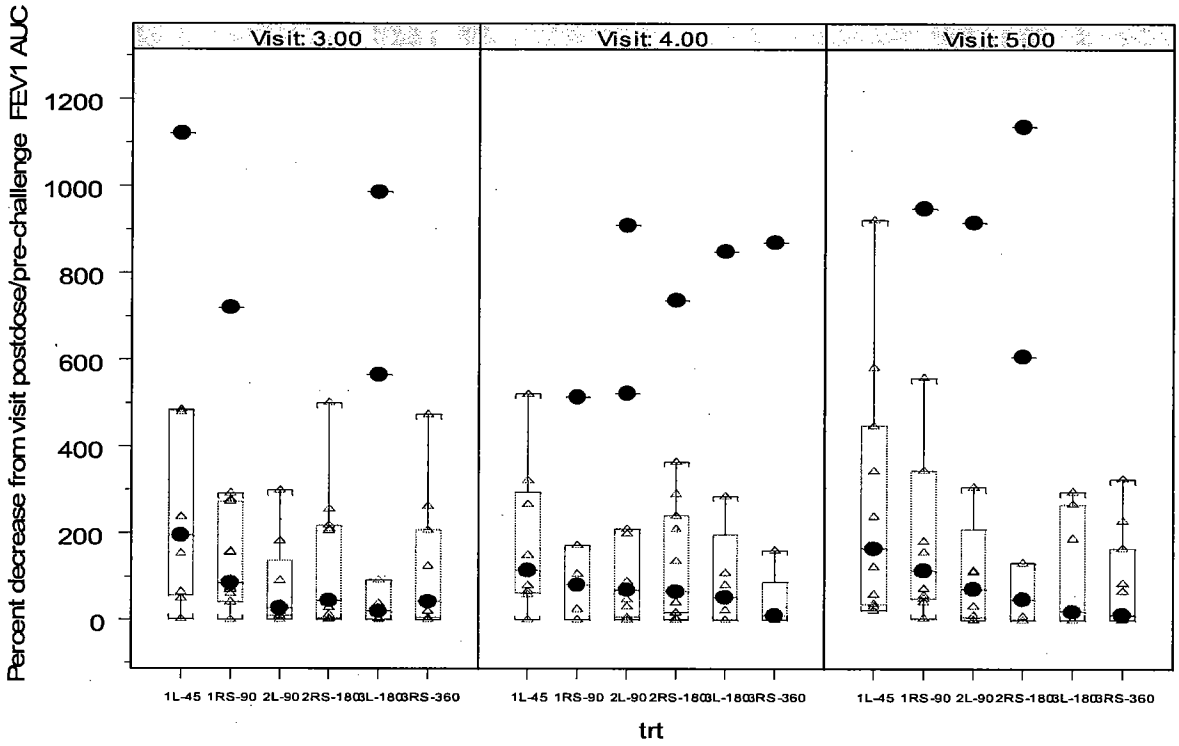


Figure 1. Percent Decrease from Visit Postdose/Pre-challenge FEV_1 AUC by Treatment, visit and Dose Level (levalbuterol doses (L) of 45-, 90- and 180 µg; racemic albuterol doses (RS) of 90-, 180, and 360 µg) in asthmatic adolescent and adults. (Data taken from study 051-308).

Table 2: Maximum Percent Decrease from Visit Postdose/Pre-challenge FEV_1 by Treatment and Dose Level (CR Excluding 621 and As-Treated Populations)

Population	Levalbuterol			Racemic Albuterol		
	45 µg (1X)	90 µg (2X)	180 µg (4X)	90 µg (1X)	180 µg (2X)	360 µg (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 µg versus LEV 180 µg p=0. 055			RAC 90 µg versus RAC 360 µg p=0.026		
	Relative Potency and 90% C.I. 0.684 (0.211, 1.801)					
As-Treated	27	27	26	32	34	32
Mean (SD)	9.34 (8.39)	5.83 (6.27)	4.79 (6.42)	7.90 (8.33)	6.00 (7.10)	3.59 (4.69)
LSMean (±)	8.94 ± 1.60		4.51 ± 1.62	7.67 ± 1.30		3.65 ± 1.30
Median	4.43	3.64	2.94	6.09	3.27	2.47
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 µg versus LEV 180 µg p=0.018			RAC 90 µg versus RAC 360 µg p=0.008		
	Relative Potency (90% C.I.) 0.834 (0.367, 1.781)					

NOTE: Maximum percent decrease from visit postdose/pre-challenge FEV_1 was defined as the largest percent decrease observed during 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 timepoints, the maximum percent decrease was set to zero.

PEDIATRICS

A dose-response relationship for change in FEV_1 was not observed in the range of 45- to 180 µg for levalbuterol or in the range of 90- to 360 µg for racemic albuterol in asthmatic subjects 6 to 11 years of age. The median maximum percent decrease from visit postdose/pre-challenge in FEV_1 were 1.87%, 5.82%, and 2.24% for the 45 µg, 90 µg, and 180 µg doses of levalbuterol, respectively, and were 0.00%, 1.70%, and 1.00% with the comparable doses of racemic albuterol, respectively. The degree of bronchoprotection did not appear to improve much beyond that which was observed after administration of the 1X doses (Figure 2, Table 3).

These results come from study 051-312, 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 28 (12 to 16/treatment arm) asthmatic children 6 to 11 years of age. Treatments: levalbuterol HFA MDI (1, 2, and 4 actuations of 45 µg /actuation) or racemic albuterol HFA MDI (1, 2, and 4 actuations of 90 µg /actuation). All study medications were administered via a plastic spacer

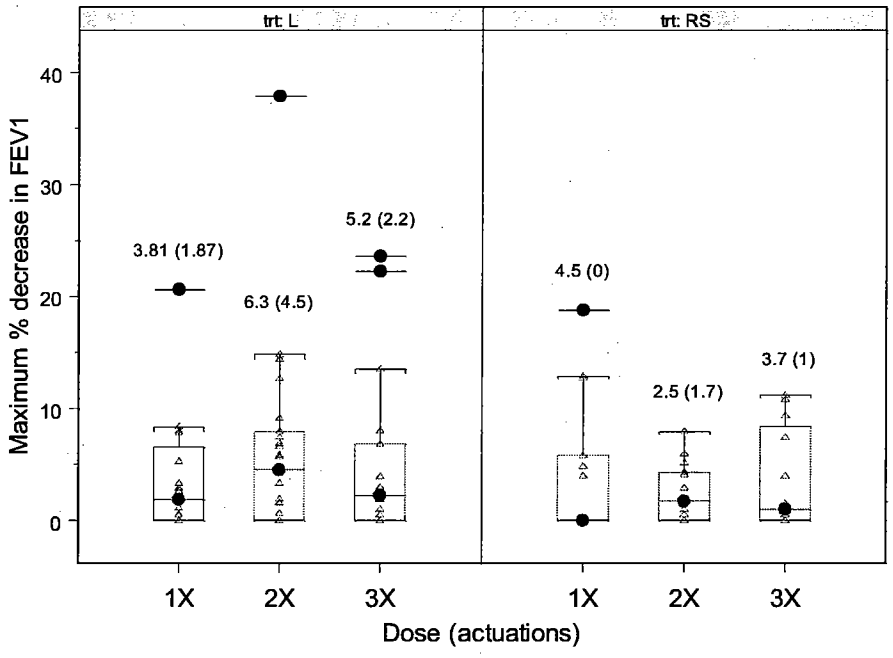


Figure 2. Individual (number represent mean, (median)) maximum percent decrease in FEV_1 post-dose/pre-challenge in asthmatic children. (Data taken from study 051-312)

Table 3. Maximum Percent Decrease in FEV_1 from Visit Postdose/Pre-Challenge (EVAL) in asthmatic children

	Levalbuterol			Racemic Albuterol		
	45 µg (1X) (n=16)	90 µg (2X) (n=17)	180 µg (4X) (n=17)	90 µg (1X) (n=13)	180 µg (2X) (n=13)	360 µg (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 zero, it was set to zero.

2.2.4.2 What are the characteristics of the systemic exposure relationships for safety?

ADULTS

The changes in mean heart rate, systolic blood pressure, and glucose levels generally increased with increasing mean concentrations of (R)-albuterol within each treatment group (levalbuterol 1x, 2x, 4x, 8x and 16x the dose, or racemic albuterol 1x, 2x, 4x, 8x and 16x the dose). The changes in mean diastolic blood pressure and potassium levels generally decreased with increasing mean concentrations of (R)-albuterol within each treatment group (Figure 3). Similar concentrations of (R)-albuterol had comparable effects on each of these safety endpoints, independent of the source of (R)-albuterol (i.e., from either the levalbuterol or racemic albuterol products) and the use of spacer.

The cumulative plasma concentrations of (R)-albuterol were higher after treatment with the racemic albuterol MDI than after the levalbuterol MDI; the median ratios of LEV/RAC (R)-albuterol concentrations were similar for each cumulative dose and were about 0.6 when spacer was used and about 0.7 to 0.9 when no spacer was used.

These results come from two studies: Study 051-309 and Study 051-310. These were randomized, modified-blind, active-controlled, multicenter, two-way crossover study of Levalbuterol HFA MDI and Proventil® HFA MDI in subjects 12 years of age and older with asthma. The major difference in design between the two studies is that spacers were not used in Study 051-309. Subjects received cumulative doses (16 puffs total) of Levalbuterol HFA MDI (45 µg/actuation) or Proventil HFA MDI (90 µg/actuation). Plasma samples were collected for (R)- and (S)-albuterol assay and for serum potassium and glucose determination.

PEDIATRICS

Serum glucose levels tended to increase and serum potassium levels tended to decrease with increasing (R)-albuterol concentrations. The change in heart rate vs. plasma concentration of (R)-albuterol was highly variable; no trend was apparent upon visual inspection of the data. For each of these safety parameters, the changes observed with both treatments in each cohort were observed primarily following the 4X or 8X doses, with minimal to no changes occurring following the 1X or 2X doses. The spacer cohort had greater median increases in heart rate for both treatment groups and greater median decreases in serum potassium for the levalbuterol group than the non-spacer cohort. The racemic albuterol non-spacer group had greater increases in serum glucose than the racemic albuterol spacer group. Systolic and diastolic blood pressure changed minimally in both spacer and non-spacer cohorts.

There was a trend for lower (R)-albuterol concentrations after administration of levalbuterol MDI compared with racemic albuterol MDI, regardless of spacer use. In general, subjects who used spacers had slightly higher (R)-albuterol concentrations than those who did not. This observation was more pronounced in subjects given levalbuterol.

These results from pediatric subjects are in agreement with observations in adults and adolescents that measures of drug safety are comparable to Proventil HFA, and are related to (R)-albuterol concentration.

In this study (Study 051-312), pediatric subjects received cumulative doses (8 puffs total) of Xopenex HFA MDI (45 µg/puff) or Proventil HFA MDI (90 µg/puff); plasma samples were collected for both (R)- and (S)-albuterol assay and for serum potassium and glucose determination.

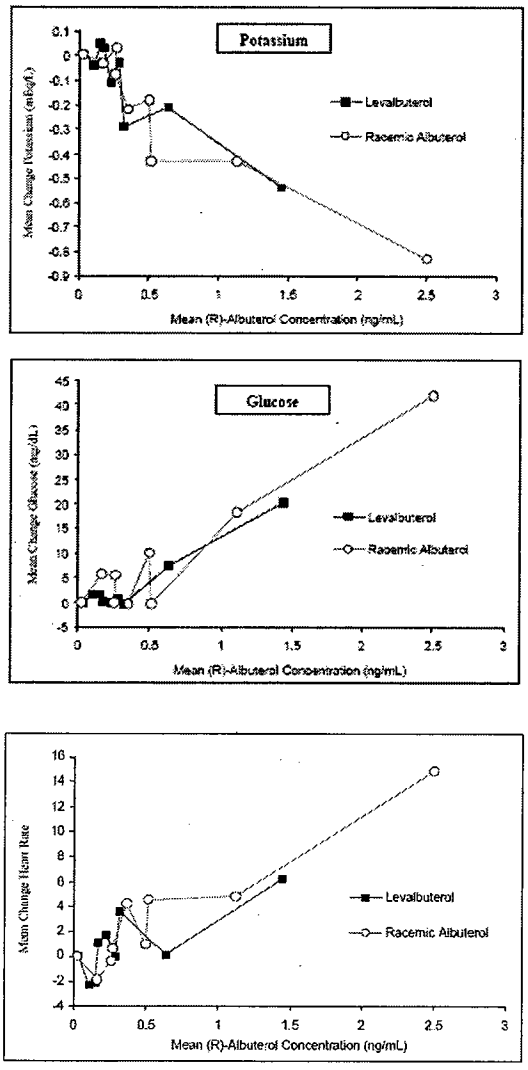


Figure 3. Time-Matched Mean Serum Potassium, Glucose Levels and Heart Rate and Mean (R)-Albuterol Concentration: Change from Visit Predose to each Postdose Time Point (As treated). (Data taken from study 051-310: spacer used).

2.2.4.3 Does this drug prolong the QT or QTc interval?

The changes in mean QT_{c-F} increased with increasing plasma concentrations of (R)-albuterol following cumulative doses of levalbuterol in asthmatic adolescents and adults and reached a maximum increase following the last dose (mean concentration of 0.9697 ng/mL). QT_{c-F} also increased following cumulative doses of racemic albuterol and reached a maximum increase after the last dose (mean concentration of 1.2356 ng/mL. The relationships between QT_{c-F} and (R)-albuterol concentration following administration of levalbuterol or racemic albuterol were similar. A similar trend was observed for QT_{c-B}.

The LS Mean changes in QT_{c-F} were not significantly different between the treatment groups, as indicated by the 95% confidence intervals that included zero (Table 4). Dose-related increases in QT_{c-F} interval were observed for both levalbuterol and racemic albuterol; the greatest increases in QT_{c-F} were observed after 16X (levalbuterol LS Mean: 9.4 ms, racemic albuterol LS Mean: 12.7 ms). Mean changes in QT_{c-F} returned to near mean baseline values within 8 hours after the last dose of levalbuterol and racemic albuterol.

A similar trend was observed for QT_{c-B} as was observed for QT_{c-F}, with the exception of the 16X dose. The LS Mean increase in QT_{c-B} from visit predose following 16X administration of racemic albuterol (20.3 beats/minute) was significantly greater than the LS Mean increase for levalbuterol (14.1 beats/minute), as indicated by the 95% confidence interval that did not include zero. No subject had QT_{c-F} values greater than 450 ms following either treatment. One subject taking levalbuterol had a QT_{c-F} increase greater than 60 ms (visit predose average QT_{c-F} = 368 ms; QT_{c-F} = 444 ms 40 minutes following 16X levalbuterol). A higher percentage of subjects had QT_{c-F} increases between 30 and 60 ms, QT_{c-B} values greater than 450 ms, QT_{c-B} increases between 30 and 60 ms, and QT_{c-B} increases greater than 60 ms following racemic albuterol treatment, compared with levalbuterol.

Table 3: Change in QTc-F (ms) from Visit Predose to 20-Minutes Post-Each Cumulative Dose (ITT Population) (Data taken from study 051-309)

		Levalbuterol (N=47)	Racemic Albuterol (N=45)	LSMean Diff (95% C.I.)
Post 1X Dose	Mean (SD)	-0.3 (8.0)	0.4 (9.5)	0.5
	LSMean ± SE	-0.6 ± 1.2	-1.1 ± 1.3	(-2.9, 3.9)
Post 2X Dose	Mean (SD)	2.4 (9.5)	1.7 (9.0)	-0.5
	LSMean ± SE	1.9 ± 1.2	2.4 ± 1.2	(-3.6, 2.7)
Post 4X Dose	Mean (SD)	3.9 (9.9)	4.6 (9.3)	-1.4
	LSMean ± SE	4.4 ± 1.2	5.8 ± 1.3	(-4.6, 1.9)
Post 8X Dose	Mean (SD)	7.3 (11.1)	8.1 (10.6)	-2.3
	LSMean ± SE	6.9 ± 1.4	9.2 ± 1.4	(-5.9, 1.3)
Post 16X Dose	Mean (SD)	10.0 (12.4)	14.5 (13.7)	-3.2
	LSMean ± SE	9.4 ± 1.6	12.7 ± 1.6	(-7.4, 0.9)

In summary, mean QTc changes observed with levalbuterol were not higher than those observed for the currently marketed Proventil (racemic albuterol) product. Mean QTc changes from baseline higher than 5 msec were observed at doses higher than those proposed in the label.

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 What are the single and multiple dose PK parameters?

Single Dose

A summary of the R-Albuterol PK paramerers following single administration of the treatments is shown in Table 5.

Table 5. Plasma PK Parameters (mean, median) of R-Albuterol Following Single Doses of 45, 90 and 180 mcg of R- albuterol and 90, 180, and 360 µg of Racemic Albuterol (Data taken from Study 051-308)

	Cmax (ng/mL)	Tmax (hr)	AUC $_{0\text{-last}}$ (ng*hr/mL)	R $_{AUC(S/R)}$	R $_{Cmax\ (S/R)}$
L-45	0.15 (0.1)	0.48 (0.6)	0.26 (0.23)		
L-90	0.45 (0.7)	0.73 (1.1)	0.61 (0.7)		
L-180	0.7 (1.1)	0.5 (0.8)	0.82 (0.7)		
RS-90	0.4 (0.34)	0.7 0.97)	0.56 (0.4)	2.16 (0.65)	1.55 (0.48)
RS-180	0.49 (0.2)	0.44 (0.4)	0.76 (0.31)	2.37 (0.6)	1.64 (0.4)
RS-360	0.9 (0.4)	0.35 (0.5)	1.41 (0.5)	2.4 (0.4)	1.7 (0.3)

Multiple Dose

Following multiple QID inhalation of either Xopenex HFA MDI or Proventil HFA MDI (reference product), (R)-Albuterol appeared rapidly in the systemic circulation; tmax was about 0.5 hr. Similar corresponding exposure parameters, Cmax and $AUC_{(0-4)}$ were observed among treatments (Figure 4, Table 6). The 90% confidence intervals for the ratio of PK parameters were within the acceptable equivalence range of 80 to 125% (Table 7). Following administration of Proventil HFA MDI the exposure to (S)-albuterol was considerably higher than to (R)-albuterol with a median ratio of AUC (RAUC(S/R)) of 4.04 and a median ratio of Cmax (RCmax(S/R)) of 2.85.

The systemic exposure of R-Albuterol appears not to accumulate following multiple inhalations: The AUC_{last} and Cmax following a single inhalation of 90 µg levalbuterol (0.56 ng*hr/mL, 0.45 ng/mL) were comparable to the AUC_{0-4} and Cmax (0.7 ng*hr/mL, 031 ng/mL, respectively) following multiple administration of the same dose.

Table 6. Summary of PK Parameters for (R)-Albuterol Following Multiple (QID) Dosing of 90 µg Levalbuterol HFA MDI (n~182) and 180 µg Proventil HFA MDI (n~102) (Visit 6, Day 56) (Data taken from Study 051-353)

	90 µg Levalbuterol HFA MDI			180 µg Proventil HFA		
	R-Albuterol			R-Albuterol		
	AUC (0-4hr)(ng*hr/mL)	AUC last	Cmax (ng/mL)	AUC (0-4hr)	AUC last	Cmax
Minimum	0.15	0.16	0.449	0.119	0.06	0.035
Mean	0.70	1.12	0.313	0.686	0.99	0.285
Median	0.527	0.737	0.198	0.57	0.82	0.22
Max	10.3	30.1	9.9	2.7	5.3	1.48
SD	0.91	2.3	0.75	0.45	0.77	0.23

Table 7. Point estimates and 90% confidence intervals for the ratio of the geometric means of PK parameters (Data from study 051-353)

PK Parameter	Point estimate	90% CI
AUC(0-4hr) (ng*hr/mL)	95.9	84.7-108.66
AUC last (ng*hr/mL)	101.28	88.6-115.8
Cmax (ng/mL)	94.9	82.9-108.6

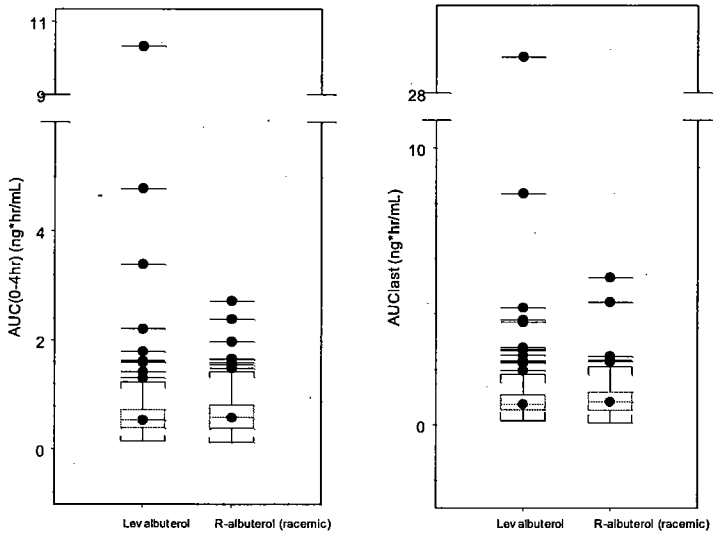


Figure 4. Individual AUC $_{(0\text{-}4),\ last}$ following multiple administration of the treatments (Data from study 051-353).

2.2.5.2 Are the PK of R-albuterol linear and dose-proportional?

Following single inhalation of 45-, 90, or 180 µg of R-albuterol, the AUC last of levalbuterol increased less than proportional to the dose: 2-fold increase in the dose resulted in 2.3 fold increase in AUC and 4-fold increase in the dose resulted in 3-fold increased in the AUC. A linear regression of the power model equation yield an R^2 value of 0.28 (Figure 5). For racemic albuterol (doses administered: 90-, 180-, or 360 µg), the increase in exposure for the lowest and middle dose was less than proportional; however, the increase from the middle to the highest dose was proportional. A linear regression of the power model equation yield an R^2 value of 0.45.

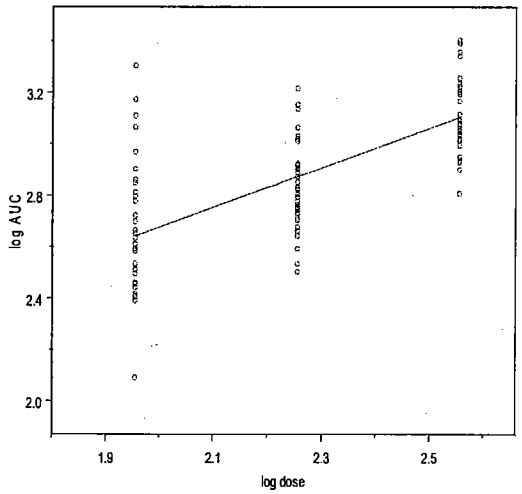


Figure 5. Levalbuterol AUClast per inhalation versus dose. Fitted line from power model : AUC = $e^{0.8}$ * $(\text{strength})^{0.93}$

2.2.5.3 What are the mass balance characteristics of the drug?

The mass balance characteristics following administration of levalbuterol have not been described by the sponsor. The package insert for the present drug product and in general for R-albuterol products do not contain information about mass balance.

2.2.5.5 What are the characteristics of drug metabolism and excretion?

The metabolic pathway of R-albuterol has been described below. The package insert for the present drug product and in general for R-albuterol products do not contain information about drug metabolism and excretion.

Metabolism

According to the sponsor, published information suggests that the primary enzyme responsible for the metabolism of albuterol enantiomers in humans is sulphotransferase (SULT1A3). There is a large first pass effect that impacts the swallowed fraction of an inhaled dose; little first pass lung metabolism has been reported in the literature. After either oral or inhalation administration of racemic albuterol, there was an 8-24 fold difference between the (R)- and (S)-albuterol area under the concentration-time curves, suggesting that (R)-albuterol is subjected to preferential first-pass metabolism, presumably by SULT1A3. After inhalation, ~80% of the (R)-albuterol is excreted in the urine as the 4-O-sulfate metabolite while only 25% of the (S)-albuterol is excreted as metabolite.

Excretion

Based on published information, the primary route of elimination of albuterol enantiomers is through renal excretion of either the parent compound or primary metabolite. Less than 20% of the drug is excreted in the feces.

2.2.5.4 What is the inter- and intra-subject variability of PK parameters?

The (R)-albuterol plasma concentrations were highly variable in both treatment groups, as evident from the large standard deviations and wide ranges of individual concentration values. Coefficient of variation for Cmax and AUClast were higher than 80%.

2.3 Intrinsic Factors

2.3.1 Does age, gender or race affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

Based on population PK analysis, body weight (kg) was found to be a significant predictor of both the apparent clearance (Cl/F) and apparent central volume of distribution (Vc/F) of (R)-albuterol in adults and pediatric subjects. Once body weight was incorporated in the population PK model, age, body surface area, creatinine clearance, gender and race did not affect the PK of R-Albuterol. Exposures were relatively constant over the range of ages studied, from approximately 4 to 81 years of age. Subjects greater than 60 years of age (n=40) and less than 12 years of age (n=81) had exposures reasonably similar to the remainder of the population (Table 8). Therefore, no dose adjustment is necessary in these subgroups.

Table 8. Model Predicted Non-Compartmental Pharmacokinetic Parameters in Pediatric and Adult Subjects Given Levalbuterol HFA MDI or Proventil HFA MDI

Study Population	Parameter	Randomized Treatment	
		Levalbuterol HFA MDI	Proventil HFA MDI
Adult subjects (≥12 years) from Studies 051-353 and 051-355	C_{max} (ng/mL)	0.199 (0.108)	0.238 (0.127)
	t_{max} (hr)	0.54 (0.15)	0.53 (0.15)
	$AUC_{(0-6)}$ (ng*hr/mL)	0.695 (0.415)	0.798 (0.378)
Pediatric subjects (<12 years) from Study 051-354	C_{max} (ng/mL)	0.163 (0.089)	0.238 (0.151)
	t_{max} (hr)	0.76 (0.35)	0.78 (0.38)
	$AUC_{(0-6)}$ (ng*hr/mL)	0.579 (0.306)	0.828 (0.504)

2.3.1.4. Does renal impairment affect the PK of the drug? Is dosage regimen adjustment recommended?

The effect of renal impairment on the PK of levalbuterol has not been addressed by the sponsor. The labeling for racemic albuterol currently marketed products do not contain information about renal impairment and its relation to the PK of this drug.

2.3.1.5 Does liver impairment affect the PK of the drug? Is dosage adjustment recommended?

The effect of liver impairment on the PK of levalbuterol has not been addressed by the sponsor. The labeling for racemic albuterol currently marketed products do not contain information about liver impairment and its relation to the PK of this drug.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, diet, smoking and alcohol used were not evaluated.

2.4.2 Drug-Drug Interactions (DDI)

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

The metabolism of levalbuterol using in vitro methods has not been evaluated by the sponsor. However, published literature suggest that the primary enzyme responsible for the metabolism of albuterol enantiomers in humans is sulphotransferase (SULT1A3).

2.4.2.2 Is the drug a substrate of CYP enzymes?

No in-vitro metabolism studies using CYP P450 enzymes were reported by the sponsor.

2.4.2.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

The potential of R-albuterol to act as an inhibitor/inducer of CYP enzymes has not been reported by the sponsor.

2.4.2.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

This has not been reported by the sponsor.

2.4.2.6. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

The proposed label contains information on the potential of R-albuterol to interact (PD interaction) with the following drugs:

- Beta-blockers
- Diuretics
- Digoxin
- Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

2.4.2.7 What is the effect of R-albuterol on the PK of other drugs? What is the effect of other drugs on the PK of R-albuterol?

The effect of other drugs on the PK of levalbuterol has not been reported by the sponsor. See 2.4.2.6 for information about the effect of R-albuterol on the PK of other drugs.

2.4.2.8 Are there any unresolved questions related to metabolism, active metabolites, or metabolic drug interactions?

The metabolic pathway of R-albuterol has not been reported by the sponsor. Therefore, the potential for DDI is unknown.

2.4.2.9 What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?

The dose-response study in pediatrics show that the levalbuterol dose of 45 μg QID is as effective as the proposed dose of 90 μg QID. The proposed labeling stated that some patients may benefit from 45 μg. This reviewer recommends that the dose regimen in children should start with 45 μg QID.

2.5 General Biopharmaceutics

2.5.1 What is the BCS Class classification for R-albuterol?

This information was not provided by the sponsor. Also, this information may not be relevant since this is not a solid dosage form.

2.5.2 Was the to-be-marketed formulation used in the PK/clinical trials?

The first generation levalbuterol HFA MDI product using HFA-134a as propellant was assessed in two Phase II trials (Studies 051-305 and 051-306). This MDI product was manufactured at — with an actuator orifice diameter of — ı. The actuator orifice diameter of the levalbuterol MDI product was modified to — so that the performance characteristics, better matched the racemic albuterol MDI products. The levalbuterol HFA-134a MDI products were nearly identical in its formulations and components (can, valve, actuator), the only one important difference was that the actuator orifice in the earlier studies was larger. The product with the smaller actuator orifice produced a substantially lower respirable dose when compared with the racemic albuterol comparator product. The pivotal Phase III Study 051-353 study utilized a later-version — manufactured product using the final actuator orifice specification. All subsequent clinical studies used the same actuator orifice size, and all MDI products were made at the proposed commercial manufacturing site (3M; Northridge, CA).

Study 051-355 included the — manufactured MDI using the — mm actuator orifice treatment arm for comparison to the product manufactured at 3M. The results from this study showed that the systemic exposure (Cmax and AUC) of levalbuterol manufactured at — was similar to that of levalbuterol manufactured at 3M (Table 9). The higher systemic exposure (Cmax and AUC) observed for levalbuterol manufactured at — is not clinically relevant.

Table 9. Relative Exposure Analysis Comparing Levalbuterol HFA MDI from the 3M and — Manufacturing Sites and Proventil HFA MDI With Respect to (R)-Albuterol, AUClast, AUC(0-4) and Cmax (Day 56)

	Point estimate	90% CI
	3M/proventil	
AUC(0-4hr) (ng*hr/mL)	88.6	73.3-107.1
AUC Last (ng*hr/mL)	90.06	74.1-109.5
Cmax (ng/mL)	91.1	73.17-113.61
	3M/ —	
AUC(0-4hr) (ng*hr/mL)	102.8	85.4-123.8
AUC Last (ng*hr/mL)	105.51	87.01-127.9
Cmax (ng/mL)	104.45	84.06-129.8

2.5.3 Are the method and dissolution specifications supported by the data provided by the sponsor?

This does not apply for this product. No in vitro dissolution studies were necessary, as R-albuterol is administered as aerosol for inhalation.

2.5.4 What is the effect of food on the BA of the drug?

Because levalbuterol is an inhaled drug, the effect of food was not studied.

2.5.5 If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

This does not apply.

2.5.6 Does the use of spacers affect the PK of R-albuterol?

Adolescent and Adults

A cross-study comparison of the systemic exposure in of (R)-albuterol was performed in asthmatic subjects using Xopenex HFA MDI (90 µg) or Proventil HFA MDI (180 µg) devices, either with or without spacers, under cumulative-dose regimens (Studies 051-309: without spacer and 051-310: with spacer).

In general, subjects who used spacers had higher (R)-albuterol concentrations than those who did not. This observation was more pronounced in subjects given racemic albuterol (Table 10).

Table 10. R-Albuterol plasma concentrations (ng/mL), summaries by treatment, cumulative dose level and use of spacer (Data taken from studies 051-309 and 051-310)

		levalbuterol		Racemic albuterol	
		With spacer	Without spacer*	With spacer	Without spacer*
Pre-1x Dose	Mean (SD) Median	0.03 (0.06) 0.05	0.016 (0.04) BLQ	0.03 (0.03) 0.01	0.013 (0.04) BLQ
Pre-2x Dose	Mean (SD) Median	0.1 (0.1) 0.2	0.06 (0.03) 0.06	0.17 (0.09) 0.14	0.084 (0.05) 0.075
Pre-4x Dose	Mean (SD) Median	0.15 (0.07) 0.12	0.14 (0.08) 0.14	0.27 (0.09) 0.26	0.16 (0.06) 0.16
Pre-8x Dose	Mean (SD) Median	0.28 (0.15) 0.28	0.3 (0.22) 0.26	0.5 (0.21) 0.47	0.32 (0.12) 0.31
Pre-16x Dose	Mean (SD) Median	0.64 (0.26) 0.62	0.51 (0.21) 0.47	1.12 (0.5) 1.11	0.63 (0.23) 0.63
30 min post-16x Dose	Mean (SD) Median	1.3 (0.7) 1.29	0.97 (0.41) 0.91	2.34 (1.2) 2.3	1.24 (0.59) 1.14

* Data taken from study 051-309

Children 4 to 11 years of age

In general, subjects who used spacers had higher (R)-albuterol concentrations than those who did not. However, contrary to what was found in adult asthmatics, this observation was more pronounced in subjects given levalbuterol.

These findings come from study 051-311 a randomized, double-blind, active-controlled, multicenter, two-treatment and two-period crossover, cumulative dose study of up to three weeks in duration in subjects 4-11 years of age with asthma. Subjects (10 to 19) were randomized to one of two treatment sequences: A) levalbuterol HFA MDI (8 cumulative actuations, 45 µg each) or B) racemic albuterol HFA MDI (8 cumulative actuations, 90 µg each). Two cohorts of subjects received treatment as described above. The first group of randomized subjects received the medication with the spacer and the second group received the medication without the spacer.

2.6 Analytical Section

2.6.1 Was the suitability of the analytical method supported by the submitted information?

(R)-albuterol and (S)-albuterol were analyzed in plasma using an chiral LC/MS/MS. The LC/MS/MS method was validated over the plasma concentration range of 2.00 pg/mL to 4000 pg/mL using a 2 mL sample volume (correlation coefficient was > 0.999). In general, an aliquot of

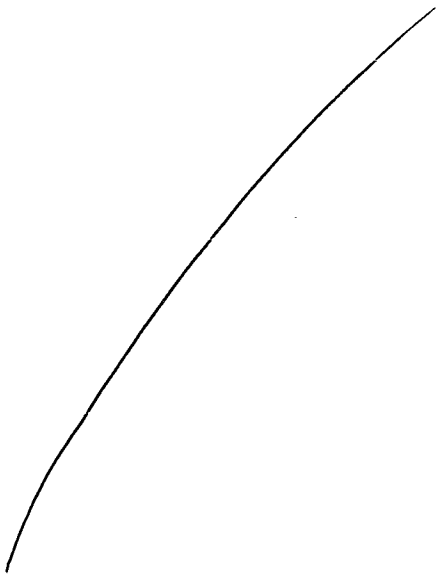
plasma for each unknown, standard, and control sample was subjected to the assay procedure. Peak heights of (R)-albuterol and (S)-albuterol were measured against internal standard (R)- and (S)-D9-albuterol. The plasma drug concentrations were obtained from a 1/(x)2 weighted linear regression of nominal drug concentrations in control human plasma against instrument response.

Intra and inter-assay precision values for analytes was $\geq$ 85% and accuracy (%Diff) values ranged from -4.60 to 14.5. The recovery values were 69.9-77.1% for (R)-albuterol and 57.7-60.6% for (S)-albuterol. The recovery values for Internal standard (R) and (S)- D9-albuterol were 70.0% and 58.8%, respectively. Extracted samples stored under injection condition were stable for at least 8 days. Representative chromatograms were submitted.

Long-term stability, freeze-thaw stability, short-term stability, and processed sample stability were assessed under a variety of conditions. (R)-albuterol and (S)-albuterol were determined to be stable in human plasma for 532 days at -20°C. They were also stable in human plasma for 72 hours under ambient conditions (bench top, room temperature). The freeze-thaw stability was also determined to be stable for five cycles for both (R)-albuterol and (S)-albuterol. Extracted and reconstituted samples of (R)-albuterol and (S)-albuterol in human plasma proved to be stable in an auto-sampler (room temperature) for eight days. Stock solution stability for (R)-albuterol and (S)-albuterol in methanol at -20°C was 1,134 days. According to the sponsor, no chiral inversion was observed during the sample work-up or following long-term storage. However, plasma samples of subjects who received levalbuterol had measurable concentrations of S-albuterol.

3. Labeling Comments

The following underlined changes are recommended for the Clinical Pharmacology Section of the label:



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_ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

4. Appendix
4.1 Individual Study Reports

"AN EFFICACY, SAFETY, AND TOLERABILITY STUDY OF DAILY DOSING WITH LEVALBUTEROL, RACEMIC ALBUTEROL, AND PLACEBO IN SUBJECTS TWELVE YEARS OF AGE AND OLDER WITH ASTHMA "

Protocol No.:	051-305
Development Phase of Study:	Phase II

Objectives
Primary Objective: To determine the comparative efficacy of two different doses of levalbuterol MDI (90 μg and 180 μg) relative to placebo in the reversal of bronchoconstriction in adolescent and adult subjects with asthma.
Secondary Objectives: To determine: 1) the efficacy of levalbuterol versus racemic albuterol; 2) the pharmacokinetics of levalbuterol in subjects 12 years of age and older with asthma; and 3) the safety and tolerability of two different doses of levalbuterol.

Methodology: Multicenter, randomized, double-blind, placebo- and active-controlled, Phase II, parallel-group study of up to five weeks in duration. The study consisted of a screening visit (Visit 1) followed by a one-week single-blind placebo period. At Visit 2, each subject was randomized to one of four treatment groups: 90 μg levalbuterol, 180 μg levalbuterol, 180 μg racemic albuterol, or placebo. All study medication was administered as 2 actuations QID for four weeks.

No. of Subjects: 185 subjects enrolled, 162 subjects randomized, and 152 completed the double-blind treatment period.

Diagnosis and Main Criteria for Inclusion: Non-smoking male and female subjects at least 12 years of age. Subjects were to have a history of non-life threatening asthma and using a β-adrenergic agonist and/or anti-asthma anti-inflammatory medication, and/or over-the-counter asthma medication for at least six months prior to Visit 1.

Test Product: Levalbuterol tartrate in an MDI delivering 45 or 90 μg of medication, vehicle (oleic acid, ethanol) and propellant (HFA 134a) per actuation. Placebo was supplied as an MDI delivering vehicle and propellant only.

Reference Product: Ventolin brand racemic albuterol supplied as an MDI delivering 90 μg of medication, vehicle (oleic acid), and CFC propellant per actuation; placebo (oleic acid, ethanol, and CFC propellant)

Dosage: 90 μg levalbuterol (2 actuations of 45 μg), 180 μg levalbuterol (2 actuations of 90 μg), 180 μg racemic albuterol (2 actuations of 90 μg)

Mode of Administration: MDI

Lot Numbers: Levalbuterol 45 μg (lot #1D633), levalbuterol 90 μg (lot #1D636), racemic albuterol 90 μg (lot #1ZP0760, GlaxoSmithKline), and placebo (lot #1C580).

Duration of Treatment: One week of single-blind placebo and up to four weeks of levalbuterol, racemic albuterol, or placebo QID.

Criteria for Evaluation:
Efficacy: The primary variable was forced expiratory volume in one second (FEV1) and the primary endpoint was the peak percent change in FEV1 from study baseline averaged over the double-blind period.

Safety: Safety evaluations included adverse event (AE) monitoring, vital signs, physical examinations, electrocardiogram (ECG) measurements, potassium and glucose levels, clinical laboratory findings, rescue medication use, asthma control days, and asthma attacks.

Pharmacokinetic Parameters:
Plasma concentrations of (R)- and (S)-albuterol following 90 μg and 180 μg levalbuterol dosing were taken at Visit 2 (predose, 1-2 hours postdose, and 4-6 hours postdose), Visit 3 (predose), and Visit 6 (predose, and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, and 8 hours postdose)

The PK parameters calculated for 90 μg levalbuterol, 180 μg levalbuterol, and 180 μg racemic albuterol included Cmax, tmax, AUC(0-τ), AUC(0-∞), and t1/2. The ratio of AUC(0-t) of the (S)-albuterol enantiomer over AUC(0-t) of the (R)-albuterol enantiomer (RAUC(S/R)) and the ratio of Cmax of the (S)-albuterol enantiomer over Cmax of the (R)-albuterol enantiomer (Rcmax(S/R)) were calculated for racemic albuterol.

Pharmacokinetic Analysis: The pharmacokinetics of (R)- and (S)-albuterol were evaluated following four weeks of QID MDI dosing. Pharmacokinetic (PK) parameters were determined by non-compartmental methods. Pharmacokinetic parameters were calculated for (R)- and (S)-isomers from the racemic albuterol treatment group, and for the (R)-isomer only from the levalbuterol treatment groups.

Pharmacodynamic Analysis: Nonlinear pharmacodynamic models were added (post hoc) to assess the relationship between mean

PHARMACOKINETIC RESULTS:

Some subjects in the levalbuterol dose groups consistently exhibited measurable levels of (S)- albuterol. Evidence of this was observed at predose in 27 subjects (Visit 3) and 23 subjects (Visit 6) receiving 90 μg levalbuterol, and in 26 subjects (Visit 3) and 29 subjects (Visit 6) receiving 180 μg levalbuterol. The mean PK parameters for (R)-Albuterol Following Multiple (QID) Dosing of 90 μg Levalbuterol and 180μg Levalbuterol are shown in Table 1. The mean PK parameters for (R)- and (S)-Albuterol Following Multiple (QID) Dosing of 180 μg g Racemic Albuterol are shown in Table 2.

Table 1. Mean (SD) Pharmacokinetic Parameters for (R)-Albuterol Following Multiple (QID) Dosing of 90 µg Levalbuterol and 180µg Levalbuterol (Visit 6, Day 28)

Parameter	(R)-Albuterol					
	n	90 µg Levalbuterol		n	180 µg Levalbuterol	
		Mean (SD)	Median (Min-Max)		Mean (SD)	Median (Min-Max)
C_{max} (ng/mL)	38	0.559 (1.85)	0.199 (0.062-11.5)	35	1.48 (4.89)	0.327 (0.093-29.0)
t_{max} (hr)	38	1.15 (0.796)	0.975 (0-3.02)	35	1.07 (1.11)	0.717 (0-5.95)
$AUC_{(0-t)}$ (ng•hr/mL)	34	1.16 (2.87)	0.647 (0.223-17.3)	34	2.10 (3.93)	0.951 (0.298-23.0)
$t_{1/2}$ (hr)	22	4.21 (1.08)	4.10 (2.66-6.69)	19	4.87 (1.54)	4.74 (2.52-7.27)

Table 2: Mean (SD) Pharmacokinetic Parameters for (R)- and (S)-Albuterol Following Multiple (QID) Dosing of 180 µg g Racemic Albuterol (Visit 6, Day 28)

Parameter	180 µg Racemic Albuterol					
	n	(R)-Albuterol		n	(S)-Albuterol	
		Mean (SD)	Median (Min-Max)		Mean (SD)	Median (Min-Max)
C_{max} (ng/mL)	33	1.03 (2.02)	0.400 (0.157-10.7)	33	1.31 (1.76)	0.881 (0.327-10.4)
t_{max} (hr)	33	0.837 (0.876)	0.517 (0-4.00)	33	1.28 (0.790)	1.03 (0.233-4.00)
$AUC_{(0-t)}$ (ng•hr/mL)	31	1.45 (1.62)	1.11 (0.404-8.64)	31	4.01 (1.90)	3.54 (1.42-10.3)
$t_{1/2}$ (hr)	24	4.11 (1.31)	4.22 (1.69-6.69)	24	5.24 (1.64)	4.98 (2.26-10.2)
$R_{AUC(S/R)}$	31	3.54 (1.28)	3.63 (1.20-6.18)			
$R_{Cmax(S/R)}$	33	2.29 (1.17)	2.05 (0.195-4.79)			

CONCLUSIONS

Subjects randomized to 180 µg levalbuterol exhibited higher concentrations of (R)-albuterol than those randomized to 90 µg levalbuterol.

The 90 µg levalbuterol and 180 µg racemic albuterol dose groups had similar (R)-albuterol t1/2 estimates (4.21 vs. 4.11 hrs, respectively) indicating that the plasma elimination of (R)-albuterol was not substantially altered by the presence of (S)-albuterol. The t1/2 estimate for 180 µg levalbuterol was 4.87 hours.

Plasma exposure parameters (AUC(0-t) and Cmax) were lower in the 90 µg levalbuterol dose group (1.16 ng*hr/mL and 0.559 ng/mL for the respective parameters) than in the 180 µg racemic albuterol dose group (1.45 ng*hr/mL and 1.03 ng/mL, respectively).

Median plasma concentration-time profiles and pharmacokinetic parameters showed that subjects receiving racemic albuterol were exposed to higher concentrations of (S)-albuterol compared to (R)-albuterol. (S)-Albuterol median RCmax(S/R) and RAUC(S/R) ratios were 2.05 and 3.63, respectively.

"A Dose Response and Pharmacodynamic Study of Levalbuterol and Racemic Albuterol HFA MDI in Subjects Twelve Years of Age and Older with Asthma"

Protocol No.: 051-308
Development Phase of Study: Phase II

Objectives
Primary Objective: To investigate, using an exercise challenge approach, the dose response of levalbuterol HFA MDI in adolescent and adult subjects with asthma.

Secondary Objectives: 1) To investigate the relative potency of levalbuterol and racemic albuterol HFA MDI in the prevention of exercise-induced bronchoconstriction (EIB). 2) To compare levalbuterol and racemic albuterol HFA MDI in the prevention of EIB at each dosing level. 3) 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. 4) To determine the safety and tolerability of levalbuterol and racemic albuterol HFA MDI in subjects with EIB.

Methodology: This was a randomized, modified-blind, active-controlled, multicenter, parallel-treatment, 3x3 dose level crossover study of up to three weeks duration.

No. of Subjects: Planned: 60 subjects (30/treatment arm). Analyzed: 95 subjects were enrolled (i.e., received at least one dose of single-blind study medication prior to the first exercise challenge at Visit 2) and 62 subjects were randomized (27 subjects in the levalbuterol arm and 35 subjects in the racemic albuterol arm). Twenty-six and 32 subjects in the respective treatment arms completed the study.

Diagnosis and Main Criteria for Inclusion: Male or female subjects at least 12 years of age with a documented diagnosis of asthma for at least six months prior to Visit 1. Subjects used either a β-adrenergic agonist, and/or over-the-counter asthma medication for at least six months prior to Visit 1. Subjects demonstrated baseline FEV1 ≥70% of predicted at Visits 1-5 and a drop in FEV1 of at least 20%, but no more than 50%, following baseline exercise challenges.

Test Product: Levalbuterol tartrate in an MDI delivering 45 µg of medication (as free base), vehicle (oleic acid and ethanol) and propellant (HFA 134a) per actuation. Placebo was supplied as an MDI delivering vehicle and propellant only.

Reference Product: Proventil brand of racemic albuterol sulfate as an MDI delivering 90 µg of medication (as free base), vehicle (oleic acid and ethanol), and propellant (HFA 134a) per actuation. All products were administered via a plastic spacer.

Rescue Medication: Maxair Autoinhaler brand of albuterol as an MDI delivering 0.2 mg per actuation.

Dosage: Levalbuterol 45 µg, 90 µg, and 180 µg (1, 2, and 4 actuations of 45 µg, respectively) or racemic albuterol 90 µg, 180 µg, and 360 µg (1, 2, and 4 actuations of 90 µg, respectively).

Mode of Administration: MDI oral inhalation

Lot Numbers: Levalbuterol 45 µg (020539, 3M), racemic albuterol 90 µg (lot # GCD011A, Schering Plough), placebo (lot # 2A221), and albuterol (rescue medication, lot # 020089, 3M)

Duration of Treatment: Period I consisted of a screening visit (Visit 1) and a baseline period, which was initiated at Visit 2. The first of two exercise challenges was performed at Visit 2; the second was performed during the seven-day (±2 days) baseline period; single-blind MDI placebo was administered prior to each challenge. Following completion of Period I, subjects were randomized to receive levalbuterol HFA MDI (1, 2, and 4 actuations of 45 µg /actuation) or racemic albuterol HFA MDI (1, 2, and 4 actuations of 90 µg /actuation) in random order. Period II consisted of three clinic visits (Visits 3-5) at which subjects were administered study medication; there was a five-day (±2 days) washout between doses. Period III consisted of a final safety visit (Visit 6/Early Termination [ET]). Throughout the study, all subjects were given open-label pirbuterol MDI (0.2 mg/actuation) as rescue medication.

Criteria for Evaluation

Efficacy: The primary efficacy variable was FEV1, which was obtained prior to dosing at Visits 3 to 5, 20 minutes after dosing with blinded study medication, and 1, 5, 10, 15, 30, 45, and 60 minutes post-exercise challenge.

The primary efficacy parameter was the area under the percent decrease from visit postdose/pre-challenge FEV1 curve (percent decrease from visit postdose/pre-challenge FEV1 AUC). The key secondary efficacy parameter was the maximum percent FEV1 decrease from visit postdose/pre-challenge FEV1 (maximum percent decrease from visit postdose/pre-challenge FEV1).

Safety: Safety evaluations included adverse event monitoring, vital signs, physical examinations, electrocardiogram (ECG) measurements, potassium and glucose levels, and clinical laboratory findings.

Pharmacokinetics: All subjects had plasma serial blood samples obtained at Visits 3, 4, and 5 (at predose and 10, 20, 45, 55, 70, 85, 115, 180, and 240 minutes postdose). For the racemic albuterol treatment group, pharmacokinetic parameters were calculated using noncompartmental methods for both (R)- and (S)-isomers. For the levalbuterol treatment group, only the pharmacokinetic parameters for the (R)-isomer were calculated.

Statistical Methods

The primary population of interest was the Correctly Randomized population, which consisted of all randomized subjects who received at least one dose of the double-blind study medication to which they were correctly randomized. 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.

Safety: Adverse events, vital signs, ECG measurements, and potassium and glucose levels were summarized by treatment and dose. Descriptive statistics were presented for vital signs, ECG measurements, potassium and glucose levels, clinical laboratory findings, and physical examinations. Changes from predose or pre-challenge to select postdose or post-challenge were summarized descriptively for vital signs, ECG measurements, and potassium and glucose levels.

Pharmacokinetics: Drug concentrations for (R)-albuterol and (S)-albuterol were summarized descriptively for each time point. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) were calculated for all pharmacokinetic parameters for both (R)- and (S)-albuterol. Plasma concentrations for both (R)- and (S)-isomers and pharmacokinetic parameters for the (R)-isomer were presented for both treatment groups. PK parameters for the (S)-isomer were presented for racemic albuterol only.

Pharmacodynamics: Scatter plots of plasma concentrations by potassium and glucose levels were presented. In addition, exploratory models were used to describe univariate relationships between (R)-albuterol pharmacokinetic (PK) exposure parameters (AUC(20-85 min), AUC(0-last), AUC(0-85 min), and Cmax) and pharmacodynamic (PD) outcomes (percent change from visit postdose/pre-challenge FEV1 AUC and minimum percent change from visit postdose/pre-challenge FEV1) for seven pairs of PK/PD measures.

RESULTS

PHARMACOKINETICS

The pharmacokinetic parameter estimates showed that exposure to (R)-albuterol increased with dose for both treatment groups (Figure 1, Table 1). The PK parameters demonstrated that subjects treated with levalbuterol had a lower exposure to (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

The majority of the individual concentration-time profiles had quantifiable predose concentrations of either (R)- or (S)-albuterol prior to administration of the study medication. In addition, there were several subjects who were randomized to receive levalbuterol who had measurable (S)-albuterol concentrations during the entire pharmacokinetic profile. For those subjects who received levalbuterol, approximately 73% and 65% had at least one visit with a quantifiable pre-dose (R)- and (S)-albuterol concentration, respectively.

Figure 2 shows that the AUC last of levalbuterol increased less than proportional to the dose: 2-fold increase in the dose resulted in 2.3 fold increase in AUC and 4-fold increase in the

dose resulted in 3-fold increased in the AUC. A linear regression of the power model equation yield an R2 value of 0.28. For racemic albuterol, the increase in exposure for the lowest and middle dose was less than proportional; however, the increase from the middle to the highest dose was proportional. A linear regression of the power model equation yield an R2 value of 0.45

Table 1. Plasma Pharmacokinetic Parameters (mean, median) of R-Albuterol Following Single Doses of 45, 90 and 180 mcg of R- albuterol and 90, 180, and 360 µg of Racemic Albuterol (As-Treated Population)

	Cmax (ng/mL)	**Tmax (hr)**	**AUC $_{0\text{-last}}$ (ng*hr/mL)**	**R $_{AUC(S/R)}$**	**R $_{Cmax\ (S/R)}$**
L-45	0.15 (0.1)	0.48 (0.6)	0.26 (0.23)		
L-90	0.45 (0.7)	0.73 (1.1)	0.61 (0.7)		
L-180	0.7 (1.1)	0.5 (0.8)	0.82 (0.7)		
RS-90	0.4 (0.34)	0.7 0.97)	0.56 (0.4)	2.16 (0.65)	1.55 (0.48)
RS-180	0.49 (0.2)	0.44 (0.4)	0.76 (0.31)	2.37 (0.6)	1.64 (0.4)
RS-360	0.9 (0.4)	0.35 (0.5)	1.41 (0.5)	2.4 (0.4)	1.7 (0.3)

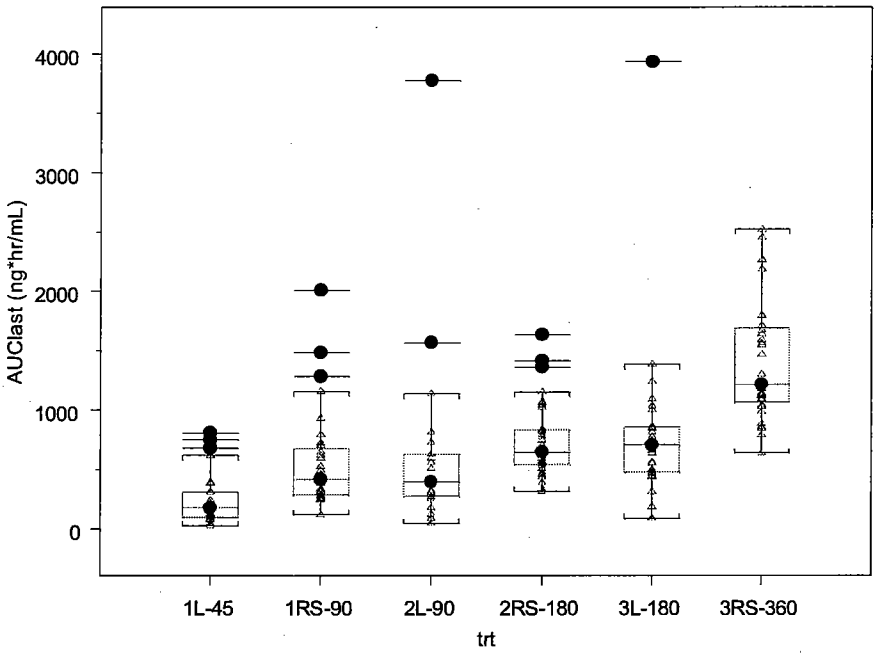

Figure 1. Individual/box plot AUC of R and (S)-Albuterol following Single Doses of 45, 90 and 180 mcg of R- albuterol and 90, 180, and 360 µg of Racemic Albuterol (As-Treated Population)

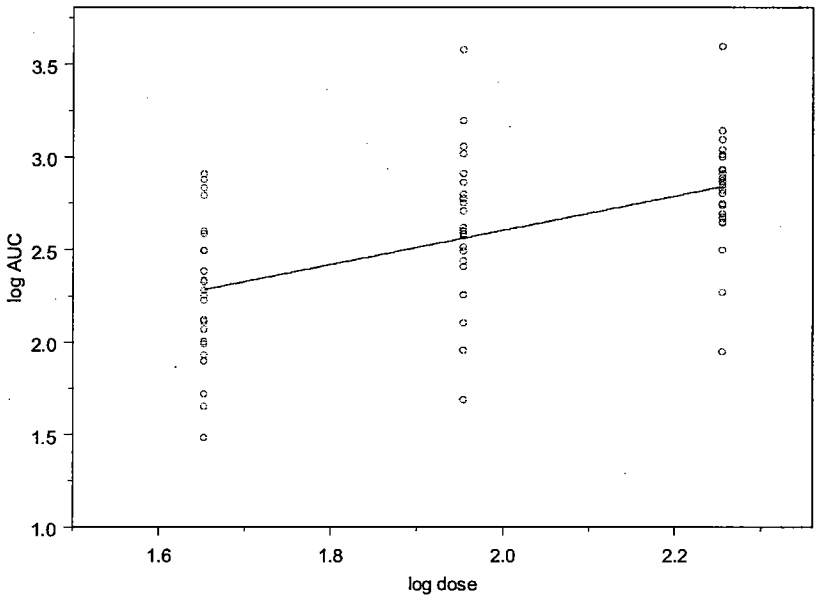

Figure 2. Levalbuterol AUClast per inhalation versus dose. Fitted line from power model : AUC = $e^{0.8}$ * $(strength)^{0.93}$

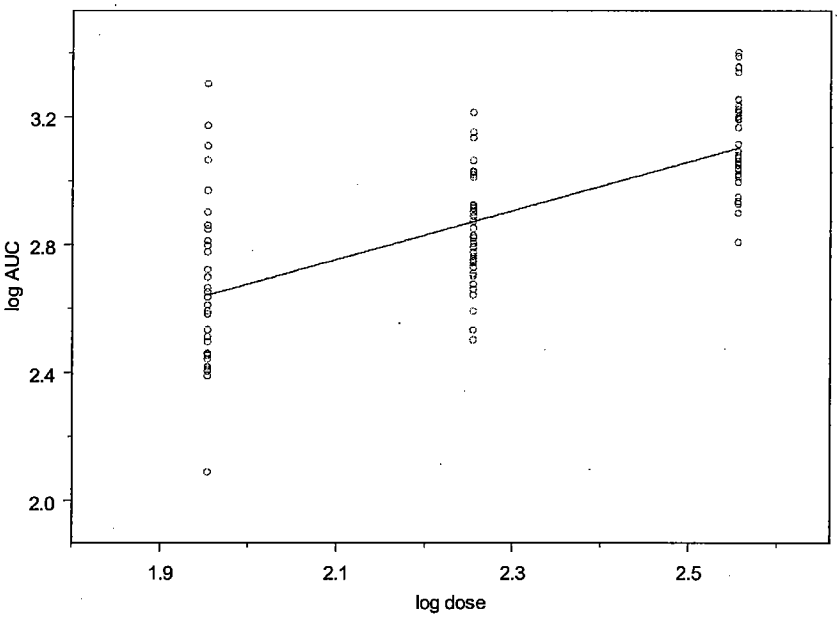

Figure 3. R-albuterol (from RS) AUClast per inhalation versus dose. Fitted line from power model : AUC = $e^{1.15}$ * $(strength)^{0.78}$

Dose-Response

There was a trend for dose-response (percent decrease from visit postdose/pre-challenge FEV1 AUC) with increasing doses of levalbuterol (Figure 3, Table 2), however, the difference between the 1X and 4X dose levels was not statistically significant for this endpoint (Table 2). A dose response for racemic albuterol was observed; the difference between 90 µg and 360 µg racemic albuterol was marginally significant (Table 2).

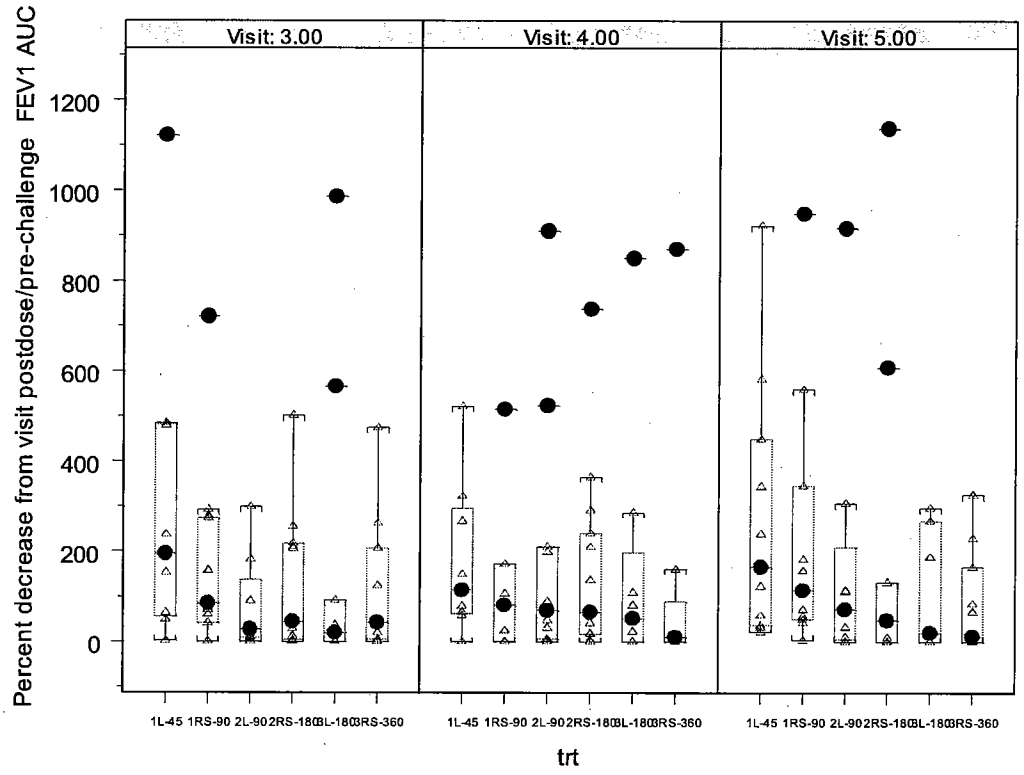

Figure 4. Percent Decrease from Visit Postdose/Pre-challenge FEV1 AUC by Treatment, visit and Dose Level .

Table 2: Percent Decrease from Visit Postdose/Pre-challenge FEV_1 AUC at visit 5.

	Percent decrease from visit postdose/pre-challenge FEV1 AUC					
	L-45	**L-90**	**L-180**	**RS-90**	**RS-180**	**RS-360**
Mean	271	186	112	242	189	81
Median	165	72	20	114	48	11
SD	285	312	134	302	360	113
Min-Max	22-922	0-915.8	0-297	4-949	0-1136.7	0-326

Table 3: Percent Decrease from Visit Postdose/Pre-challenge FEV_1 AUC by Treatment and Dose Level (CR Excluding 621 and As-Treated Populations)

Population	Levalbuterol			Racemic Albuterol		
	45 µg (1X)	90 µg (2X)	180 µg (4X)	90 µg (1X)	180 µg (2X)	360 µg (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 (±)	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 µg versus LEV 180 µg p=0.164			RAC 90 µg versus RAC 360 µg p=0.070		
	Relative Potency and 90% C.I. 0.491 (0.028, 2.836)					
As-Treated	27	27	26	32	34	32
Mean (SD)	260.230 (282.7)	156.126 (250.6)	148.587 (264.3)	175.434 (224.8)	161.347 (251.2)	102.044 (182.1)
LSMean (±)	251.807 ± 57.726		139.028 ± 58.382	171.715 ± 39.449		106.064 ± 39.410
Median	152.684	47.385	21.089	82.661	48.772	14.084
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 µg versus LEV 180 µg p=0.061			RAC 90 µg versus RAC 360 µg p=0.048		
	Relative Potency (90% C.I.) 0.546 (0.081, 2.210)					

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.

The LSMean maximum percent decreases from visit postdose/pre-challenge FEV_1 (a secondary endpoint) for the 1X and 4X doses were 9.45 and 5.45, respectively. The difference between the 1X and 4X doses was nearly significant (p=0.055). In addition, the 2X dose of levalbuterol (mean maximum percent decrease= 5.95) was more bronchoprotective than the 1X dose (9.75). Similar results were observed in the As-Treated population, although the difference between the 1X and 4X dose levels was significant (p=0.018) (Table 4).

A dose response for racemic albuterol also was observed; the difference between 90 µg and 360 µg racemic albuterol was significant in both populations (p=0.026 and 0.008 for the respective populations).

Table 4: Maximum Percent Decrease from Visit Postdose/Pre-challenge FEV_1 by Treatment and Dose Level (CR Excluding 621 and As-Treated Populations)

Population	Levalbuterol			Racemic Albuterol		
	45 µg (1X)	90 µg (2X)	180 µg (4X)	90 µg (1X)	180 µg (2X)	360 µg (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 µg versus LEV 180 µg p=0. 055			RAC 90 µg versus RAC 360 µg p=0.026		
	Relative Potency and 90% C.I. 0.684 (0.211, 1.801)					
As-Treated	27	27	26	32	34	32
Mean (SD)	9.34 (8.39)	5.83 (6.27)	4.79 (6.42)	7.90 (8.33)	6.00 (7.10)	3.59 (4.69)
LSMean (±)	8.94 ± 1.60		4.51 ± 1.62	7.67 ± 1.30		3.65 ± 1.30
Median	4.43	3.64	2.94	6.09	3.27	2.47
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 µg versus LEV 180 µg p=0.018			RAC 90 µg versus RAC 360 µg p=0.008		
	Relative Potency (90% C.I.) 0.834 (0.367, 1.781)					

NOTE: Maximum percent decrease from visit postdose/pre-challenge FEV_1 was defined as the largest percent decrease observed during 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 timepoints, the maximum 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.

SUMMARY OF FINDINGS

- The exposure to (R)-albuterol increased with dose for levalbuterol; however, the increments were less than proportional to the dose for the highest strength (180 mcg).
- 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.
- Median plasma concentration-time profiles and PK parameters showed that subjects treated with racemic albuterol were exposed to much higher concentrations of (S)-albuterol compared with (R)-albuterol. The median of the ratios of Cmax and AUC(0-last) of (S)-albuterol compared with (R)-albuterol across dose levels were approximately 1.6- and 2.3-fold higher, respectively.
- For the primary efficacy endpoint, there was a trend for dose-response with increasing doses of levalbuterol, however, the difference between the 1X and 4X dose levels was not statistically significant for this endpoint.
- Based on the percent decreases from visit postdose/pre-challenge FEV_1 (a secondary endpoint) a dose response was observed with a maximum response observed for the 2x dose. No difference was observed between the 2x and 4x dose.

CONCLUSIONS

- The exposure (AUC) of levalbuterol increases less than proportional to the dose for the highest dose. The exposure (AUC) of racemic albuterol increases less than proportional to the dose when comparing the lowest to the middle dose.
- A trend of dose-response for efficacy for levalbuterol was observed in the range of 45- to 180 mcg based on the primary efficacy endpoint. Based on a secondary endpoint, it appears that the maximum response to efficacy is achieved at 90 mcg.
- A dose response for racemic albuterol was observed; the difference between 90 µg and 360 µg racemic albuterol was significant.

" A CUMULATIVE DOSE TOLERABILITY STUDY OF LEVALBUTEROL HFA AND RACEMIC ALBUTEROL HFA IN SUBJECTS TWELVE YEARS OF AGE AND OLDER WITH ASTHMA "

Protocol No.:	051-309
Development Phase of Study:	Phase II

Objectives

Primary Objective

- To compare the safety and tolerability of cumulative dosing with levalbuterol HFA MDI (16 cumulative actuations, 45 μg each) versus racemic albuterol HFA MDI (16 cumulative actuations, 90 μg each).

Secondary Objectives

- To investigate the efficacy of cumulative dosing with levalbuterol HFA MDI versus racemic albuterol HFA MDI in adolescent and adult subjects with asthma, to investigate the relative potency of levalbuterol and racemic albuterol HFA MDIs based on improvement in FEV1, and to summarize plasma concentrations of (R)- and (S)-albuterol.

Methodology

This was a randomized, modified-blind, active-controlled, multicenter, two-way crossover study of up to three weeks in duration. The study consisted of a screening visit (Visit 1) followed by a seven-day (±2 days) period to ensure completion of safety laboratory analysis and a thorough washout of excluded medication. At Visit 2, subjects were notified of eligibility via a telephone valuation. At Visit 3, subjects were randomized to one of two treatment sequences (A→B or B→A): A) levalbuterol HFA MDI (16 cumulative actuations, 45 μg each) or B) racemic albuterol HFA MDI (16 cumulative actuations, 90 μg each). Dosing occurred every 30 minutes over a 2-hour period followed by an 8-hour safety observation period. Following a seven-day (±2 days) washout period, the second treatment period (Visit 4) began. Following a three-day (±1 day) washout period, Visit 5 included the final safety evaluation. Pirbuterol (0.2 mg per actuation) was provided as rescue medication to be used as needed throughout the study.

No. of Subjects: Planned: 32 (completed), Enrolled: 49, Randomized: 49, Completed: 43.

Diagnosis and Main Criteria for Inclusion: Male or female subjects at least 12 years of age with a documented diagnosis of asthma of at least six months duration prior to Visit 1, no steroid use within 21 days prior to Visit 1, a baseline FEV1 between 45% and 75% (inclusive) of predicted, and a ≥15% reversibility of airflow obstruction within 15 to 30 minutes following inhalation of racemic albuterol MDI (2 actuations of 90 μg each). Subjects were to have stable baseline asthma and have been using a β-adrenergic agonist, and/or anti-asthma anti-inflammatory medication, and/or over-the-counter asthma medication for at least six months prior to Visit 1.

Test Product: Levalbuterol tartrate HFA MDI (microcrystalline suspension of levalbuterol tartrate in HFA-134a propellant, containing ethanol and oleic acid).

Reference Product: Proventil brand of racemic albuterol sulfate HFA MDI (microcrystalline suspension of racemic albuterol sulfate in HFA-134a propellant, containing ethanol and oleic acid). All products were administered directly without a spacer for the entire study.

Rescue Medication: Maxair Autohaler brand of open-label pirbuterol was supplied as an MDI delivering 0.2 mg per actuation.

Reversibility Testing Product: Racemic albuterol was supplied as a CFC MDI delivering 90 µg of medication per actuation, based on the free base, for reversibility testing.

Dosage: Cumulative doses of levalbuterol HFA MDI (16 cumulative actuations, 45 µg each) and racemic albuterol (16 cumulative actuations, 90 µg each). Cumulative dosing for each treatment was administered without the use of a spacer according to the following schedule: one puff at 0 and 30 minutes, two puffs at 60 minutes, four puffs at 90 minutes, and eight puffs at 120 minutes.

Mode of Administration: Oral inhalation via MDI.
Lot Numbers: Levalbuterol 45 µg HFA (lot # 020539), Proventil 90 µg HFA (lot # GDE018A, Schering Plough), pirbuterol 0.2 mg (rescue medication, lot # 020089, 3M), and racemic albuterol 90 µg CFC (lot # 2BBS-530).

Duration of Treatment: One day of cumulative dosing of either levalbuterol or racemic albuterol MDI, a seven-day (±2 days) washout, and then one day of cumulative dosing of the alternate treatment.

Criteria for Evaluation
Safety: The primary endpoints were increases in heart rate and blood pressure, and changes in potassium and glucose from visit predose to post-each dose. Other safety evaluations included adverse events, vital signs, electrocardiogram measurements, clinical laboratory evaluations, physical examination findings, rescue medication use, and asthma attacks.

- *Electrocardiogram Measurements* :ECG data were recorded at Visit 1 (Screening) and Visit 3 through Visit 5. At Visit 1, ECGs were performed after predose spirometry and prior to reversibility testing. During Visits 3 and 4, ECGs were performed prior to spirometry at predose, 20 minutes after each cumulative dose and at 40 minutes, 1, 6, and 8 hours after the final dose (three consecutive ECGs were collected one minute apart at each time point). At Visit 5, ECGs were performed prior to spirometry and 30 minutes after spirometry testing. All ECGs were overread by a central cardiologist.
- ECG parameters collected included ventricular heart rate, QT interval, PR interval, QRS duration, QTc interval, and RR interval. All ECGs were overread at a central laboratory ( ) using standardized procedures by a licensed cardiologist. All calculations for ECG parameters were performed on the centrally overread ECGs; The average of the three consecutive measures was calculated at each time point (i.e., predose, 20 minutes after each cumulative dose, and 40 minutes, 1, 6, and 8 hours after the final dose). These average values were used for all parameter estimates and summaries. The three consecutive measures at each time point were listed only. QTc-F was the primary

QTc correction. Fredericia's QTc interval (QTc-F) and Bazett.s QTc interval (QTc-B) were calculated.

- *Potassium and Glucose Measurements:* During Visits 3 and 4, potassium and glucose levels were obtained at each visit predose, immediately prior to each cumulative dose, and 30 minutes, 4, 6, and 8 hours after the last dose. Potassium and glucose levels were also obtained at Visit 5 predose.

Drug Concentrations: All subjects had blood samples collected for analysis of plasma drug levels at Visit 1 (Screening), Visit 3, and Visit 4 when the safety laboratory samples were taken. The blood samples were collected at Visits 3 and 4 at the following intervals: predose, immediately prior to each cumulative dose, and 30 minutes, 4, 6, and 8 hours after the final dose (9 total samples per visit). Individual (R)- and (S)-albuterol plasma concentrations were determined by a validated analytical method. The limit of quantification for the assay was 0.002 ng/mL for a 2 mL plasma sample.

Efficacy: Efficacy endpoints, which were secondary, included FEV1, FVC, and FEF25-75%. Efficacy endpoints included the percent change in each of these variables from visit predose to 25 minutes after each cumulative dose. The change in FEV1, percent of predicted FEV1, and number of cumulative actuations received were also efficacy endpoints.

Statistical Methods

The primary population was the ITT population, which included all randomized subjects who received at least one dose of blinded study medication. All safety and efficacy evaluations were summarized for the ITT population.

Safety: Safety variables reported were adverse events, rescue medication use, and asthma attacks; and changes in clinical laboratory tests, vital signs, 12-lead ECG intervals, and physical examination findings.

Pharmacokinetics: Concentrations of (R)- and (S)-albuterol were summarized prior to and during cumulative dosing, and during the postdose observation period (up to eight hours postdose). The relationship between each time-matched PD parameter (change in heart rate, systolic blood pressure, diastolic blood pressure, potassium, glucose, QTc-F, QTc-B, and FEV1) and the (R)-albuterol concentration was examined using descriptive statistics and graphical presentation.

Efficacy: The efficacy endpoints were presented descriptively by treatment and cumulative dose (1X, 2X, 4X, 8X, and 16X). For each FEV1 endpoint, ANOVA methodology described for the primary safety endpoints was utilized to assess the treatment and treatment-by-log (dose) interaction; no statistical inference was performed on FVC and FEF25-75%.

RESULTS

Analytical Method

Eleven calibration standards were used in singlet ranging from 2.00 (lower limit of quantitation) to 4000 pg/mL. The average correlation coefficient for the analytical runs in this

project was 0.9988 for (R)-albuterol, and 0.9987 for (S)-albuterol. For (R)-albuterol, the inter-assay coefficients of variation of the quality controls for the analytical runs ranged from 5.15 to 7.28%, with percent differences from theoretical ranging from -2.21 to 1.35%. For (S)-albuterol, the inter-assay coefficients of variation of the quality controls for the analytical runs ranged from 5.53 to 7.11%, with percent differences from theoretical ranging from -0.598 to 0.527%. Representative chromatograms were submitted.

PHARMACOKINETICS

Mean plasma concentrations of (R)- and (S)-albuterol are shown over time in Figure 1. Plasma concentrations of (R)-albuterol and (S)-albuterol over time are summarized in Tables 1 and 2, respectively. Twenty of 46 samples had measurable predose (R)-albuterol concentrations for levalbuterol, compared with 16 of 43 samples with measurable predose (R)-albuterol concentrations for racemic albuterol. Thirteen of 46 samples had measurable predose (S)-albuterol concentrations for levalbuterol, compared with 16 of 43 samples with measurable predose (S)-albuterol concentrations for racemic albuterol. The median (R)-albuterol concentrations appear to rise in a nearly dose-proportional manner after administration of either levalbuterol or racemic albuterol (Table 1). Median plasma concentrations of (R)-albuterol following each cumulative dose of levalbuterol were approximately 10 to 28% less than those observed following the corresponding doses of racemic albuterol.

Table 1: Mean and Median Plasma Concentrations of (R)-Albuterol (ng/mL) Following Treatment with Escalating Doses of Levalbuterol or Racemic Albuterol at Visits 3 and 4 (ITT Population)

		Levalbuterol (n=47)				Racemic Albuterol (n=45)			
Dose	Time (hrs)	N	BLQ	Mean (SD)	Median (Min, Max)	N	BLQ	Mean (SD)	Median (Min, Max)
Pre-1X	Predose	46	26	0.016 (0.043)	BLQ (BLQ,)	43	27	0.013 (0.037)	BLQ (BLQ,)
Pre-2X	0.5	43	1	0.062 (0.034)	0.061 (BLQ,)	40	0	0.084 (0.054)	0.075 ( )
Pre-4X	1	45	0	0.140 (0.078)	0.135 ( )	40	0	0.159 (0.062)	0.163 ( )
Pre-8X	1.5	43	0	0.300 (0.216)	0.260 ( )	40	0	0.320 (0.118)	0.313 ( )
Pre-16X	3	44	0	0.507 (0.205)	0.469 ( )	42	0	0.625 (0.232)	0.629 ( )
30 min post-last dose	2.5	41	0	0.970 (0.410)	0.912 ( )	40	0	1.236 (0.586)	1.135 ( )
4 hrs post-last dose	4	43	0	0.302 (0.104)	0.293 ( )	44	0	0.388 (0.205)	0.346 ( )
6 hrs post-last dose	6	43	0	0.205 (0.071)	0.195 ( )	42	0	0.251 (0.076)	0.241 ( )
8 hrs post-last dose	8	40	0	0.147 (0.050)	0.139 ( )	41	0	0.182 (0.061)	0.171 ( )

Table 2: Mean and Median Plasma Concentrations of (S)-Albuterol (ng/mL) Following Treatment with Escalating Doses of Levalbuterol or Racemic Albuterol at Visits 3 and 4 (ITT Population)

		Levalbuterol (n=47)				Racemic Albuterol (n=45)			
Dose	Time (hrs)	N	BLQ	Mean (SD)	Median (Min, Max)	N	BLQ	Mean (SD)	Median (Min, Max)
Pre-1X	Predose	46	33	0.020 (0.052)	BLQ (BLQ,	43	27	0.028 (0.102)	BLQ (BLQ,
Pre-2X	0.5	43	31	0.014 (0.041)	BLQ (BLQ,	40	0	0.147 (0.123)	0.119
Pre-4X	1	45	28	0.020 (0.042)	BLQ (BLQ,	40	0	0.327 (0.149)	0.304
Pre-8X	1.5	43	28	0.047 (0.194)	BLQ (BLQ,	40	0	0.736 (0.269)	0.672
Pre-16X	2	44	26	0.021 (0.039)	BLQ (BLQ,	42	0	1.513 (0.493)	1.480
30 min post-last dose	2.5	41	32	0.013 (0.035)	BLQ (BLQ,	40	0	3.027 (1.064)	3.110
4 hrs post-last dose	4	43	25	0.011 (0.023)	BLQ (BLQ,	44	0	2.055 (0.541)	2.020
6 hrs post-last dose	6	43	21	0.013 (0.021)	0.004 (BLQ,	42	0	1.421 (0.298)	1.420
8 hrs post-last dose	8	40	26	0.011 (0.025)	BLQ (BLQ,	41	0	1.106 (0.259)	1.100

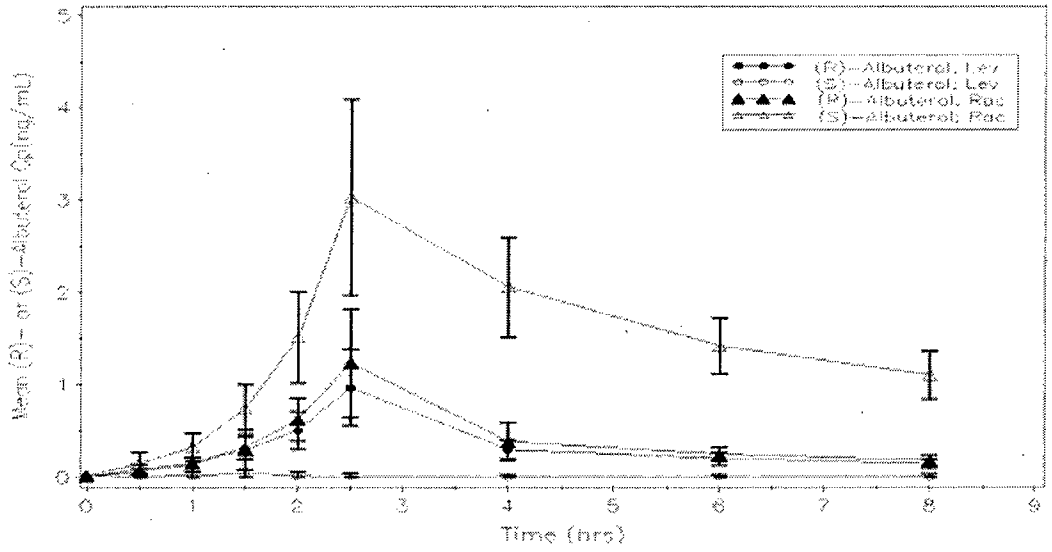

Figure 1. Mean (±SD) Plasma Concentration-Time Profiles of (R)- and (S)-Albuterol (ITT Population)

Changes in Heart Rate, Blood Pressure, Potassium, and Glucose and Time-Matched (R)-Albuterol Concentrations.

The mean change in heart rate from visit predose to each postdose time point and the corresponding time-matched mean (R)-albuterol concentration are plotted in Figure 2. The mean change in serum potassium and glucose levels from visit predose to each postdose time point and the corresponding time-matched mean (R)-albuterol concentration are plotted in Figure 3. The changes in mean heart rate, systolic blood pressure, and glucose levels generally increased with increasing mean concentrations of (R)-albuterol within each treatment group. The changes in mean diastolic blood pressure and potassium levels generally decreased with increasing mean concentrations of (R)-albuterol within each treatment group. Similar concentrations of (R)-albuterol had comparable effects on each of these safety endpoints, independent of the source of (R)-albuterol (i.e., from either the levalbuterol or racemic albuterol products.

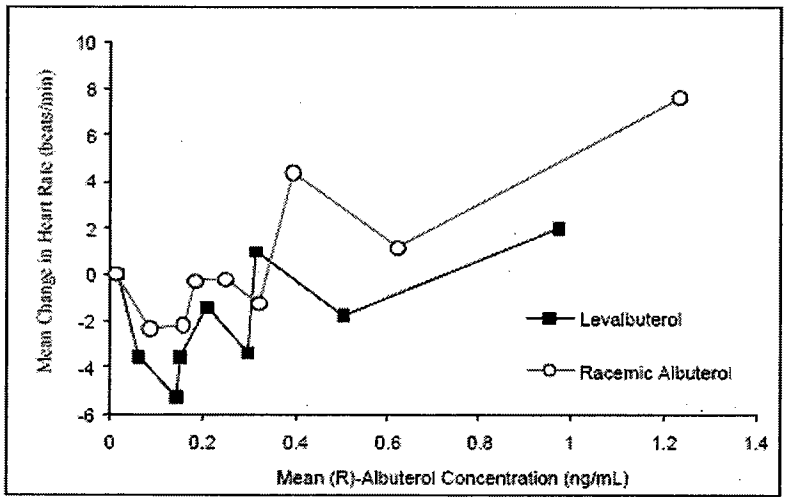

Figure 2. Time-Matched Mean Heart Rate and Mean (R)-Albuterol Concentration: Change from Visit Predose to each Postdose Time Point (ITT Population)

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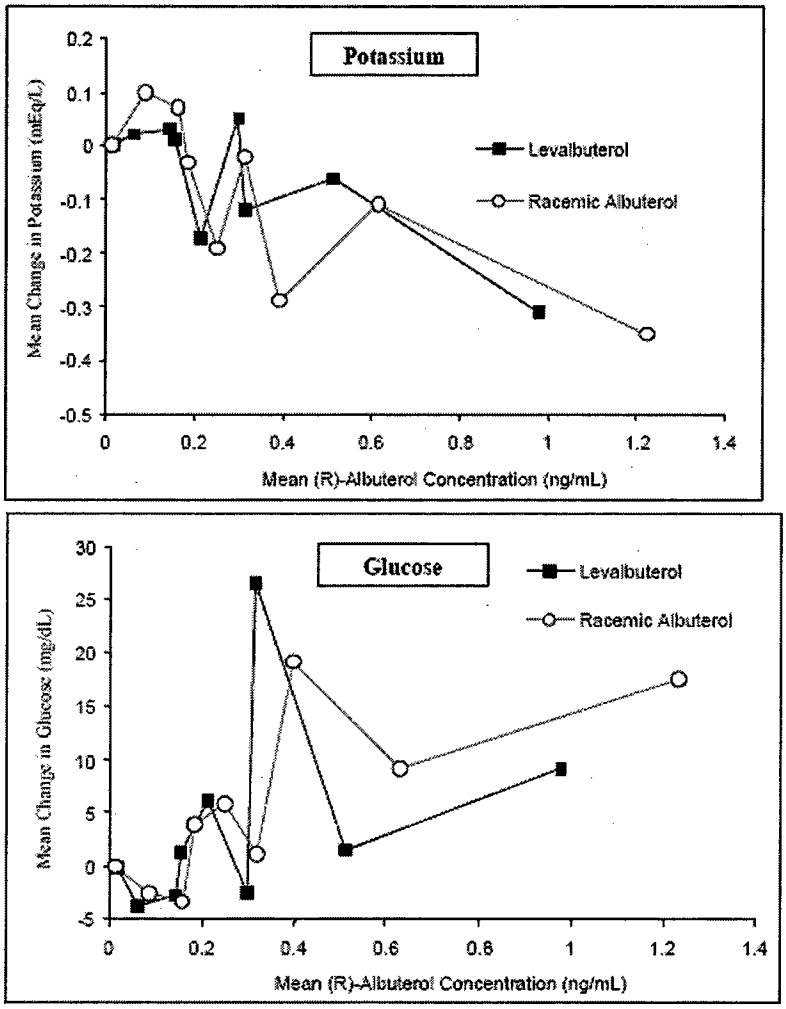


Figure 3: Time-Matched Mean Serum Potassium and Glucose Levels and Mean (R)-Albuterol Concentration: Change from Visit Predose to each Postdose Time Point (ITT Population)

Concentration-Response Relationships for Heart Rate, Blood Pressure, Potassium, and Glucose

There was an apparent trend towards increases in heart rate with increasing (R)-albuterol concentrations (Figure 2). A similar observation was made for systolic blood pressure and serum glucose. There was an apparent trend towards decreases in diastolic blood pressure with increasing (R)-albuterol concentrations. A similar observation was made for serum potassium (Figure 3).

A statistical analysis was also conducted by the sponsor to assess the relationship between exposure to (R)-albuterol and changes in PD measures (heart rate, systolic blood pressure, glucose levels, and potassium levels). There was a significant relationship between the (R)-albuterol concentration and each PD measure, with the exception of diastolic blood pressure, as indicated by the 95% confidence intervals that did not include zero. However, the (R)-albuterol-concentration-by-treatment interaction effect was not significant for each PD measure, as

indicated by the 95% confidence intervals that included zero. Thus, there was no apparent difference between the treatment groups in the nature of the PK/PD relationship.

Rate-Corrected QT Interval

The mean changes in QT_{c-F} from visit predose to 20 minutes after each cumulative dose of levalbuterol and racemic albuterol are summarized in Table 4. The LSMean changes in QT_{c-F} were not significantly different between the treatment groups, as indicated by the 95% confidence intervals that included zero. Dose-related increases in QT_{c-F} interval were observed for both levalbuterol and racemic albuterol; the greatest increases in QT_{c-F} were observed after 16X (levalbuterol LSMean: 9.4 ms, racemic albuterol LSMean: 12.7 ms). Mean changes in QT_{c-F} returned to near mean baseline values within 8 hours after the last dose of levalbuterol and racemic albuterol.

A similar trend was observed for QT_{c-B} as was observed for QT_{c-F}, with the exception of the 16X dose. The LSMean increase in QT_{c-B} from visit predose following 16X administration of racemic albuterol (20.3 beats/minute) was significantly greater than the LSMean increase for levalbuterol (14.1 beats/minute), as indicated by the 95% confidence interval that did not include zero.

No subject had QT_{c-F} values greater than 450 ms following either treatment. One levalbuterol subject had a QT_{c-F} increase greater than 60 ms (visit predose average QT_{c-F} = 368 ms; QT_{c-F} = 444 ms 40 minutes following 16X levalbuterol). A higher percentage of subjects had QT_{c-F} increases between 30 and 60 ms, QT_{c-B} values greater than 450 ms, QT_{c-B} increases between 30 and 60 ms, and QT_{c-B} increases greater than 60 ms following racemic albuterol treatment, compared with levalbuterol (Table 4)

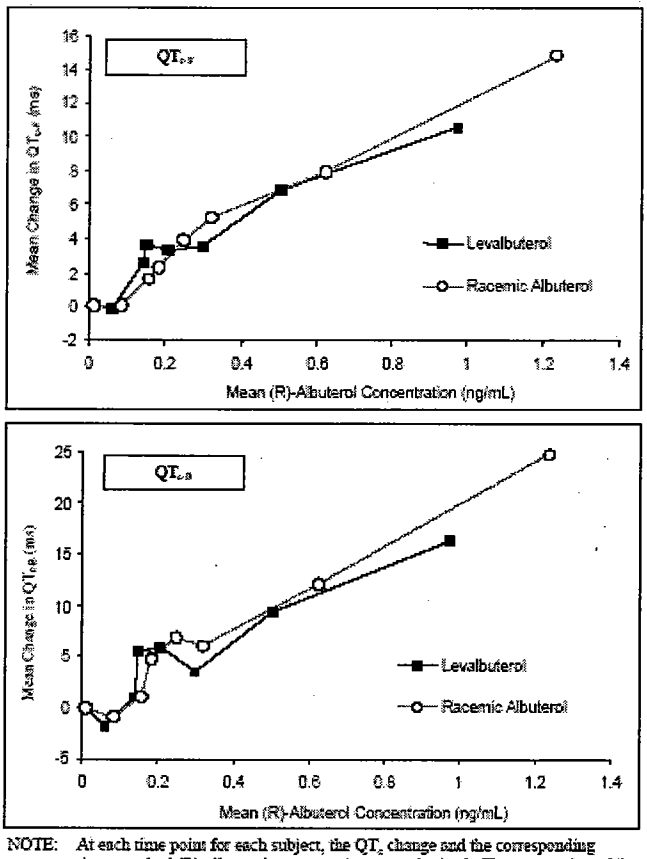
Table 3: Change in QTc-F (ms) from Visit Predose to 20-Minutes Post-Each Cumulative Dose (ITT Population)

		Levalbuterol (N=47)	Racemic Albuterol (N=45)	LSMean Diff (95% C.I.)
Post 1X Dose	Mean (SD)	-0.3 (8.0)	0.4 (9.5)	0.5
	LSMean ± SE	-0.6 ± 1.2	-1.1 ± 1.3	(-2.9, 3.9)
Post 2X Dose	Mean (SD)	2.4 (9.5)	1.7 (9.0)	-0.5
	LSMean ± SE	1.9 ± 1.2	2.4 ± 1.2	(-3.6, 2.7)
Post 4X Dose	Mean (SD)	3.9 (9.9)	4.6 (9.3)	-1.4
	LSMean ± SE	4.4 ± 1.2	5.8 ± 1.3	(-4.6, 1.9)
Post 8X Dose	Mean (SD)	7.3 (11.1)	8.1 (10.6)	-2.3
	LSMean ± SE	6.9 ± 1.4	9.2 ± 1.4	(-5.9, 1.3)
Post 16X Dose	Mean (SD)	10.0 (12.4)	14.5 (13.7)	-3.2
	LSMean ± SE	9.4 ± 1.6	12.7 ± 1.6	(-7.4, 0.9)

Table 4: Number (%) of Subjects with QTc-F and QTc-B Categories (ITT Population)

	Treatment			
	Levalbuterol N=47		Racemic Albuterol N=45	
	N (%)	Events	N (%)	Events
QT_{c-F}				
>450 ms	0		0	
Change from visit predose between 30 and 60 ms	5 (10.6)	8	7 (15.6)	11
Change from visit predose greater than 60 ms	1 (2.1)	1	0	
QT_{c-B}				
>450 ms	3 (6.4)	7	5 (11.1)	14
Change from visit predose between 30 and 60 ms	13 (27.7)	34	18 (40.0)	40
Change from visit predose greater than 60 ms	1 (2.1)	3	2 (4.4)	3

The changes in mean QT_{c-F} increased with increasing plasma concentrations of (R)-albuterol following cumulative doses of levalbuterol and reached a maximum increase following the last dose (mean concentration of 0.9697 ng/mL). QT_{c-F} also increased following cumulative doses of racemic albuterol and reached a maximum increase after the last dose (mean concentration of 1.2356 ng/mL The relationships between QT_{c-F} and (R)-albuterol concentration following administration of levalbuterol or racemic albuterol were similar. A similar trend was observed for QT_{c-B} (Figure 4).



NOTE: At each time point for each subject, the QT_c change and the corresponding time-matched (R)-albuterol concentration were obtained. The mean value of the QT_c change and time-matched concentration were then calculated and plotted for each time point.

Figure 4: Time-Matched QTc-F and QTc-B Intervals and (R)-Albuterol Concentrations: Change from Visit Predose to each Postdose Measure (ITT Population)

SUMMARY OF FINDINGS

- Changes in mean heart rate for the 1X and 2X doses did not differ significantly between the levalbuterol and racemic albuterol groups. However, the 4X, 8X, and 16X changes in mean heart rate were significantly higher for racemic albuterol compared with levalbuterol.
- The mean changes were not significantly different between the treatment groups for systolic blood pressure, diastolic blood pressure, potassium, and glucose.
- The changes in mean heart rate, systolic blood pressure, and glucose levels generally increased with increasing mean concentrations of (R)-albuterol within each treatment group. The changes in mean diastolic blood pressure and potassium levels generally decreased with increasing mean concentrations of (R)-albuterol within each treatment group. Similar concentrations of (R)-albuterol had comparable effects on each of these safety endpoints, independent of the source of (R)-albuterol (i.e., from either the levalbuterol or racemic albuterol products).
- Both median (R)- and (S)-albuterol concentrations appeared to increase proportionally with increasing doses of racemic albuterol. Median (R)-albuterol concentrations appeared to increase proportionally with dose following administration of levalbuterol.
- When subjects received racemic albuterol, median (S)-albuterol concentrations were consistently 2- to 5-fold higher, compared with (R)-albuterol.
- Median plasma concentrations of (R)-albuterol following each cumulative dose of levalbuterol were approximately 10 to 28% less than those observed following the corresponding doses of racemic albuterol.
- The changes in $QT_{c\text{-}F}$ were not significantly different between the treatment groups. Dose-related increases in $QT_{c\text{-}F}$ interval were observed for both levalbuterol and racemic albuterol; the greatest increases in $QT_{c\text{-}F}$ were observed after 16X (levalbuterol LSMean: 9.4 ms, racemic albuterol LSMean: 12.7 ms).
- Newly-emergent ECG changes (e.g., flat, biphasic, or inverted T-waves; abnormal U-waves; first degree block; sinus bradycardia; depressed ST segment; sinus pauses, arrhythmia) were experienced by 9 subjects following dosing with levalbuterol and by 10 subjects following dosing with racemic albuterol; these abnormalities resolved before discharge.
- Four subjects had ECG findings that caused discontinuation from the study.

" A CUMULATIVE DOSE TOLERABILITY STUDY OF LEVALBUTEROL HFA AND RACEMIC ALBUTEROL HFA IN SUBJECTS TWELVE YEARS OF AGE AND OLDER WITH ASTHMA "

Protocol No.:	051-310
Development Phase of Study:	Phase II

Objectives

Primary Objective

- To compare the safety and tolerability of cumulative dosing with levalbuterol HFA MDI (16 cumulative actuations, 45 μg each) versus racemic albuterol HFA MDI (16 cumulative actuations, 90 μg each).

Secondary Objectives

- To investigate the efficacy of cumulative dosing with levalbuterol HFA MDI versus racemic albuterol HFA MDI in adolescent and adult subjects with asthma, to investigate the relative potency of levalbuterol and racemic albuterol HFA MDIs based on improvement in FEV1, and to summarize plasma concentrations of (R)- and (S)-albuterol.

Methodology

This was a randomized, modified-blind, active-controlled, multicenter, two-way crossover study of up to three weeks in duration. The study consisted of a screening visit (Visit 1) and was followed by a one-week single-blind placebo run-in period (initiated at Visit 2). At Visit 3, subjects were randomized to one of two treatment sequences (A→B or B→A): A) levalbuterol HFA MDI (16 cumulative actuations, 45 μg each) or B) racemic albuterol HFA MDI (16 cumulative actuations, 90 μg each). Pirbuterol was provided as rescue medication to be used as needed throughout the study.

No. of Subjects: Planned: 24 (completed), Enrolled: 34, Randomized: 32, Completed: 30.

Diagnosis and Main Criteria for Inclusion: Male or female subjects at least 12 years of age with a documented diagnosis of asthma for at least six months prior to Visit 1, a baseline FEV1 between 45% and 80% of predicted, and a ≥12% reversibility of airflow obstruction within 15-30 minutes following inhalation of
racemic albuterol MDI (2 actuations of 90 μg each). Subjects were to have been using either a R-adrenergic agonist, and/or over-the-counter asthma medication for at least six months prior to Visit 1.

Test Product: Levalbuterol tartrate in an MDI delivering 45 μg of medication (as free base), vehicle (oleic acid and ethanol) and propellant (HFA 134a) in each actuation. Placebo was supplied as an MDI delivering vehicle and propellant only.

Reference Product: Proventil HFA brand of racemic albuterol as an MDI delivering 90 μg of medication (as free base), vehicle (oleic acid and ethanol), and propellant (HFA 134a) in each actuation.

All products were administered via a plastic spacer

Rescue Medication: Maxair⇔ Autohaler⇔ brand of pirbuterol as an MDI delivering 0.2 mg per actuation.

Dosage: Cumulative doses of levalbuterol HFA MDI (16 cumulative actuations, 45 µg each) and racemic albuterol (16 cumulative actuations, 90 µg each).

Mode of Administration: Oral inhalation.

Lot Numbers: Levalbuterol 45 µg (lot # 2A260), racemic albuterol 90 µg (lot # GCD011A, Schering Plough), placebo (lot # 2A221), and pirbuterol (rescue medication, lot # 020089, 3M).

Duration of Treatment: One-week of single-blind placebo, followed by one day of cumulative dosing of either levalbuterol or racemic albuterol MDI at Visit 3, a seven-day washout, and then one day of cumulative dosing of the alternate treatment at Visit 4.

Criteria for Evaluation

Safety: The primary endpoints were increases in heart rate and blood pressure, and changes in potassium and glucose from visit predose to post-each dose. Other safety evaluations included adverse events, vital signs, electrocardiogram measurements, clinical laboratory evaluations, physical examination findings, rescue medication use, and asthma attacks.

Electrocardiogram Measurements : ECG data were recorded at Visit 1 (Screening) and Visit 3 through Visit 5. At Visit 1, ECGs were performed after spirometry and prior to reversibility testing. During Visits 3 and 4, ECGs were performed prior to spirometry at predose, 20 minutes after each cumulative dose at 30, 60, 90, and 120 minutes, and 1, 6, and 8 hours after the final dose. At Visit 5, ECGs were performed prior to spirometry and 30 minutes after spirometry testing. All ECGs were overread by a central cardiologist.

- ECG parameters collected included ventricular heart rate, QT interval, PR interval, QRS duration, QTc interval, and RR interval. QTc-F was the primary QTc correction. Fredericia's QTc interval (QTc-F) and Bazett.s QTc interval (QTc-B) were calculated.

Potassium and Glucose Measurements: During Visits 3 and 4, potassium and glucose levels were obtained at each visit predose, immediately prior to each cumulative dose, and 30 minutes, 4, 6, and 8 hours after the last dose. Potassium and glucose levels were also obtained at Visit 5 predose.

Drug Concentrations: All subjects had serial plasma drug levels tested at Visits 3 and 4 at the same time that potassium and glucose samples were taken. The blood samples were collected at the following intervals: predose, immediately prior to each cumulative dose at 30, 60, 90, and 120 minutes, 30 minutes after the final 120 minute dose, and 4, 6, and 8 hours postdose (9 total samples per visit). Individual (R)- and (S)-albuterol plasma concentrations were determined by a

validated analytical method. The limit of quantification for the assay was 0.002 ng/mL for a 2 mL plasma sample.

Efficacy: Secondary efficacy variables included FEV1, FVC, and FEF25-75%. Secondary efficacy endpoints included the percent change in each of these variables from visit predose to 25 minutes after each cumulative dose.

Statistical Methods

All subjects who received at least one dose of double-blind study medication were summarized by the treatment received (As-Treated population). All safety and efficacy evaluations were summarized for the As-Treated population.

No statistical testing was performed. For continuous variables, statistical summaries included number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries included counts and percentages. As an exploratory analysis, the potency of levalbuterol relative to racemic albuterol was assessed using the parallel line assay method as described by Finney.[1]

Pharmacokinetics: Mean cumulative plasma concentrations of (R)- and (S)-albuterol were summarized by treatment group.

Safety: Safety variables reported were adverse events, changes in clinical laboratory tests, changes in 12-lead ECG intervals and changes in physical examination findings.

RESULTS

PHARMACOKINETICS

Individual plasma concentrations of (R)- albuterol are shown over time in Figure 1. Mean (R)-albuterol plasma concentrations increased as a function of dose for both levalbuterol and racemic albuterol. However, plasma concentrations of (R)-albuterol were higher following the racemic albuterol MDI than with the levalbuterol MDI at an equivalent (R)-albuterol dose (Table 1). Mean and median plasma concentrations of (S)-Albuterol (ng/mL) following treatment with escalating doses of Levalbuterol or Racemic Albuterol at visits 3 and 4 are shown in Table 2. The ratios of LEV/RAC (R)-albuterol concentrations averaged approximately 0.63 and were similar for each cumulative dose (Table 3).

Table 1. R-Albuterol plasma concentrations (ng/mL), summaries by treatment, cumulative dose level and use of spacer

		levalbuterol		Racemic albuterol	
		With spacer	Without spacer*	With spacer	Without spacer*
Pre-1x Dose	Mean (SD) Median	0.03 (0.06) 0.05	0.016 (0.04) BLQ	0.03 (0.03) 0.01	0.013 (0.04) BLQ
Pre-2x Dose	Mean (SD) Median	0.3 (0.1) 0.4	0.06 (0.03) 0.06	0.17 (0.09) 0.14	0.084 (0.05) 0.075
Pre-4x Dose	Mean (SD) Median	0.15 (0.07) 0.12	0.14 (0.08) 0.14	0.27 (0.09) 0.26	0.16 (0.06) 0.16
Pre-8x Dose	Mean (SD) Median	0.28 (0.15) 0.28	0.3 (0.22) 0.26	0.5 (0.21) 0.47	0.32 (0.12) 0.31
Pre-16x Dose	Mean (SD) Median	0.64 (0.26) 0.62	0.51 (0.21) 0.47	1.12 (0.5) 1.11	0.63 (0.23) 0.63
30 min post-16x Dose	Mean (SD) Median	1.3 (0.7) 1.29	0.97 (0.41) 0.91	2.34 (1.2) 2.3	1.24 (0.59) 1.14

* Data taken from study 051-309

Table 2: Mean and Median Plasma Concentrations of (S)-Albuterol (ng/mL) Following Treatment with Escalating Doses of Levalbuterol or Racemic Albuterol at Visits 3 and 4

	Levalbuterol				Racemic Albuterol			
Dose	N	BLQ	Mean (SD)	Median (Min, Max)	N	BLQ	Mean (SD)	Median (Min, Max)
Predose	31	11	0.044 (0.094)	0.005 (BLQ, [illegible])	31	6	0.055 (0.116)	0.014 (BLQ [illegible])
Pre-2X	31	11	0.026 (0.063)	0.009 (BLQ, [illegible])	29	0	0.287 (0.151)	0.239 [illegible]
Pre-4X	28	7	0.039 (0.086)	0.009 (BLQ, [illegible])	28	0	0.521 (0.188)	0.492 [illegible]
Pre-8X	27	5	0.044 (0.097)	0.017 (BLQ, [illegible])	28	0	0.997 (0.438)	0.890 [illegible]
Pre-16X	27	7	0.056 (0.117)	0.016 (BLQ, [illegible])	30	0	2.204 (0.920)	2.150 [illegible]
30 min post-last dose	28	14	0.047 (0.108)	0.005 (BLQ, [illegible])	30	0	5.002 (2.191)	4.660 [illegible]

Table 3: (R)-Albuterol Concentration Ratios (LEV/RAC)

	Number Cumulative Actuations				
	1X	2X	4X	8X	16X
N	28	26	24	24	22
Mean (SD)	1.004* (1.901)	0.638 (0.420)	0.647 (0.379)	0.631 (0.403)	0.662 (0.354)
Median	0.552	0.454	0.573	0.548	0.629
Min, Max	0.14, 10.50	0.11, 1.82	0.16, 1.60	0.17, 2.14	0.23, 1.70

NOTE: The (R)-albuterol concentration ratio was defined as the levalbuterol (R)- concentration value divided by the racemic albuterol (R)- concentration value.

* Mean LEV/RAC ratio higher following 1X dosing when compared with the other cumulative doses due to one subject with a mean ratio of 10.50.

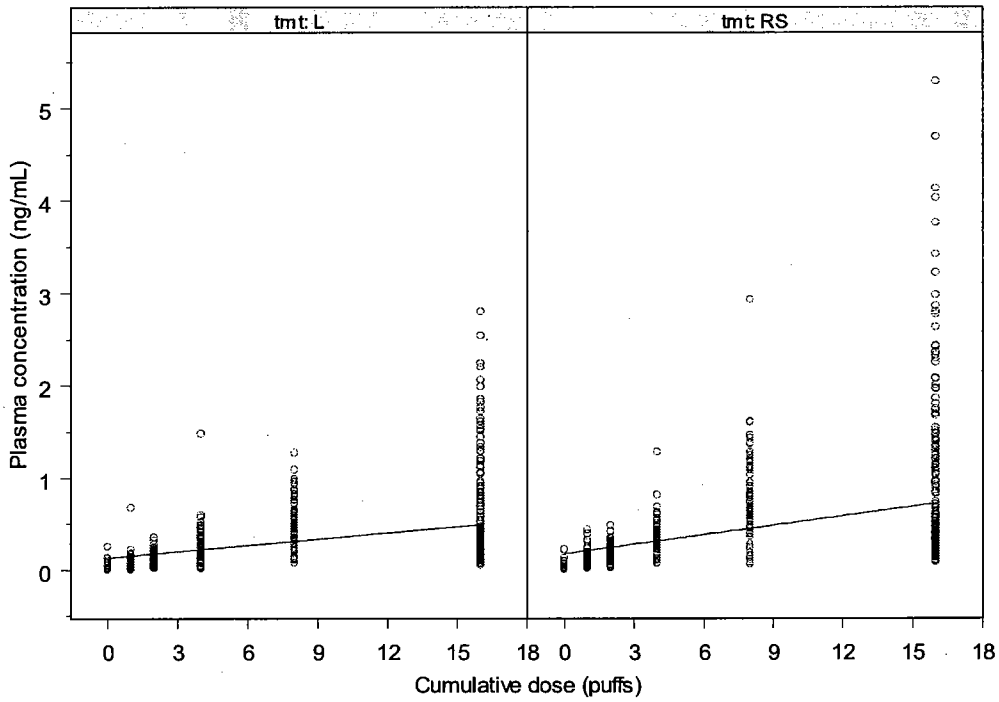


Figure 1. Mean (±SD) Plasma Concentration-Time Profiles of (R)- and (S)-Albuterol (ITT Population)

Concentration-Response Relationships for Safety Outcomes

The time-matched plasma potassium and glucose levels and (R)-albuterol concentrations (obtained after each cumulative dose and during the eight-hour washout) are presented in Figure 2.

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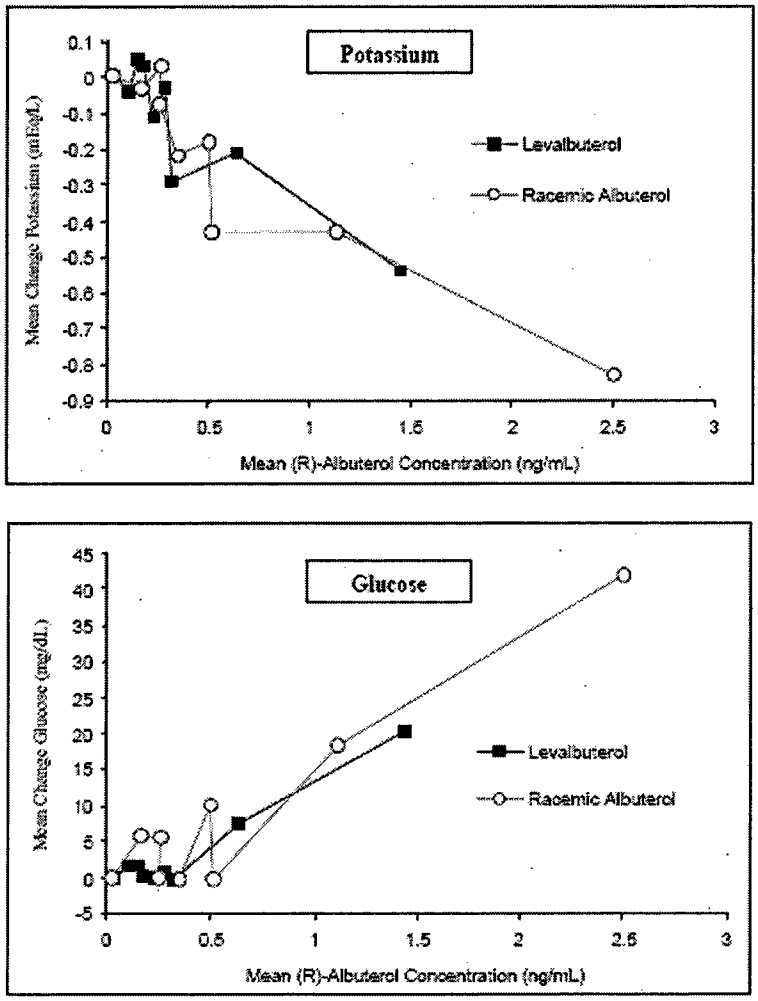

Figure 2: Time-Matched Mean Serum Potassium and Glucose Levels and Mean (R)-Albuterol Concentration: Change from Visit Predose to each Postdose Time Point (As treated).

Rate-Corrected QT Interval

ECGs showed dose- and exposure-related increases in $QT_{c\text{-}F}$ and $QT_{c\text{-}B}$ for both treatments. At the therapeutic doses (i.e., 90 µg or 2X levalbuterol and 180 µg or 2X racemic albuterol) the changes in $QT_{c\text{-}F}$ were smaller (1.9 and 3.8 ms, respectively) (Table 4). Dose-related increases in $QT_{c\text{-}F}$ and $QT_{c\text{-}B}$ intervals were observed for both levalbuterol and racemic albuterol; the greatest increases in $QT_{c\text{-}F}$ were observed after 4X racemic albuterol (9.7 ms), compared with 16X levalbuterol (8.9 ms). The maximum changes in the $QT_{c\text{-}B}$ interval were similar for both treatment groups following the 16X doses. A summary of $QT_{c\text{-}F}$ and $QT_{c\text{-}B}$ categories is provided for each cumulative dose of levalbuterol and racemic albuterol in Table 5.

Table 4: Mean (SD) Changes in QTc-F and QTc-B from Visit Predose to 20 Minutes after Each Cumulative Dose (As-Treated)

		Number Cumulative Actuations				
		1X	2X	4X	8X	16X
Change QT_{cF} (ms)						
Levalbuterol	N	31	31	31	28	28
	Mean (SD)	0.3 (13.9)	1.9 (12.4)	2.8 (13.6)	3.9 (14.3)	8.9 (18.4)
Racemic Albuterol	N	31	31	29	28	28
	Mean (SD)	1.9 (11.9)	3.8 (10.9)	9.7 (12.0)	8.3 (16.8)	4.5 (18.9)
Change QT_{cB} (ms)						
Levalbuterol	N	31	31	31	28	28
	Mean (SD)	0.1 (19.6)	3.5 (18.8)	5.0 (22.3)	9.7 (23.0)	22.3 (27.1)
Racemic Albuterol	N	31	31	29	28	28
	Mean (SD)	-0.5 (16.1)	4.0 (14.7)	13.1 (16.1)	16.4 (19.9)	22.3 (18.6)

NOTE: ECGs were centrally overread.

Table 5: Number (%) of Subjects with QTc-F and QTc-B Categories (As-Treated)

	Treatment					
	Levalbuterol N=31		Racemic Albuterol N=31		Total N=32	
	N (%)	Events	N (%)	Events	N (%)	Events
QT_{cF}						
>450 ms	0		0		0	
Change from visit predose between 30 and 60 ms	6 (19.4)	12	7 (22.6)	12	13 (40.6)	24
Change from visit predose greater than 60 ms	0		0		0	
QT_{cB}						
>450 ms	2 (6.5)	2	1 (3.2)	1	2 (3.2)	1
Change from visit predose between 30 and 60 ms	15 (48.4)	38	20 (64.5)	37	23 (71.9)	75
Change from visit predose greater than 60 ms	3 (9.7)	5	1 (3.2)	2	4 (12.5)	7

NOTE: ECGs were centrally overread.

SUMMARY OF FINDINGS

- Both (R)- and (S)-albuterol concentrations appeared to increase proportionally with increasing doses of racemic albuterol.
- (R)-Albuterol concentrations appeared to increase proportionally with dose following administration of levalbuterol, based upon inspection of the plots and tables of the mean results.
- Following treatment with racemic albuterol, mean (S)-albuterol concentrations were approximately 2- to 5-fold higher than the mean (R)-albuterol concentrations.
- Plasma concentrations of (R)-albuterol were higher after treatment with the racemic albuterol MDI than after the levalbuterol MDI; the median ratios of LEV/RAC (R)-albuterol concentrations were similar for each cumulative dose.
- Graphical examinations revealed a trend for increasing glucose concentration and decreasing potassium concentration with increasing (R)-albuterol concentrations.
- There was a trend for an increase in heart rate and systolic blood pressure with increasing (R)-albuterol concentrations when mean values were examined, which was less apparent when individual values were examined.

CONCLUSIONS

- The cumulative plasma concentrations of (R)-albuterol were higher after treatment with the racemic albuterol MDI than after the levalbuterol MDI; the median ratios of

LEV/RAC (R)-albuterol concentrations were similar for each cumulative dose and were about 0.6

- The changes in mean heart rate, blood pressure, potassium, and glucose levels increased with increasing exposure to (R)-albuterol. The relationship between these safety endpoints and (R)-albuterol concentration was similar following administration of either the levalbuterol or racemic albuterol MDIs.

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"A CUMULATIVE DOSE TOLERABILITY STUDY OF LEVALBUTEROL HFA AND RACEMIC ALBUTEROL HFA IN PEDIATRIC SUBJECTS WITH ASTHMA"

Protocol No.:	051-311
Development Phase of Study:	Phase II

Objectives

Primary Objective: To compare the safety and tolerability of cumulative dosing with levalbuterol HFA MDI (8 cumulative actuations, 45 µg each) versus racemic albuterol HFA MDI (8 cumulative actuations, 90 µg each).

Secondary Objectives: To investigate the efficacy of cumulative dosing with levalbuterol HFA MDI versus racemic albuterol HFA MDI in pediatric subjects with asthma, and summarize plasma concentrations of (R)- and (S)-albuterol (when applicable).

Methodology

This was a randomized, double-blind, active-controlled, multicenter, two-treatment and two-period crossover, cumulative dose study of up to three weeks in duration in subjects 4-11 years of age with asthma. The study consisted of a screening visit (Visit 1) and was followed by a one-week single-blind placebo run-in period (initiated at Visit 2) after satisfactory laboratory results were obtained. At Visit 3, subjects were randomized to one of two treatment sequences (A→B or B→A): A) levalbuterol HFA MDI (8 cumulative actuations, 45 µg each) or B) racemic albuterol HFA MDI (8 cumulative actuations, 90 µg each). Two cohorts of subjects received treatment as described above. The first group of randomized subjects administered MDI study medication with the [redacted] spacer and the second group of randomized subjects administered MDI study medication without the [redacted] spacer. Commercially available Xopenex Inhalation Solution 1.25 mg unit dose vials (UDVs) for use with a nebulizer and compressor were provided as rescue medication to be used as needed throughout the study.

No. of Subjects: Planned: 24 (completed), Enrolled: 35, Randomized: 31, Completed: 31 (12 subjects in spacer cohort, 19 subjects in non-spacer cohort).

Diagnosis and Main Criteria for Inclusion: Male or female subjects 4 to 11 years of age (inclusive) with a documented diagnosis of asthma for at least six months prior to Visit 1, a baseline FEV1 ≥45% and ≤80% of predicted, and a ≥12% reversibility of airflow obstruction within 15-30 minutes following inhalation of racemic albuterol MDI (2 actuations of 90 µg each). Subjects were to have been using either a β-adrenergic agonist, and/or over-the-counter asthma medication for at least six months prior to Visit 1.

Test Product: Levalbuterol tartrate HFA MDI (microcrystalline suspension of levalbuterol tartrate in HFA-134a propellant, containing ethanol and oleic acid).

Reference Product: Placebo was supplied as a vehicle-only HFA MDI (HFA-134a propellant containing only ethanol and oleic acid). Proventil HFA brand of racemic albuterol sulfate HFA MDI (microcrystalline suspension of racemic albuterol sulfate in HFA-134a propellant, containing ethanol and oleic acid).

In the first cohort of subjects (n=12), study medication was administered via a plastic spacer ( ). In the second cohort of subjects (n=19), study medication was administered without a spacer.

Rescue Medication: Commercially available Xopenex Inhalation Solution (1.25 mg UDVs) delivered with a PARI LC Plus nebulizer and a mouthpiece or face mask and a DURA-NEB 3000 compressor.

Dosage: Cumulative doses of levalbuterol HFA MDI (8 cumulative actuations, 45 µg each) and racemic albuterol (8 cumulative actuations, 90 µg each). Cumulative dosing for each treatment was administered according to the following schedule: one puff at 0 and 30 minutes, two puffs at 60 minutes, and four puffs at 90 minutes.

Mode of Administration: Oral inhalation.
Lot Numbers: Levalbuterol 45 µg (lot # 020539, 3M), racemic albuterol 90 µg (lot # GC1025A, Schering Plough), and levalbuterol 1.25 mg unit dose vials (rescue medication, lot #S2H070, Sepracor).

Duration of Treatment: Seven days of single-blind placebo, followed by one day of cumulative dosing of either levalbuterol or racemic albuterol MDI, a seven-day washout, and then one day of cumulative dosing of the alternate treatment.

Criteria for Evaluation
Safety: The primary endpoints were increases in heart rate, blood pressure, and changes in potassium and glucose from predose to each postdose measurement. Other safety evaluations included assessment of adverse events, vital signs, electrocardiogram measurements, clinical laboratory evaluations, and physical examination findings.

- *Electrocardiogram Measurements:* ECG data were recorded at Visit 1 (Screening) and Visit 3 through Visit 5. At Visit 1, ECGs were performed after spirometry and prior to reversibility testing. During Visits 3 and 4, ECGs were performed prior to spirometry at predose, 20 minutes after each cumulative dose, and 1, and 6 hours after the final dose (8 hours for subjects enrolled prior to Amendment #2). At Visit 5, ECGs were performed prior to spirometry and 30 minutes after spirometry testing. All ECGs were over-read by a cardiologist at a central facility.
- *Potassium and Glucose Measurements:* Potassium and glucose levels were obtained at Visit 1 (Screening) and Visit 3 through Visit 5. During Visits 3 and 4, potassium and glucose levels were obtained at each visit predose, immediately prior to each cumulative dose, at 30 minutes after the final 90-minutes dose, and 4 and 6 hours after the last dose (8 hours for subjects enrolled prior to Amendment #2).

Efficacy: Secondary endpoints included the percent change in FEV1, FVC, and FEF25-75% from visit predose to each postdose time point.

Drug Concentrations: All subjects had serial plasma drug levels tested at Visits 3 and 4 at the same times that potassium and glucose samples were taken. The blood samples were collected at the following intervals: predose, immediately prior to each cumulative dose at 30, 60, and 90 minutes, 30 minutes after the final 90-minute dose, and 4, and 6 hours (8 hours for subjects enrolled prior to Amendment #2) after the last dose (7 total samples per visit). Individual (R)- and (S)-albuterol plasma concentrations were determined by a validated analytical method. The limit of quantification for the assay was a nominal 0.002 ng/mL.

Statistical Methods

All subjects who received at least one dose of double-blind study medication were summarized by the treatment received (intent-to-treat [ITT] population). The ITT population consisted of two cohorts: spacers and non-spacers. The spacer cohort included subjects enrolled prior to Amendment #2, and the non-spacer cohort included subjects enrolled after Amendment #2. (Amendment #2, dated 24 April 2003, was implemented 14 May 2003 following IRB approval.) All summaries and analyses were performed for all subjects in the ITT population within each cohort. The cohorts were not combined.

No statistical testing was performed. For continuous variables, statistical summaries included number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries included counts and percentages.

Pharmacokinetics: Descriptive statistics of cumulative plasma concentrations of (R)- and (S)-albuterol were summarized by treatment group.

Safety: The primary safety comparisons were assessed with respect to changes from visit predose to each postdose measurement in heart rate, blood pressure, serum potassium, and serum glucose. Other safety variables reported were adverse events, changes in clinical laboratory tests, changes in 12-lead ECG intervals, and changes in physical examination findings.

RESULTS

PHARMACOKINETICS

Mean plasma concentrations of (R)-albuterol are shown over time in Figure 1. Plasma concentrations of (R)-albuterol and (S)-albuterol over time are summarized in Tables 1 and 2, respectively. In the spacer cohort, eight subjects receiving levalbuterol and eight subjects receiving racemic albuterol had measurable predose (R)-albuterol concentrations, and in the non-spacer cohort, nine subjects receiving levalbuterol and 12 subjects receiving racemic albuterol had measurable predose (R)-albuterol concentrations.

Although the (R)- and (S)-albuterol plasma concentrations were highly variable with both treatments, there was a clear trend for lower (R)-albuterol concentrations after administration of levalbuterol MDI as compared with racemic albuterol MDI, regardless of spacer use. Mean (R)-albuterol concentrations in subjects given levalbuterol MDI were about 25-50% less than those observed following administration of racemic albuterol. In general, those subjects who used

spacers had slightly higher (R)-albuterol concentrations than those who did not. This observation was more pronounced in subjects when given levalbuterol.

Table 1: Mean and Median Plasma Concentrations of (R)-Albuterol (ng/mL) Following Treatment with Escalating Doses of Levalbuterol or Racemic Albuterol Stratified by Spacer or Non-Spacer Use (ITT Population)

Time from 1st Dose	Cumulative Dose		Levalbuterol		Racemic Albuterol	
			Non-Spacer	Spacer	Non-Spacer	Spacer
0 (Pre-1X)	0	n	19	10	19	12
		Mean (SD)	0.027 (0.044)	0.052 (0.058)	0.051 (0.074)	0.047 (0.1)
		Median	BLQ	0.029	0.016	0.010
		Range	(BLQ, —	(BLQ, —	(BLQ —	(BLQ, —
0.5 (Pre-2X)	1	n	19	10	19	12
		Mean (SD)	0.062 (0.064)	0.111 (0.111)	0.098 (0.062)	0.15 (0.166)
		Median	0.044	0.065	0.082	0.097
		Range	(BLQ —	—	(BLQ —	—
1 (Pre-4X)	2	n	17	10	19	12
		Mean (SD)	0.1 (0.037)	0.171 (0.098)	0.174 (0.1)	0.288 (0.23)
		Median	0.106	0.130	0.145	0.159
		Range				
1.5 (Pre-8X)	4	n	19	12	17	12
		Mean (SD)	0.187 (0.096)	0.308 (0.268)	0.362 (0.258)	0.368 (0.242)
		Median	0.170	0.205	0.291	0.292
		Range				
2 (30-Minutes Post 8X)	8	n	19	10	17	11
		Mean (SD)	0.406 (0.234)	0.493 (0.366)	0.526 (0.259)	0.837 (0.788)
		Median	0.386	0.413	0.461	0.548
		Range				
5.5 (4-Hours Post 8X)	8 (Washout)	n	19	10	19	12
		Mean (SD)	0.159 (0.064)	0.157 (0.046)	0.214 (0.079)	0.217 (0.09)
		Median	0.167	0.171	0.241	0.207
		Range				

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Table 2: Mean and Median Plasma Concentrations of (S)-Albuterol (ng/mL) Following Treatment with Escalating Doses of Levalbuterol or Racemic Albuterol stratified by spacer and non-spacer use (ITT Population)

Time from 1st Dose	Cumulative Dose		Levalbuterol		Racemic Albuterol	
			Non-Spacer	Spacer	Non-Spacer	Spacer
0 (Pre-1X)	0	n	19	10	19	12
		Mean (SD)	0.020 (0.039)	0.019 (0.036)	0.073 (0.170)	0.014 (0.024)
		Median	BLQ	0.008	0.009	BLQ
		Range	(BLQ,)	(BLQ,)	(BLQ,)	(BLQ)
0.5 (Pre-2X)	1	n	19	10	19	12
		Mean (SD)	0.018 (0.036)	0.007 (0.008)	0.208 (0.153)	0.192 (0.149)
		Median	BLQ	0.005	0.175	0.140
		Range	(BLQ)	(BLQ,)	( )	( )
1 (Pre-4X)	2	n	17	10	19	12
		Mean (SD)	0.012 (0.029)	0.014 (0.020)	0.406 (0.229)	0.513 (0.281)
		Median	BLQ	0.006	0.397	0.416
		Range	(BLQ,)	(BLQ,)	( )	( )
1.5 (Pre-8X)	4	n	19	12	17	12
		Mean (SD)	0.014 (0.029)	0.020 (0.039)	0.952 (0.581)	0.834 (0.478)
		Median	BLQ	0.020	0.865	0.790
		Range	(BLQ,)	(BLQ)	( )	( )
2 (30-Minutes Post 8X)	8	n	19	10	17	11
		Mean (SD)	0.123 (0.402)	0.011 (0.012)	1.480 (0.903)	1.902 (1.442)
		Median	BLQ	0.010	1.200	1.430
		Range	(BLQ,)	(BLQ,)	( )	( )

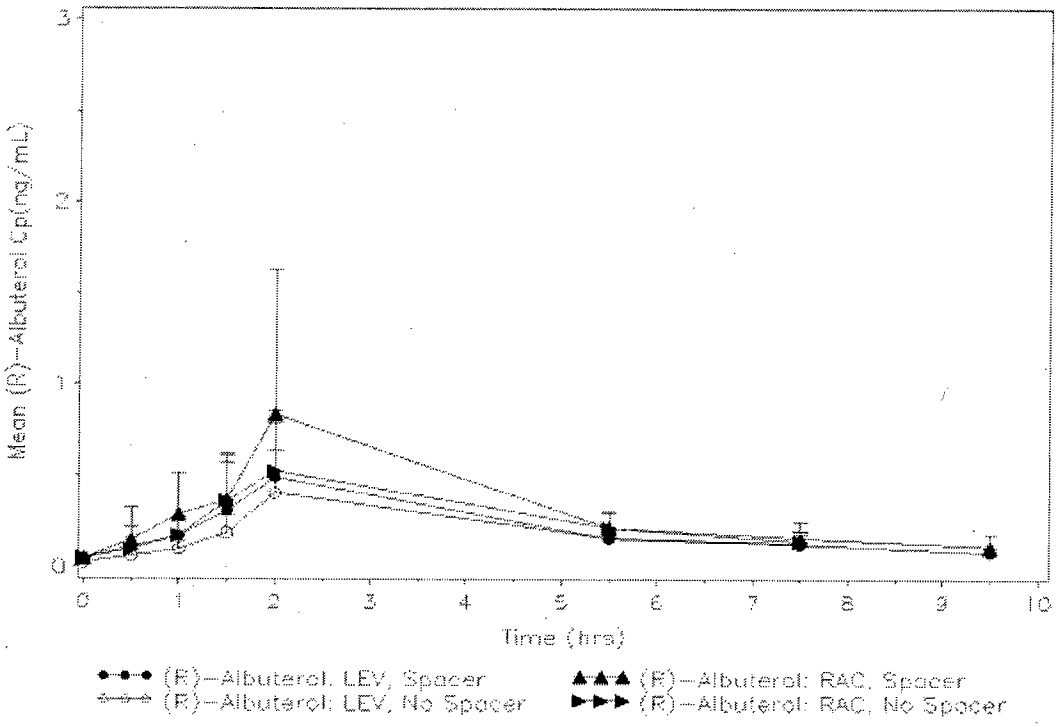

Figure 1. Mean (±SD) Plasma Concentration-Time Profiles of (R)-Albuterol (ITT Population)

Changes in Heart Rate, Blood Pressure, Potassium, and Glucose and Time-Matched (R)-Albuterol Concentrations.

A dose-related increases in heart rate occurred with both levalbuterol and racemic albuterol treatment. Subjects treated with racemic albuterol experienced greater median increases from visit predose following each cumulative dose and during the 8-hour post-last dose time period. Treatment differences were most evident 15 minutes following the 4X dose (median increases of 0.5 and 9.0 beats/minute with levalbuterol and racemic albuterol, respectively) and 8X dose (median increases of 2.0 and 14.0 beats/minute, respectively), and 30 minutes after the 8X dose (median increases of 1.0 and 17.5 beats/minute, respectively).

Changes in both systolic and diastolic blood pressure measurements were minimal following cumulative dosing with levalbuterol and racemic albuterol (Figure 2).

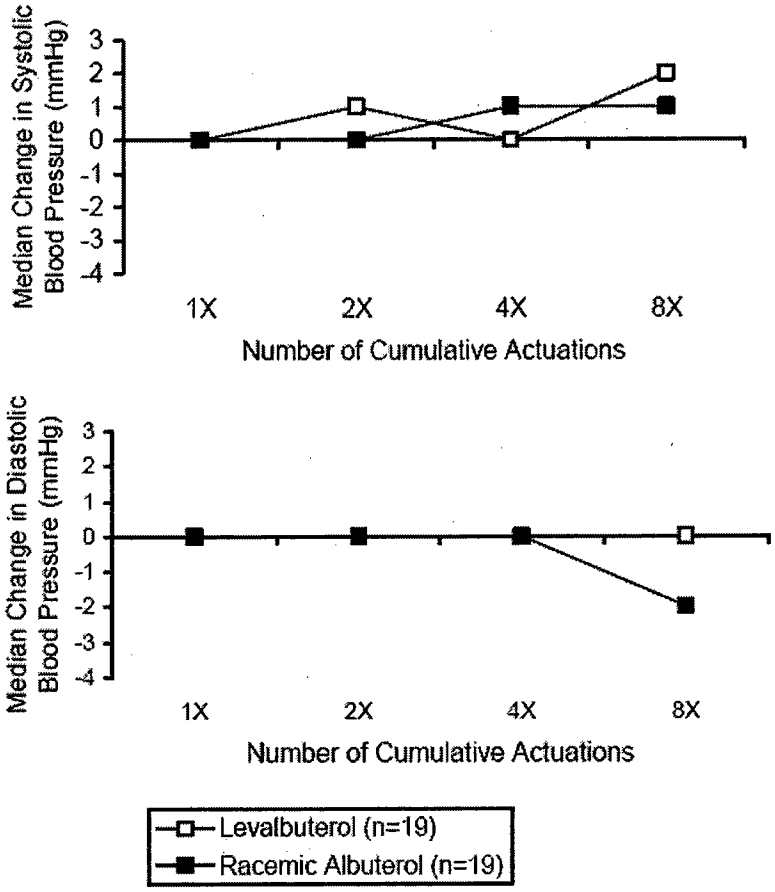

Figure 2. Median change in systolic (upper plot) and diastolic (lower plot) blood pressure (mmHg) from visit predose to the 15-minute postdose measurement following each cumulative dose level: Non-spacer cohort (ITT).

Similar dose-related declines in serum potassium were observed with both treatments. The serum potassium was lower than the predose value 30 minutes after the 1X, 2X, 4X, and 8X doses of both levalbuterol (median decreases of 0.20 mEq/L, 0.30 mEq/L, 0.55 mEq/L, and 0.80 mEq/L, respectively) and racemic albuterol (median decreases of 0.20 mEq/L, 0.40 mEq/L, 0.50 mEq/L, and 0.60 mEq/L, respectively), as well as during the 8-hour post-last dose time period (median decreases of 0.60 mEq/L, 0.35 mEq/L, and 0.50 mEq/L occurring 4-hours, 6-hours, and 8-hours, respectively, after the 8X dose of levalbuterol, and a median decreases of 0.35 mEq/L, 0.45 mEq/L, and 0.15 mEq/L occurring 4-hours, 6-hours, and 8-hours, respectively, after the 8X dose of racemic albuterol) (Figure 3).

Serum glucose increased minimally following cumulative dosing with both levalbuterol and racemic albuterol. Increases were greatest 30 minutes after the 8X dose of levalbuterol (median increase of 9.0 mg/dL) and six hours after the 8X dose of racemic albuterol (median increase of 8.5 mg/dL).

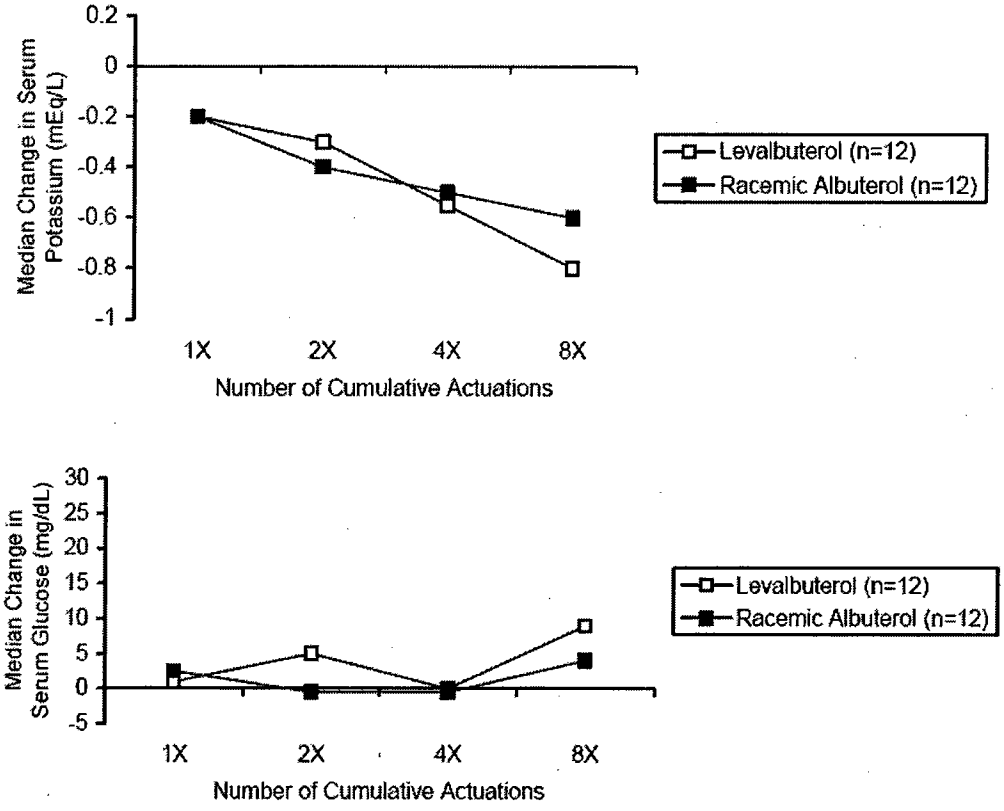

Figure 3: Median Change in Serum Potassium (mEq/L) (upper plot) and serum glucose (lower plot) from Visit Predose to the 30-Minute Postdose Measurement Following Each Cumulative Dose Level: Spacer Cohort (ITT)

For each of the key safety parameters, the changes observed with both treatments in each cohort were observed primarily following the 4X or 8X doses, with minimal to no changes occurring

following the 1X or 2X doses. The spacer cohort had greater median increases in heart rate for both treatment groups and greater median decreases in serum potassium for the levalbuterol group than the non-spacer cohort. The racemic albuterol non-spacer group had greater increases in serum glucose than the racemic albuterol spacer group. Systolic and diastolic blood pressure changed minimally in both spacer and non-spacer cohorts.

SUMMARY OF FINDINGS

- A large degree of inter-individual variability in (R)- and (S)-albuterol concentrations was observed.
- There was a trend for marginally lower (R)-albuterol concentrations after administration of levalbuterol MDI compared with racemic albuterol MDI, regardless of spacer use.
- In general, subjects who used spacers had slightly higher (R)-albuterol concentrations than those who did not. This observation was more pronounced in subjects given levalbuterol.
- For each of the key safety parameters, the changes observed with both treatments in each cohort were observed primarily following the 4X or 8X doses, with minimal to no changes occurring following the 1X or 2X doses. The spacer cohort had greater median increases in heart rate for both treatment groups and greater median decreases in serum potassium for the levalbuterol group than the non-spacer cohort. The racemic albuterol non-spacer group had greater increases in serum glucose than the racemic albuterol spacer group. Systolic and diastolic blood pressure changed minimally in both spacer and non-spacer cohorts.

CONCLUSIONS

- The plasma concentration of (R)-albuterol in children 4 to 11 year of age were lower after administration of levalbuterol MDI compared with racemic albuterol MDI regardless of spacer use.
- There were no clinically relevant differences in safety parameters between the levalbuterol HFA MDI and the racemic albuterol HFA MDI in either treatment cohort.
- Dose-related increases in heart rate and decreases in serum potassium were greater in subjects who used spacers to administer study medication, consistent with higher (R)-albuterol exposures in subjects who used spacers.

" A Dose Response Study of Levalbuterol and Racemic Albuterol HFA MDI in Pediatric Subjects with Asthma"

Protocol No.:	051-312
Development Phase of Study:	Phase II

Objectives

Primary Objective: To investigate, using an exercise challenge approach, the dose response of levalbuterol HFA MDI in pediatric subjects with asthma.

Secondary Objectives: 1) To compare levalbuterol and racemic albuterol HFA MDI in the prevention of EIB at each dosing level. 2) To determine the safety and tolerability of levalbuterol and racemic albuterol HFA MDI in subjects with EIB.

Methodology: This was a randomized, double-blind, active-controlled, multicenter, parallel-treatment, 3 x 3 dose crossover study of three weeks duration.

No. of Subjects: Planned: 9-18 subjects per treatment arm (completed), Enrolled: 58, Randomized (19 subjects in levalbuterol treatment arm, 14 in racemic albuterol treatment arm): 33, Completed: 28 (16 subjects in levalbuterol treatment arm, 12 subjects in racemic albuterol treatment arm).

Diagnosis and Main Criteria for Inclusion: Male or female subjects between the ages of 6 to 11 years (inclusive) with a documented diagnosis of asthma for at least six months prior to Visit 1. 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 demonstrated baseline FEV1 ≥70% of predicted at Visits 1-5 and 20-50% decrease in FEV1 following both baseline exercise challenges.

Test Product: Levalbuterol tartrate in an MDI delivering 45 µg of medication per actuation (as free base), vehicle (oleic acid and ethanol) and propellant (HFA 134a).

Reference Product: Proventil brand of racemic albuterol as an MDI delivering 90 µg of medication per actuation, vehicle (oleic acid and ethanol), and propellant (HFA 134a).

Rescue Medication: Open-label levalbuterol (1.25 mg UDVs) and Proventil HFA MDI (90 µg/actuation).

Dosage: Levalbuterol 45 µg, 90 µg, and 180 µg (1, 2, and 4 actuations of 45 µg, respectively) or racemic albuterol 90 µg, 180 µg, and 360 µg (1, 2, and 4 actuations of 90 µg, respectively).

Mode of Administration: Oral inhalation via MDI.

Lot Numbers: Levalbuterol 45 µg MDI HFA (Lot # 020539), Proventil HFA 6.7g (Lot # GC1045A, Schering Plough), placebo MDI HFA (Lot # 2A221; [redacted], and levalbuterol 1.25 mg/3 mL (Lot # 04801A)

Duration of Treatment: Period I consisted of a screening visit (Visit 1) and a baseline period, which was initiated at Visit 2. The first of two qualifying exercise challenges was performed at Visit 2; the second was performed during the seven-day (±2 days) baseline period; single-blind MDI placebo was administered prior to each challenge. Following successful completion of Period I, subjects were randomized to receive levalbuterol HFA MDI (1, 2, and 4 actuations of 45 µg/actuation) or racemic albuterol HFA MDI (1, 2, and 4 actuations of 90 µg/actuation). Period II consisted of three clinic visits (Visits 3-5) at which subjects were administered study medication and an exercise challenge was performed (similar to Period 1); there was a five-day (±2 days) washout between doses. Period III consisted of a final safety visit (Visit 6/Early Termination [ET]). Levalbuterol (1.25 mg UDV) and back-up Proventil HFA MDI was provided for use as rescue medication between Visits 1 and 6.

Criteria for Evaluation:

Efficacy: The primary efficacy variable was FEV1, and was obtained at screening (Visit 1); predose, 20 minutes after dosing with single-blind study medication, and at approximately 3, 10, 20, 30, 45, and 60 minutes post-exercise challenge at Visit 2; predose, 20 minutes after dosing with double-blind study medication, and at approximately 3, 10, 20, 30, 45, and 60 minutes post-exercise challenge at Visits 3, 4,
and 5; and at the final evaluation (Visit 6/ET).

The primary efficacy parameter was the maximum percent decrease in FEV1 from visit postdose/pre-challenge FEV1. Secondary FEV1 efficacy endpoints included: FEV1 AUC(0-60 min) (percent decrease and percent change relative to postdose/pre-challenge), FEV1 AUC(0-60 min) (percent decrease and percent change relative to predose), minimum percent change in FEV1 (relative to postdose/pre-challenge and relative to predose), time to FEV1 recovery (relative to postdose/pre-challenge and relative to predose), protected/unprotected subject counts based upon maximum percent decrease in FEV1 from postdose/pre-challenge (subjects were categorized as unprotected [>20% decrease], moderately protected [between 10% and 20% decrease, inclusive], and protected [<10% decrease]), and percent change in FEV1 from visit predose to visit postdose/pre-challenge,

Safety: Safety evaluations included adverse event monitoring, vital signs, physical examinations, electrocardiogram (ECG) measurements, potassium and glucose levels, and clinical laboratory findings.

Pharmacokinetics: No blood samples for PK analysis were analyzed.

Statistical Methods

Efficacy: For continuous variables, statistical summaries included means, medians, standard deviations, maxima, and minima, and 95% confidence interval of the mean. For categorical variables, statistical summaries included counts and percentages.

Efficacy parameters were summarized descriptively by treatment (levalbuterol and racemic albuterol and dose level (1X, 2X, and 4X). In addition, a graphical display of the mean and median values at each treatment and dose level were used to assess the within treatment dose

response. No statistical inference was performed. The maximum percent decrease in FEV1 relative to postdose/pre-challenge was categorized (unprotected [>20% decrease], moderately protected [between 10-20% decrease, inclusive], and protected [<10% decrease]) and summarized by treatment and dose level.

Safety: Adverse events, vital signs, ECG measurements, and potassium and glucose levels were summarized by treatment and dose. Descriptive statistics were presented for vital signs, ECG measurements, potassium and glucose levels, clinical laboratory findings, and physical examinations. Changes from predose or postdose/pre-challenge to selected postdose or post-challenge were summarized by descriptive statistics for vital signs, ECG measurements, and potassium and glucose levels.

RESULTS

Dose-Response

The maximum percent decrease in FEV1 from visit postdose/pre-challenge, is presented by treatment and dose level in Figure 1 and Table 1. The percent decreased from post-dose/pre-challenge FEV1 AUC is presented in Figure 2. 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 protective effect. Despite significant decreases in FEV1 following baseline exercise challenges in this population of subjects (median decreases in FEV1 ranging from 23.8% to 28.5%), a single actuation afforded nearly complete protection. In general, there was no dose response for either the levalbuterol MDI or the racemic albuterol MDI. The degree of bronchoprotection did not appear to improve much beyond that which was observed after administration of the 1X doses.

Table 1. Maximum Percent Decrease in FEV1 from Visit Postdose/Pre-Challenge (EVAL)

	Levalbuterol			Racemic Albuterol		
	45 µg (1X) (n=16)	90 µg (2X) (n=17)	180 µg (4X) (n=17)	90 µg (1X) (n=13)	180 µg (2X) (n=13)	360 µg (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 zero, it was set to zero.

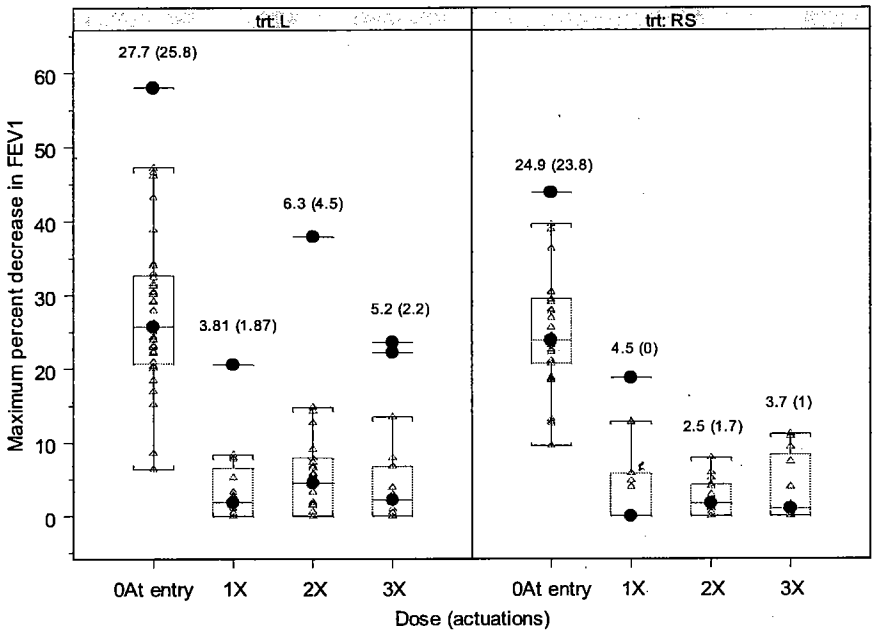

Figure 1. Individual (number represent mean, (median)) maximum percent decrease in FEV1 post-dose/pre-challenge.

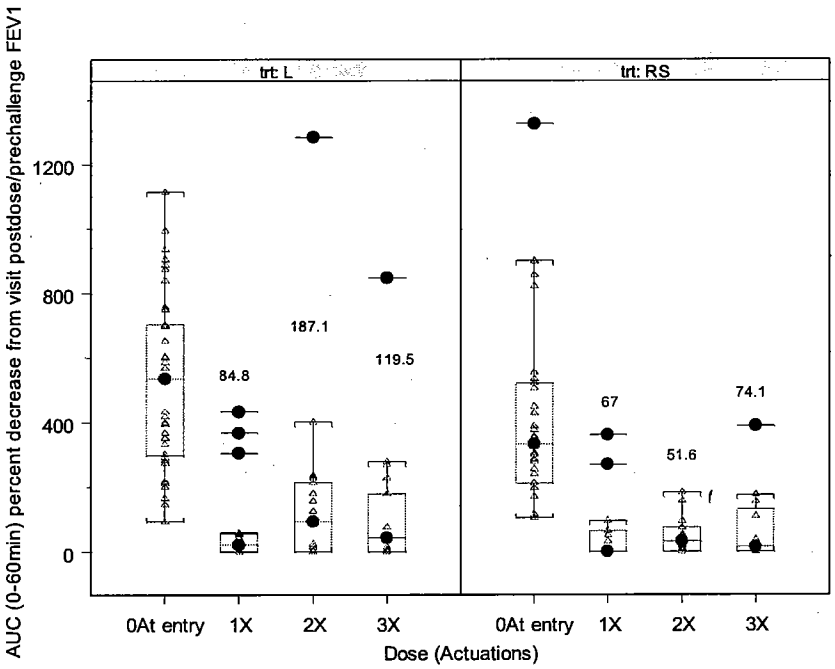

Figure 2. Individual Area Under the Percent Decrease from Visit Postdose/Pre-Challenge FEV1 Curve (0-60 minutes.

Safety

Increases in heart rate, blood pressure (systolic and diastolic), and respiratory rate were greatest immediately post-challenge and appeared to be related to exercise rather than treatment or dose, because similar increases in these parameters were observed during the qualifying challenges with placebo, and no dose response was observed.

There were no subjects with a clinically significant EGG abnormality or clinically significant changes in $QT_{c\text{-}F}$ or $QT_{c\text{-}B}$.

SUMMARY OF FINDINGS

- A dose-response relationship was not observed with either treatment. The median decreases maximum percent decrease in from visit postdose/pre-challenge in FEV1 were 1.87%, 5.82%, and 2.24% with 45 µg, 90 µg, and 180 µg doses of levalbuterol, respectively, and were 0.00%, 1.70%, and 1.00% with the comparable doses of racemic albuterol, respectively.
- Increases in heart rate, blood pressure (systolic and diastolic), and respiratory rate were greatest immediately post-challenge and appeared to be related to exercise rather than treatment or dose, because similar increases in these parameters were observed during the qualifying challenges with placebo, and no dose response was observed.
- There were no subjects with a clinically significant EGG abnormality or clinically significant changes in QTc-F or QTc-B.

CONCLUSIONS

- It appears that 45 mcg is as effective than the 90 mcg dose. Therefore, the use of the 90 mcg dose in the phase III clinical trial in pediatrics is not justified.

" An Efficacy and Safety Study of Levalbuterol, Racemic albuterol and Placebo in Subjects Twelve Years of Age and Older with Asthma"

Protocol No.:	051-353
Development Phase of Study:	Phase III

Objectives

Primary Objective

- To investigate the efficacy of levalbuterol 90 μg (2 actuations, 45 μg each) versus placebo (2 actuations) in the treatment and prevention of bronchoconstriction in adolescent and adult subjects with asthma, with both treatments administered QID.

Secondary Objectives

- To investigate the efficacy of levalbuterol 90 μg versus racemic albuterol 180 μg; to characterize the pharmacokinetics of (R)-albuterol and (S)-albuterol in subjects 12 years of age and older with asthma; to determine the safety and tolerability of levalbuterol.

Methodology: Multicenter, randomized, double-blind, placebo- and active-controlled, parallel group study of up to nine weeks in duration. 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 μg levalbuterol, 180 μg racemic albuterol, or placebo. Randomization occurred in a 2:1:1 ratio of levalbuterol to racemic albuterol to placebo. All study medication was administered as 2 actuations QID for 8 weeks.

No. Of Subjects: 500 subjects enrolled, 445 subjects randomized, 389 (87.4%) subjects completed the double-blind treatment period.

Diagnosis and Main Criteria for Inclusion: Male or female subjects ≥12 years of age with at least a 6-month history of non-life-threatening asthma, a baseline FEV1 of ≥45% to ≤75% of predicted, and with a ≥12% reversibility of airflow obstruction within 15-30 minutes following inhalation of 180 μg racemic albuterol. Subjects were using a β-adrenergic agonist, and/or an anti-asthma anti-inflammatory medication, and/or an over-the-counter asthma medication for at least 6 months prior to Visit 1.

Test Product: Levalbuterol tartrate HFA MDI (microcrystalline suspension of levalbuterol tartrate in HFA-134a propellant, containing ethanol and oleic acid).

Reference Product: Placebo was supplied as vehicle-only HFA MDI (HFA-134a propellant containing only ethanol and oleic acid). Proventil brand of racemic albuterol sulfate HFA MDI (microcrystalline suspension of racemic albuterol sulfate in HFA-134a propellant containing ethanol and oleic acid).

Rescue Medication: Racemic albuterol CFC MDI (90 μg per actuation) was supplied as rescue medication for all subjects during the run-in period, and for subjects who received double-blind

placebo and racemic albuterol treatment; levalbuterol (45 µg per actuation) was supplied as rescue medication for subjects who received double-blind levalbuterol treatment.

Reversibility Testing Product: Racemic albuterol was supplied as a CFC MDI delivering 90 µg of medication per actuation, based on the free base, for reversibility testing of all subjects.

Dosage: 90 µg levalbuterol (2 actuations of 45 µg); 180 µg racemic albuterol (2 actuations of 90 µg).

Mode of Administration: Oral inhalation.

Lot Numbers: Levalbuterol 45 µg HFA MDI (Lot #2A260, [redacted]; PLACEBO HFA MDI (Lot #2A221, [redacted]; Proventil HFA 6.7g (Lot # GCD011A, Schering); PLACEBO MDI (to match racemic) (Lot #CM020023 and #CM020024, 3M).

Duration of Treatment: One week of single-blind placebo followed by eight weeks of double-blind placebo, levalbuterol, or racemic albuterol QID.

Criteria for Evaluation

Efficacy: The primary efficacy variable was forced expiratory volume in one second (FEV1), and the primary endpoint was the peak percent change in FEV1 from visit predose averaged over the 8-week double-blind period, calculated as the average of the peak percent change in FEV1 values for Visits 2, 4, and 6 (ie, Week 0 [first dose], Week 4, and Week 8, respectively).

Pharmacokinetics:

All subjects had plasma drug levels tested at Visits 2, 3, and 6. Serial blood samples were obtained at the following intervals:

- Visit 2 (Randomization): predose, 1-2 hours postdose, and 4-6 hours postdose.
- Visit 3 (7 days post randomization): a predose sample was obtained with the collection of a safety laboratory sample.
- Visit 6 (28 days post randomization): predose, 15 and 30 minutes postdose, and 1, 2, 4, and 8 hours postdose.

Safety: Safety was evaluated by assessment of adverse events (AEs), clinical laboratory assessments (including potassium and glucose), physical examinations, vital signs (blood pressure, heart rate, respiratory rate, and body temperature), 12-lead ECG (ventricular heart rate, PR interval, RR interval, QT interval, QTC-F, QTC-B and QRS duration), rescue medication use, asthma control days, asthma attacks, and paradoxical bronchoconstriction.

Statistical Methods

PK

The plasma pharmacokinetic parameters for (R)-albuterol and (S)-albuterol, obtained at steady-state were determined by non-compartmental methods (AUC(0-4) was used for statistical

analysis instead of AUC(0-last) because in some subjects plasma concentrations increased after the 4-hour post-dose blood sample).

For AUC(0-4), an ANOVA with the natural logarithm of AUC as the dependent variable and treatment as a fixed effect was fitted. Relative exposure testing was performed using contrasts from the overall ANOVA model. Relative exposure was assessed by estimating the geometric mean ratio and the 90% confidence interval of the geometric mean ratio of AUC(0-4) with the racemic albuterol MDI as the reference formulation. Treatments were considered to have comparable relative exposure if the 90% confidence interval of the ratio fell within 80% to 125%. The relative exposure analyses were the same for Cmax.

Safety: Safety variables reported were adverse events, changes in clinical laboratory tests, changes in 12-lead ECG intervals and changes in physical examination findings.

RESULTS

PHARMACOKINETICS

Median plasma concentrations at steady state of (R)- and (S)-albuterol following 90 mg Levalbuterol HFA MDI or 180 mg Proventil HFA MDI dosing are shown in Figure 1. According to the sponsor, median concentrations are presented because they represent a better measure of central tendency given the skewness in the distribution of concentrations across the population. Mean and median PK parameters are summarized in Table 1. Summary statistics for (R)-albuterol pharmacokinetic parameters following administration of Levalbuterol HFA MDI and Proventil HFA MDI are presented in Table 2. Figure 2 and 3 show the individual Cmax and Tmax and AUC following administration of the treatments, respectively.

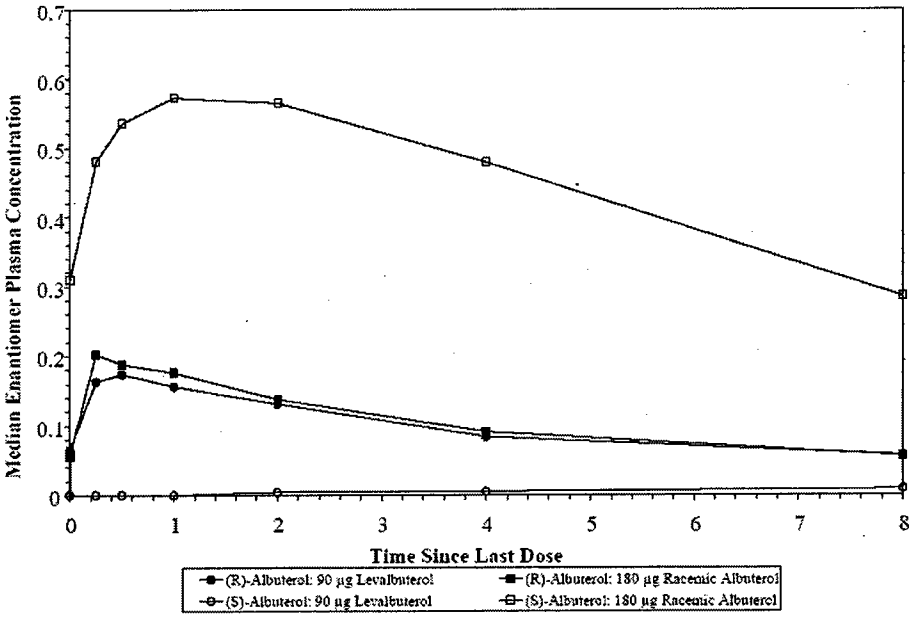

Figure 1: Median (R)- and (S)-Albuterol Plasma Concentration Versus Time Profiles in Subjects Following Multiple (QID) Dosing of 90 µg Levalbuterol HFA MDI and 180 µg Proventil® HFA MDI (Visit 6, Day 56) (Study 051-353)

Table 1: Summary Statistics of the Pharmacokinetic Parameters for (R)-Albuterol Following Multiple (QID) Dosing of 90 µg Levalbuterol HFA MDI and 180 µg Proventil HFA MDI (Visit 6, Day 56) (Study 051-353)

	90 µg Levalbuterol HFA MDI			**180 µg Proventil HFA MDI**		
	(R)-Albuterol			**(R)-Albuterol**		
	n	**Mean (SD)**	**Median (Min-Max)**	**n**	**Mean (SD)**	**Median (Min-Max)**
C_{max} (ng/mL)	182	0.314 (0.753)	0.198 (0.045 – 9.900*)	102	0.286 (0.228)	0.227 (0.036 – 1.480)
t_{max} (hr)	182	0.85 (1.07)	0.52 (0.0 – 8.0)	102	0.72 (0.80)	0.50 (0.0 – 4.0)
$AUC_{(0\text{-}last)}$ (ng•hr/mL)	182	1.117 (2.318)	0.737 (0.157 – 30.119)	102	0.993 (0.771)	0.821 (0.063 – 5.313)
$AUC_{(0\text{-}4)}$ (ng•hr/mL)	168	0.701 (0.909)	0.528 (0.147 – 10.320)	97	0.687 (0.460)	0.574 (0.120 – 2.72)
$R_{AUC(S/R)}$				102	4.31 (1.60)	4.04 (1.0 – 8.7)
$R_{Cmax(S/R)}$				102	3.15 (1.50)	2.85 (0.8 – 8.9)

Table 2. Relative Exposure Analysis Comparing Levalbuterol HFA MDI and Proventil® HFA MDI Treatments with Respect to (R)- Albuterol AUC(0-4) and Cmax (Visit 6, Day 56) (Study 051-353)

PK Parameter	**Geometric Mean**		**Ratio (90% confidence limits)**
	Levalbuterol HFA MDI	**Proventil HFA MDI**	
$AUC_{(0\text{-}4)}$ (ng•hr/mL)	0.550 (n=168)	0.574 (n=97)	0.959 (0.847, 1.09)
C_{max} (ng/mL)	0.216 (n=182)	0.227 (n=102)	0.949 (0.829, 1.09)

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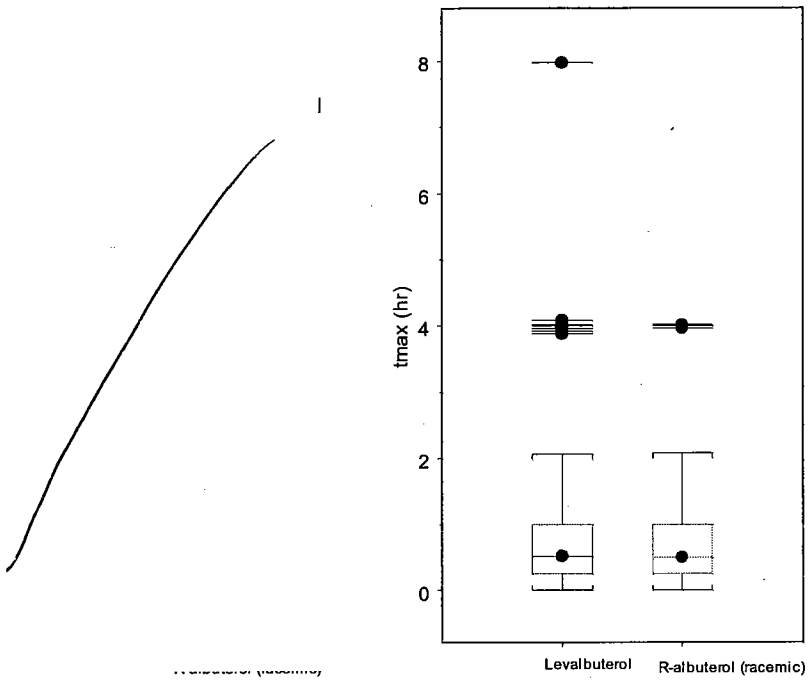

Figure 2. Individual Cmax and Tmax for R-albuterol following multiple administration of the treatments.

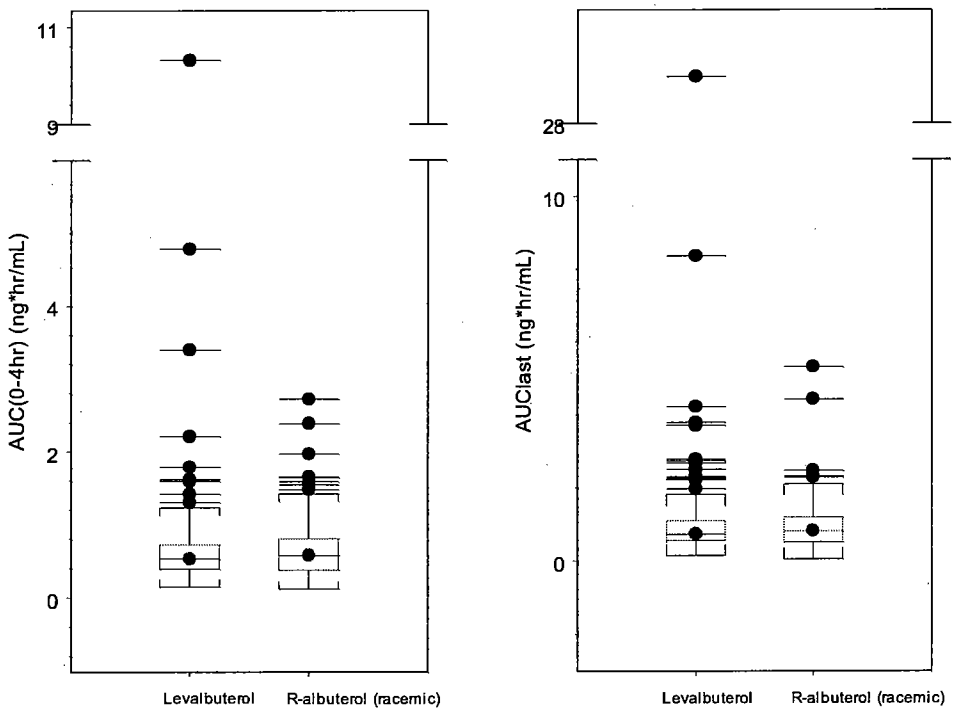

Figure 2. Individual AUC 0-4 and AUClast for R-albuterol following multiple administration of the treatments.

CONCLUSIONS

- The ratio of AUC(0-4) for Levalbuterol HFA MDI versus Proventil HFA MDI was 95.9%. The 90% confidence interval was 84.7% to 109% and is within the acceptable range of 80 to 125%.
- The corresponding values for Cmax were 94.9 and the 90% confidence interval was 82.8-109%. These results indicate that the two products provide similar (R)-albuterol exposure.

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"Population Pharmacokinetic and Pharmacodynamic Analysis of (R)- and (S)- Albuterol Following Administration of Levalbuterol and Racemic Albuterol to Adult and Pediatric Subjects"

Technical Report:	051-000-CP03
Date of Final Report:	March 18, 2004
Phase:	II and III

INTRODUCTION

The population pharmacokinetics of R- and S-albuterol were characterized in pediatric and adult asthmatic subjects (4-81 years of age) following inhalation dosing of levalbuterol or racemic albuterol via a metered dose inhaler (MDI). Data from several randomized, double-blind, active- and placebo-controlled, multi-center clinical trials (SEPR Study Nos. 051-305, 051-306, 051-353, 051-354, and 051-355) were utilized. In each trial, levalbuterol was administered via Xopenex HFA MDI, while racemic albuterol was administered via Proventil® HFA MDI or Ventolin® CFC MDI.

OBJECTIVES

Develop a validated population pharmacokinetic model that:

- characterizes the pharmacokinetic profile of (R)-albuterol and (S)- albuterol in adult and pediatric subjects given levalbuterol or racemic albuterol using an MDI;
- characterizes and compares exposure to (R)-albuterol following administration of inhalation formulations containing either levalbuterol and/or racemic albuterol; and
- evaluates the effect of patient characteristics on the key pharmacokinetic parameters of interest of (R)-albuterol and (S)-albuterol;

Description of Studies Used for Pharmacokinetic Analyses

The population PK analysis of (R)-albuterol utilized subjects enrolled in Studies 051-353, 051-354, and 051-355 who were randomized to receive either 90 µg Levalbuterol HFA MDI or 180 µg Proventil® HFA MDI. A total of 3,791 (R)-albuterol plasma concentrations were available from 632 subjects for the population PK model development. Table 1 provides a summary of demographic statistics for the population used in the analyses. Subjects enrolled in Studies 051-353 and 051-355 were 12 years of age or older with at least a 6-month history of asthma and an FEV_1 of ≥45% to ≤75% of predicted, measured prior to randomization, with a ≥12% reversibility to racemic albuterol 180 µg (2 actuations, 90 µg each). Subjects enrolled in Study 051-354 were 4-11 years of age with at least a 6-month history of asthma and an FEV1 of ≥45% to ≤80% of predicted, measured prior to randomization, with a ≥12% reversibility to Proventil HFA MDI 180 µg (2 actuations, 90 µg each).

Table 1. Summary Statistics of Subjects Included in the Population PK Analysis of (R)-Albuterol

Variable	N	Mean	SD	Min	25th %	Median	75th %	Max
Age (months)	632	391.8	210.5	50.0	195.0	390.0	560.5	981.0
Weight (kg)	632	75.2	26.0	14.5	59.0	74.8	90.7	167.5
Height (cm)	632	164.7	15.6	96.5	158.8	167.0	173.8	198.1
Body Surface Area (m^2)	632	1.9	0.4	0.6	1.7	1.9	2.1	3.0
Creatinine Clearance (mL/min)	632	129.8	43.5	41.9	100.2	122.8	151.2	310.6
Gender								
Males	310							
Females	322							
Ethnicity								
Caucasian	440							
Black	122							
Asian	15							
Hispanic	47							
Other	8							

Population PK Model for (R)-Albuterol

A comprehensive population PK model was constructed which incorporated all the data from Studies 051-353, 051-354, and 051-355. In general, plasma drug concentrations quantified from blood samples drawn after the first dose of study drug (Visit 2) and at steady-state after 4 or 8 weeks of dosing (Visit 6) were used to develop the final population PK model. Data collected from pediatric subjects enrolled in Study 051-354 were sparse (only two post-dose plasma concentrations were collected each on Visits 2 and 6). Combining these sparse data with the more richly sampled PK data from Studies 051-353 and 051-355 allowed an assessment of potential differences in the pharmacokinetics of (R)-albuterol in younger subjects (<11 years) versus adolescents (12-17 years) versus adults (≥17 years). The data were best described by a two-compartment model with first-order absorption and elimination. The base structural model was parameterized with a first-order absorption rate constant (Ka), relative bioavailability (F1), apparent total body clearance (CL/F), apparent volume of distribution in the central compartment (Vc/F), volume of distribution in the peripheral compartment (Vp/F), and intercompartmental clearance (Q). To facilitate exploration of potential differences in relative bioavailabilities between 90 µg Levalbuterol HFA MDI and 180 µg Proventil® HFA MDI, as well as between studies, several relative bioavailability parameters were included in the PK model. The data from Visit 6 of the Study 051-353 Proventil HFA MDI group was utilized as the reference for relative bioavailability (F1=1).

Scatterplots for the appropriate pharmacokinetic parameters (Ka, F1, CL, and Vc) were constructed for each available subject covariate to explore any possible and relevant relationships between PK parameters and subject descriptors. Body weight was identified as a plausible modifier of the pharmacokinetics of (R)- albuterol. The relationship between apparent clearance and body weight was linear, while the association between the apparent volume of distribution and body weight was a power function. Once body weight was incorporated into the model, no other subject covariates, including age, body surface area, creatinine clearance, gender, or race, were significant predictors of (R)-albuterol pharmacokinetics.

The population mean parameter estimates and associated precision (%SEM) for this model are listed in Table 2. The precision of estimates was reasonable. The first order absorption rate constant (Ka) for adult subjects was approximately two-fold greater than in pediatrics (6.38 versus 3.12 hr-1), although both estimates describe a very rapid absorption process. The relative bioavailability of Levalbuterol HFA MDI was numerically lower than Proventil HFA MDI in all studies. Figure 1 shows the goodness-of-fit plot for individual predicted (R)-albuterol concentrations versus the measured (R)-albuterol concentrations for the final PK model.

Table 2. Final Parameter Estimates and Standard Errors for the Two-Compartment Model Fit to the Combined Dataset

Parameter	Population Mean		Magnitude of Inter-individual Variability	
	Final Estimate	%SEM	Final Estimate	%SEM
K_a (1/hr) – adult subjects (≥ 12 years)	6.38	7.9	66.41	18.0
K_a (1/hr) – pediatric subjects (< 12 years)	3.12	15.2	72.73	31.6
CL/F (L/hr)	70.8	7.9	41.35	12.9
V_c/F(L)	505	6.9	50.00	13.1
V_p/F (L)	266	14.7		
Q (L/hr)	77.5	10.3		
V_c Power term for Body Weight	0.382	27.7		
CL Slope term for Body Weight	0.475	25.7		

In the final population PK model for (R)-albuterol, body weight was a significant predictor of the typical value of CL and Vc. Body weight was a linear predictor of the typical value of apparent clearance. The typical value of apparent central volume of distribution was a power function of body weight.

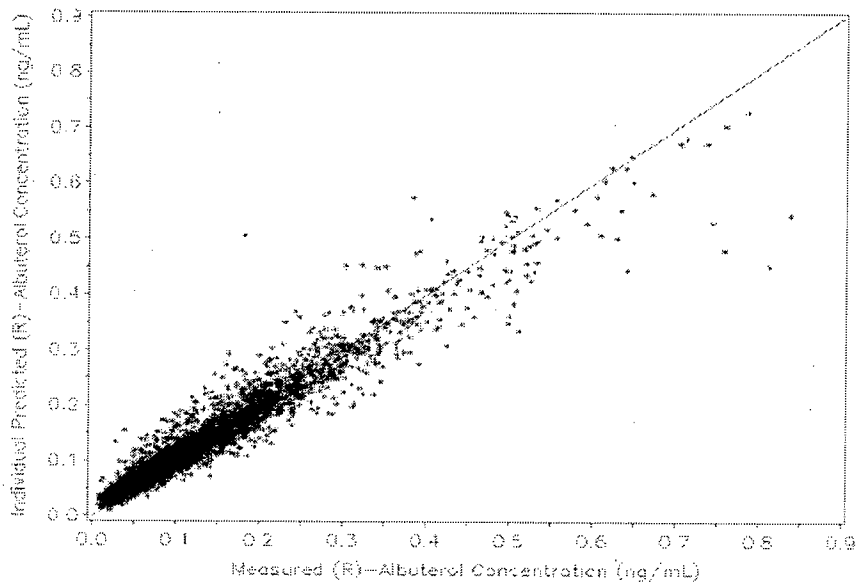


Figure 1. Goodness-of-Fit Plots for the Final Population PK Model Fit to (R)-Albuterol for the Combined Data

In order to confirm that this refined final model was appropriately accounting for all potential modifiers of PK parameters, scatterplots for the pharmacokinetic parameters (Ka, F1, CL, and Vc) were constructed for each available subject covariate, including age, weight, body surface area, creatinine clearance, gender and race. No observable trends were evident in any of these plots, suggesting that there were no covariate-parameter relationships that were unaccounted for in the PK model

Comparisons of (R)-Albuterol Pharmacokinetics between Adult and Pediatric Populations

The final PK model effectively describes the PK of (R)-albuterol in both pediatric and adult populations. Incorporation of body weight into the model as a predictor of apparent clearance and apparent central volume of distribution sufficiently accounts for any inherent pharmacokinetic differences between these two populations. Non-compartmental parameters including maximum plasma concentration (Cmax), the time to achieve Cmax (tmax), and the area under the plasma concentration-time curve from 0 to 6 hours (AUC0-6) were also calculated at steady-state from individual model-predicted plasma concentration-time profiles. Overall model determined exposures to (R)-albuterol were somewhat lower in pediatric subjects when compared to adult subjects (Table 3, Figure 2). Exposures from both Levalbuterol HFA MDI (90 μg) and Proventil HFA MDI (180 μg) were not too dissimilar in the adult population. In the pediatric population, mean predicted (R)- albuterol exposures were reduced by approximately 30% in patients receiving Levalbuterol HFA MDI compared to Proventil HFA MDI.

Table 3. Model Predicted Non-Compartmental Pharmacokinetic Parameters in Pediatric and Adult Subjects Given Levalbuterol HFA MDI or Proventil HFA MDI from the Population PK Model of Combined Studies 051-353, 051-354, and 051-355

Study Population	Parameter	Randomized Treatment	
		Levalbuterol HFA MDI	Proventil HFA MDI
Adult subjects (≥12 years) from Studies 051-353 and 051-355	C_{max} (ng/mL)	0.199 (0.108)	0.238 (0.127)
	t_{max} (hr)	0.54 (0.15)	0.53 (0.15)
	$AUC_{(0-6)}$ (ng*hr/mL)	0.695 (0.415)	0.798 (0.378)
Pediatric subjects (<12 years) from Study 051-354	C_{max} (ng/mL)	0.163 (0.089)	0.238 (0.151)
	t_{max} (hr)	0.76 (0.35)	0.78 (0.38)
	$AUC_{(0-6)}$ (ng*hr/mL)	0.579 (0.306)	0.828 (0.504)

Body Weight

In the population PK model for (R)-albuterol, body weight was a significant predictor of the typical values of CL and Vc. Body weight was a linear predictor of the typical value of apparent clearance. The typical value of apparent central volume of distribution was a power function of body weight. In the pediatric study population, body weights ranged from 14.5 to 89.4 kg. Thus, in pediatric subjects, the typical value of clearance ranged from 41.8 to 77.4 L/hr and the typical value of the central volume of distribution ranged from 268.9 to 538.7 L. In the adult patient population (body weight range: 35.8 to 167.5 kg), the typical value of clearance ranged from 51.9 to 114.5 L/hr and the typical value of the central volume of distribution ranged from 379.8 to 684.7 L.

Age

Once the effect of body weight was taken into consideration, age was not a significant predictor of (R)-albuterol exposure. Figure 2 shows a scatterplot of Bayesian predicted (R)-albuterol AUC0-4 versus age. Exposures are relatively constant over the range of ages studied, from approximately 4 to 81 years of age. Note that subjects greater than 60 years of age (n=40) and less than 12 years of age (n=81) have similar exposure to the remainder of the population.

No impact on PK was noted when race and gender were included into the model.

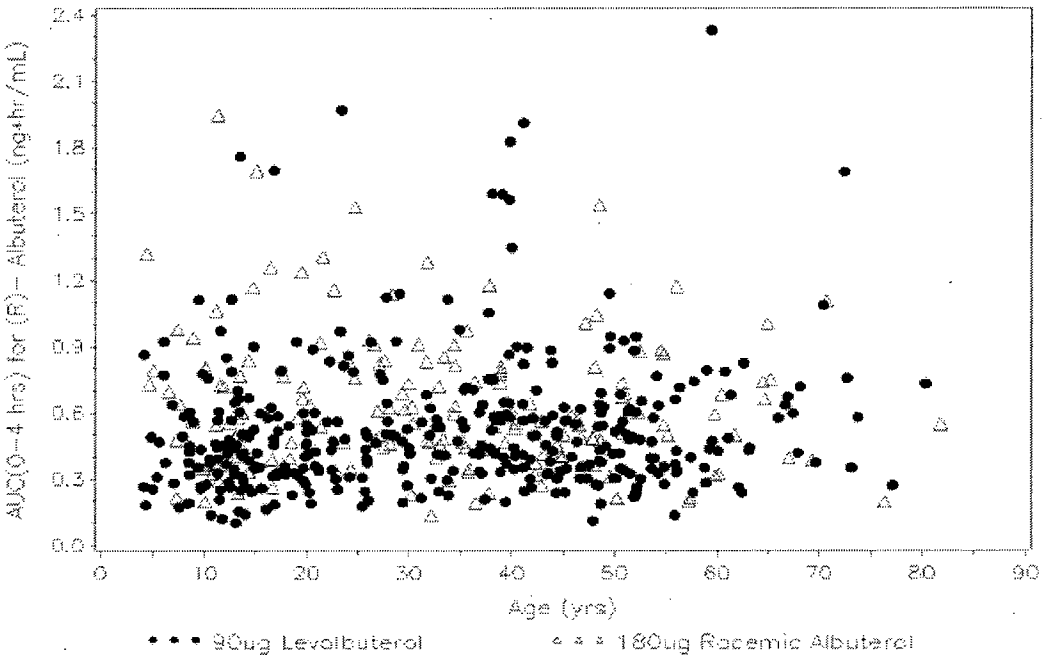


Figure 2. Scatterplot of Individual Bayesian-Predicted (R)-Albuterol AUC_{0-4} versus Age Years)

REVIEWER'S REMARKS

Dr. He Sun (pharmacometric reviewer) review the control files and data provided by the sponsor. In general, he agreed with the model performance and acknowledged the effort put by the sponsor in assessing the PK/PD of the drug. In general the models used performed well as shown by the significant reduction in the objective function values, point and interval estimates of parameters, diagnostic plots, including weighted residuals vs. predictions and observed vs. predicted values.

CONCLUSIONS

- The pharmacokinetics of (R)-albuterol after administration of Levalbuterol HFA MDI or Proventil HFA MDI were best described using a two-compartment model with inhaled administration modeled as a first-order absorption process in both pediatric and adult subjects.
- Body weight (kg) was found to be a significant predictor of both the apparent clearance (Cl/F) and apparent central volume of distribution (Vc/F) of (R)-albuterol in adults and pediatric subjects.
- Once body weight was incorporated into the (R)-albuterol population pharmacokinetic (PK) model for CL/F and Vc/F, the other subject covariates (including age, body surface area, creatinine clearance, gender, or race) had no additional predictive value.

Clinical Pharmacology and Biopharmaceutics Review

"Xopenex HFA Inhalation Aerosol for the Treatment of Bronchospasm"

NDA No.:	21-730
IND:	62,906
Sponsor:	**Xepracor**
Type:	**NDA filing package**
Drug:	**Levalbuterol**
Submission date:	**May 11, 2004**
Draft review:	**Jun 15, 2004**
Review date:	**Jun 17, 2004**
Reviewer:	**Sandra Suarez-Sharp, Ph.D.**

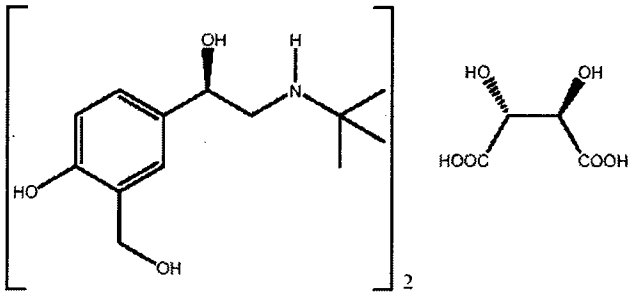
INTRODUCTION

Levalbuterol [(R)-albuterol], a potent selective β2-adrenoceptor agonist, is the (R)-isomer of the marketed product, racemic albuterol. Levalbuterol HCl Inhalation Solution (Xopenex® UDV) is currently marketed for the treatment or prevention of bronchospasm in subjects six years of age and older with reversible obstructive airway disease. The Levalbuterol HFA Inhalation Aerosol (sometimes referred to as levalbuterol HFA) development program evaluated the safety and efficacy of levalbuterol when administered via a metered dose inhaler (MDI) in adults and adolescents (≥12 years of age), and in children 4 to 11 years of age, with reversible obstructive airway disease. This NDA includes data from 12 completed clinical studies, and one ongoing safety study, utilizing single or multiple-doses ranging from 22.5 to 180 μg of Levalbuterol Inhalation Aerosol. Ten of twelve completed studies were conducted using HFA-134a as the propellant. Two early studies (Studies 051-301 and 051-304) were conducted using CFC as the propellant.

Chemistry

Drug Substance

The drug substance (R)-α1-[[(1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol L-tartrate (2:1 salt), more commonly known as levalbuterol tartrate, is a β2-adrenergic receptor agonist indicated for the treatment or prevention of bronchospasm. Levalbuterol is the pharmacologically active R-enantiomer of racemic albuterol. The molecular structure, molecular formula, and formula weight of levalbuterol tartrate are shown in Figure below:



Molecular Formula: $(C_{13}H_{21}NO_3)_2 \cdot C_4H_6O_6$
Formula Weight: 628.71

The drug substance is a — white to light-yellow solid —

Drug Product

The drug product is a pressurized metered-dose inhaler containing a suspension of micronized levalbuterol tartrate in ethanol, oleic acid and propellant HFA-134a. According to the sponsor, the ethanol and oleic acid are compendial ingredients meeting USP/NF monograph requirements.

The product is designed to deliver 45 µg levalbuterol (as free base) per actuation and a minimum of 200 actuations per canister; one dose consists of two actuations. The components and composition for the proposed commercial drug product are listed the Table 2. The batch sizes used during clinical development ranged from — to — units. The commercial batch size will be approximately — units.

Table 2. Drug Product Unit-Dose Composition

Component	Function	Amount per Actuation	Amount per Canister
Levalbuterol tartrate	Active ingredient		
Oleic Acid NF	—		
Dehydrated Alcohol USP	—		
HFA-134a	Propellant		
Total	--	60.00 mg	15.00 g

* equivalent to — of levalbuterol free base (ex-valve), to deliver 45 µg levalbuterol free base/59 µg of levalbuterol tartrate (ex-actuator)

Investigational Formulations

Two different strengths of Xopenex HFA Inhalation Aerosol were used during clinical studies: 45 µg/actuation and 90 µg/actuation. The initial 45 µg/actuation investigational product (designated as A; also referred to as early product [EP] in this NDA) used an actuator with a larger orifice (—) than the subsequent 45 µg/actuation product which used an actuator with a — orifice (designated as B; also referred to as final product [FP] in this NDA). The proposed commercial product will use an actuator with a — orifice. All Xopenex HFA Inhalation Aerosol investigational products were formulated using levalbuterol (as tartrate salt) and HFA134a as the propellant.

Human Pharmacology and Bioavailability Studies

The clinical pharmacology program for Xopenex HFA® MDI was designed to explore the key PK and PD effects of (R)-albuterol, with respect to both safety and efficacy, for subjects administered levalbuterol HFA versus Proventil® HFA. These evaluations included a relative exposure analysis of both products, cumulative dosing exposure and safety studies in adult and pediatric subjects, comparative exposure-safety profile evaluations, population pharmacokinetic and pharmacodynamic analyses, and an evaluation of the influence of subject covariates on pharmacokinetic and pharmacodynamic endpoints. The data for these evaluations were obtained from three pivotal Phase III trials (two in adult subjects and one in pediatric subjects), three cumulative dose safety studies (two in adult subjects, one in pediatric subjects) and two exercise induced bronchoconstriction studies (one in adult subjects and one in pediatric subjects) as follows:

Phase II and III

SEPR Study No. 051-308 was a dose-ranging study using a bronchoprotection model. According to the sponsor, data from this study supported the appropriateness of the dose evaluated in Phase III and provided an estimate of relative potency to Proventil HFA.

SEPR Study No. 051-310 was a cumulative-dose safety study using a bronchodilation model. According to the sponsor, this study also had the ability to assess relative potency and the data from this study also supported the appropriateness of the dose evaluated in Phase III.

SEPR Study No. 051-309, was another cumulative-dose study. The objectives of this study were to clarify the results observed in the previous Phase II trials and to confirm the safety of the levalbuterol MDI through a range of doses well above the recommended dose. According to the sponsor, this study was chosen because bronchodilation is a clinically relevant model for a bronchodilator agent.

In addition to the Phase II trials, efficacy data in adult and adolescent asthmatics is presented from two Phase III trials in which study medication was administered QID for eight weeks (SEPR Study Nos. 051-353 and 051-355).

Studies in Pediatric Subjects

Similar to the studies in adults and adolescents, efficacy data from a dose-ranging and cumulative-dose safety study (SEPR Study Nos. 051-312 and 051-311, respectively) is presented. In addition, efficacy in pediatric subjects (ages four to 11) is presented from one Phase III trial in which study medication was administered QID for four weeks (SEPR Study No. 051 -354).

According to the sponsor, these studies support several key conclusions regarding the exposure to (R)-albuterol observed following administration of 90 µg levalbuterol HFA MDI. First, the relative systemic exposure to (R)-albuterol after administration of 90 µg Levalbuterol HFA MDI was modestly less than after administration of 180 µg Proventil HFA MDI. Second, the exposure safety relationships for heart rate, serum glucose, and serum potassium were similar for levalbuterol HFA and Proventil HFA in both adult and pediatric subjects over the range of observed drug concentrations. Third, the exposures achieved after the administration of 90 µg levalbuterol HFA in the two pivotal trials, resulted in clinically comparable pharmacologic effects as observed with 180 µg Proventil HFA. Finally, (R)-albuterol exposures were relatively constant over the range of ages studied, from approximately 4 to 81 years of age.

This reviewer's Comments

The following table summarizes the overall content of the clinical pharmacology and biopharmaceutics information (electronic submission) provided by the sponsor to support the request for the approval of this NDA. It appears that all the pivotal PK/PD studies were conducted using the to-be marketed formulation. The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues. The following table summarizes the CPB content of the NDA:

OBJECTIVES:

- to evaluate the relative exposure analysis of R-albuterol delivered from levalbuterol HFA versus Proventil® HFA
- to determine the cumulative dosing exposure and safety studies in adult and pediatric subjects,
- to conduct a population PK and PK/PD analyses to evaluate the influence of subject covariates on pharmacokinetic and pharmacodynamic endpoints

Study Title/Description	Tabular listing/PK/PD summary	Analytical method	PK/PD parameters	Statistical analysis
Study 051-308: A Dose Response and PD Study of Levalbuterol and Racemic Albuterol HFA MDI in Subjects Twelve Years of Age and Older with Asthma	√	• LC/MS/MS • Pre-study/In-study validation data	Individual and average PK parameters.	Descriptive statistics were calculated for all PK parameters for both (R)- and (S)-albuterol.
Study 051-309: A Cumulative Dose Tolerability Study of Levalbuterol HFA and Racemic Albuterol HFA in Subjects Twelve Years of Age and Older with Asthma .	√	• LC/MS/MS • Pre-study/In-study validation data	Individual and average PK/PD parameters.	Descriptive statistics were calculated for all PK parameters for both (R)- and (S)-albuterol.
Study 051-310: A Cumulative Dose Tolerability Study of Levalbuterol HFA and Racemic Albuterol HFA in Subjects Twelve Years of Age and Older with Asthma	√	• LC/MS/MS • Pre-study/In-study validation data	Individual and average PK parameters.	Mean cumulative plasma concs of (R)- and (S)-albuterol were summarized by treatment group.
Study 051-311: A Cumulative Dose Tolerability Study of Levalbuterol HFA and Racemic Albuterol HFA in Pediatric Subjects with Asthma.	√	• LC/MS/MS • Pre-study/In-study validation data	Individual and average PK parameters.	Mean cumulative plasma conc of (R)- and (S)-albuterol were summarized by treatment group.

Study 051-312: A Dose Response Study of Levalbuterol and Racemic Albuterol HFA MDI in Pediatric Subjects with Asthma.	√	• LC/MS/MS • Pre-study/In-study validation data	Individual and average PK parameters.	Descriptive statistics were calculated for all PK parameters for both (R)- and (S)-albuterol.
Study 051-353: An Efficacy and Safety Study of Levalbuterol, Racemic Albuterol and Placebo in Subjects Twelve Years of Age and Older with Asthma	√	• LC/MS/MS • Pre-study/In-study validation data	Population PK analysis	• Summary statistics were provided for all pop PK parameters.
Study 051-355: An Efficacy and Safety Study of Levalbuterol, Racemic Albuterol and Placebo in Subjects Twelve Years of Age and Older with Asthma .	√	• LC/MS/MS • Pre-study/In-study validation data	Population PK analysis	• Summary statistics were provided for all pop PK parameters.
Study 051-354: An Efficacy, Safety, and Tolerability Study of Daily Dosing with Levalbuterol, Racemic Albuterol, and Placebo in Pediatric Subjects with Asthma	√	• LC/MS/MS • Pre-study/In-study validation data	Population PK analysis	• Summary statistics were provided for all pop PK parameters. • The 95% CI for the AUCpop ratio (pediatric/adult) was evaluated

CONCLUSION: Submission is filiable

COMMENTS TO SPONSOR

- Provide data sets and NONMEM control stream files and output files generated from the population PK analysis for levalbuterol and S-albuterol.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, the Division of Pharmaceutical Evaluation II (OCPB/DEP-II) has reviewed the NDA package submission (NDA 21-730) for Xopenex HFA inhalation aerosol received on May, 2004. The OCPB/DEP-II is aware of the series of pharmacokinetic, pharmacodynamics and PK/PD population studies that the sponsor included in this NDA submission. The NDA is filable from a CPB stand point. Please forward the above comment to the sponsor.

Sandra Suarez-Sharp, Ph.D.
Pharmacokinetics Reviewer, DPEII, OCPB

Concurrence:

Emmanuel Fadiran Ph. D.
Team Leader, DPEII, OCPB

cc:
HFD-570 Div., Bosken, Syemor, Green
HFD-870 Malinowski, Hunt, Fadiran, Suarez-Sharp

General Information About the Submission

	Information		Information
NDA Number	21-730	**Brand Name**	Xopenex HFA
OCPB Division (I, II, III)	II	**Generic Name**	levalbuterol
Medical Division	DPADP	**Drug Class**	**Beta agonist**
OCPB Reviewer	**Sandra Suarez-Sharp**	**Indication(s)**	**Treatment of bronchospasm**
OCPB Team Leader	Emmanuel Fadiran	**Dosage Form**	MDI
PM Reviewer		**Dosing Regimen**	Adults and children 4 years of age and older: 2 inhalations (90 mcg) repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient.
Date of Submission	May 12, 2004	**Route of Administration**	Oral Inhalation
Estimated Due Date of OCPB Review	Feb 2005	**Sponsor**	Sepracor
PDUFA Due Date	March 12, 2005	**Priority Classification**	**Standard**
Division Due Date	**Feb 26, 2005**		

3 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**	**1**		

multiple dose:				
Patients-				
single dose:				
multiple dose:	x	8		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	6		
Phase 3 clinical trial:	x	3		
Population Analyses -				
Data rich:	x	2		
Data sparse:	x	2		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		8		

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. • **Provide data sets and NONMEM control stream files and output files generated from the population PK analysis for levalbuterol and S-albuterol.**		
QBR questions (key issues to be considered)	1. Dose-response for safety 2. Relative BA to Proventil HFA **3.** Covariate effects on the PK of the drug **4.** Comparative systemic exposure in adults vs. children			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-658, HFD-870 (Electronic Entry or Lee), HFD-570 (Jackson), HFD-870 (Fadiran, Hunt, Malinowski)), CDR (B. Murphy)

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

/s/

Sandra Suarez
3/7/05 10:57:57 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
3/7/05 11:04:42 AM
BIOPHARMACEUTICS
I concur

Clinical Pharmacology and Biopharmaceutics Review

"Xoponex HFA Inhalation Aerosol for the Treatment of Bronchospasm"

NDA No.:	**21-730**
IND:	**62,906**
Sponsor:	Xepracor
Type:	NDA filing package
Drug:	Levalbuterol
Submission date:	May 11, 2004
Draft review:	Jun 15, 2004
Review date:	Jun 17, 2004
Reviewer:	Sandra Suarez-Sharp, Ph.D.

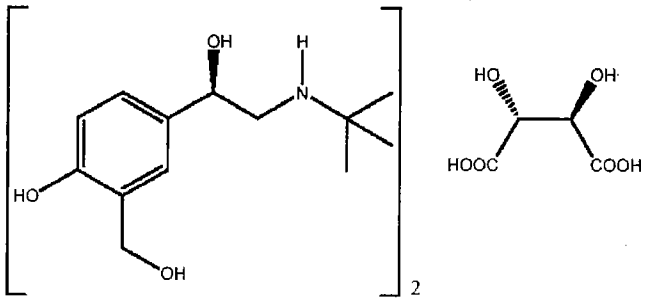
INTRODUCTION

Levalbuterol [(R)-albuterol], a potent selective β2-adrenoceptor agonist, is the (R)-isomer of the marketed product, racemic albuterol. Levalbuterol HCl Inhalation Solution (Xopenex® UDV) is currently marketed for the treatment or prevention of bronchospasm in subjects six years of age and older with reversible obstructive airway disease. The Levalbuterol HFA Inhalation Aerosol (sometimes referred to as levalbuterol HFA) development program evaluated the safety and efficacy of levalbuterol when administered via a metered dose inhaler (MDI) in adults and adolescents (≥12 years of age), and in children 4 to 11 years of age, with reversible obstructive airway disease. This NDA includes data from 12 completed clinical studies, and one ongoing safety study, utilizing single or multiple-doses ranging from 22.5 to 180 μg of Levalbuterol Inhalation Aerosol. Ten of twelve completed studies were conducted using HFA-134a as the propellant. Two early studies (Studies 051-301 and 051-304) were conducted using CFC as the propellant.

Chemistry

Drug Substance

The drug substance (R)-α1-[[(1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol L-tartrate (2:1 salt), more commonly known as levalbuterol tartrate, is a β2-adrenergic receptor agonist indicated for the treatment or prevention of bronchospasm. Levalbuterol is the pharmacologically active R-enantiomer of racemic albuterol. The molecular structure, molecular formula, and formula weight of levalbuterol tartrate are shown in Figure below:



Molecular Formula: $(C_{13}H_{21}NO_3)_2 \cdot C_4H_6O_6$
Formula Weight: 628.71

The drug substance is a — white to light-yellow solid —

Drug Product

The drug product is a pressurized metered-dose inhaler containing a suspension of micronized levalbuterol tartrate in ethanol, oleic acid and propellant HFA-134a. According to the sponsor, the ethanol and oleic acid are compendial ingredients meeting USP/NF monograph requirements.

The product is designed to deliver 45 µg levalbuterol (as free base) per actuation and a minimum of 200 actuations per canister; one dose consists of two actuations. The components and composition for the proposed commercial drug product are listed the Table 2. The batch sizes used during clinical development ranged from — to — units. The commercial batch size will be approximately —

Table 2. Drug Product Unit-Dose Composition

Component	Function	Amount per Actuation	Amount per Canister
Levalbuterol tartrate	Active ingredient		
Oleic Acid NF	—		
Dehydrated Alcohol USP	—		
HFA-134a	Propellant		
Total	--	60.00 mg	15.00 g

* equivalent to — µg of levalbuterol free base (ex-valve), to deliver 45 µg levalbuterol free base/59 µg of levalbuterol tartrate (ex-actuator)

Investigational Formulations

Two different strengths of Xopenex HFA Inhalation Aerosol were used during clinical studies: 45 µg/actuation and 90 µg/actuation. The initial 45 µg/actuation investigational product (designated as A; also referred to as early product [EP] in this NDA) used an actuator with a larger orifice [redacted] mm) than the subsequent 45 µg/actuation product which used an actuator with a [redacted] mm orifice (designated as B; also referred to as final product [FP] in this NDA). The proposed commercial product will use an actuator with a [redacted] mm orifice. All Xopenex HFA Inhalation Aerosol investigational products were formulated using levalbuterol (as tartrate salt) and HFA134a as the propellant.

Human Pharmacology and Bioavailability Studies

The clinical pharmacology program for Xopenex HFA® MDI was designed to explore the key PK and PD effects of (R)-albuterol, with respect to both safety and efficacy, for subjects administered levalbuterol HFA versus Proventil® HFA. These evaluations included a relative exposure analysis of both products, cumulative dosing exposure and safety studies in adult and pediatric subjects, comparative exposure-safety profile evaluations, population pharmacokinetic and pharmacodynamic analyses, and an evaluation of the influence of subject covariates on pharmacokinetic and pharmacodynamic endpoints. The data for these evaluations were obtained from three pivotal Phase III trials (two in adult subjects and one in pediatric subjects), three cumulative dose safety studies (two in adult subjects, one in pediatric subjects) and two exercise induced bronchoconstriction studies (one in adult subjects and one in pediatric subjects) as follows:

Phase II and III

SEPR Study No. 051-308 was a dose-ranging study using a bronchoprotection model. According to the sponsor, data from this study supported the appropriateness of the dose evaluated in Phase III and provided an estimate of relative potency to Proventil HFA.

SEPR Study No. 051-310 was a cumulative-dose safety study using a bronchodilation model. According to the sponsor, this study also had the ability to assess relative potency and the data from this study also supported the appropriateness of the dose evaluated in Phase III.

SEPR Study No. 051-309, was another cumulative-dose study. The objectives of this study were to clarify the results observed in the previous Phase II trials and to confirm the safety of the levalbuterol MDI through a range of doses well above the recommended dose. According to the sponsor, this study was chosen because bronchodilation is a clinically relevant model for a bronchodilator agent.

In addition to the Phase II trials, efficacy data in adult and adolescent asthmatics is presented from two Phase III trials in which study medication was administered QID for eight weeks (SEPR Study Nos. 051-353 and 051-355).

Studies in Pediatric Subjects

Similar to the studies in adults and adolescents, efficacy data from a dose-ranging and cumulative-dose safety study (SEPR Study Nos. 051-312 and 051-311, respectively) is presented. In addition, efficacy in pediatric subjects (ages four to 11) is presented from one Phase III trial in which study medication was administered QID for four weeks (SEPR Study No. 051 -354).

According to the sponsor, these studies support several key conclusions regarding the exposure to (R)-albuterol observed following administration of 90 µg levalbuterol HFA MDI. First, the relative systemic exposure to (R)-albuterol after administration of 90 µg Levalbuterol HFA MDI was modestly less than after administration of 180 µg Proventil HFA MDI. Second, the exposure safety relationships for heart rate, serum glucose, and serum potassium were similar for levalbuterol HFA and Proventil HFA in both adult and pediatric subjects over the range of observed drug concentrations. Third, the exposures achieved after the administration of 90 µg levalbuterol HFA in the two pivotal trials, resulted in clinically comparable pharmacologic effects as observed with 180 µg Proventil HFA. Finally, (R)-albuterol exposures were relatively constant over the range of ages studied, from approximately 4 to 81 years of age.

This reviewer's Comments

The following table summarizes the overall content of the clinical pharmacology and biopharmaceutics information (electronic submission) provided by the sponsor to support the request for the approval of this NDA. It appears that all the pivotal PK/PD studies were conducted using the to-be marketed formulation. The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues. The following table summarizes the CPB content of the NDA:

OBJECTIVES:

- to evaluate the relative exposure analysis of R-albuterol delivered from levalbuterol HFA versus Proventil® HFA
- to determine the cumulative dosing exposure and safety studies in adult and pediatric subjects,
- to conduct a population PK and PK/PD analyses to evaluate the influence of subject covariates on pharmacokinetic and pharmacodynamic endpoints

Study Title/Description	Tabular listing/PK/PD summary	Analytical method	PK/PD parameters	Statistical analysis
Study 051-308: A Dose Response and PD Study of Levalbuterol and Racemic Albuterol HFA MDI in Subjects Twelve Years of Age and Older with Asthma	√	• LC/MS/MS • Pre-study/In-study validation data	Individual and average PK parameters.	Descriptive statistics were calculated for all PK parameters for both (R)- and (S)-albuterol.
Study 051-309: A Cumulative Dose Tolerability Study of Levalbuterol HFA and Racemic Albuterol HFA in Subjects Twelve Years of Age and Older with Asthma .	√	• LC/MS/MS • Pre-study/In-study validation data	Individual and average PK/PD parameters.	Descriptive statistics were calculated for all PK parameters for both (R)- and (S)-albuterol.
Study 051-310: A Cumulative Dose Tolerability Study of Levalbuterol HFA and Racemic Albuterol HFA in Subjects Twelve Years of Age and Older with Asthma	√	• LC/MS/MS • Pre-study/In-study validation data	Individual and average PK parameters.	Mean cumulative plasma concs of (R)- and (S)-albuterol were summarized by treatment group.

Study 051-311: A Cumulative Dose Tolerability Study of Levalbuterol HFA and Racemic Albuterol HFA in Pediatric Subjects with Asthma.	√	• LC/MS/MS • Pre-study/In-study validation data	Individual and average PK parameters.	Mean cumulative plasma conc of (R)- and (S)-albuterol were summarized by treatment group.
Study 051-312: A Dose Response Study of Levalbuterol and Racemic Albuterol HFA MDI in Pediatric Subjects with Asthma.	√	• LC/MS/MS • Pre-study/In-study validation data	Individual and average PK parameters.	Descriptive statistics were calculated for all PK parameters for both (R)- and (S)-albuterol.
Study 051-353: An Efficacy and Safety Study of Levalbuterol, Racemic Albuterol and Placebo in Subjects Twelve Years of Age and Older with Asthma	√	• LC/MS/MS • Pre-study/In-study validation data	Population PK analysis	• Summary statistics were provided for all pop PK parameters.
Study 051-355: An Efficacy and Safety Study of Levalbuterol, Racemic Albuterol and Placebo in Subjects Twelve Years of Age and Older with Asthma .	√	• LC/MS/MS • Pre-study/In-study validation data	Population PK analysis	• Summary statistics were provided for all pop PK parameters.
Study 051-354: An Efficacy, Safety, and Tolerability Study of Daily Dosing with Levalbuterol, Racemic Albuterol, and Placebo in Pediatric Subjects with Asthma	√	• LC/MS/MS • Pre-study/In-study validation data	Population PK analysis	• Summary statistics were provided for all pop PK parameters. • The 95% CI for the AUCpop ratio (pediatric/adult) was evaluated

CONCLUSION: Submission is filiable

COMMENTS TO SPONSOR

- Provide data sets and NONMEM control stream files and output files generated from the population PK analysis for levalbuterol and S-albuterol.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, the Division of Pharmaceutical Evaluation II (OCPB/DEP-II) has reviewed the NDA package submission (NDA 21-730) for Xoponex HFA inhalation aerosol received on May, 2004. The OCPB/DEP-II is aware of the series of pharmacokinetic, pharmacodynamics and PK/PD population studies that the sponsor included in this NDA submission. The NDA is filable from a CPB stand point. Please forward the above comment to the sponsor.

Sandra Suarez-Sharp, Ph.D.
Pharmacokinetics Reviewer, DPEII, OCPB

Concurrence:

Emmanuel Fadiran Ph. D.
Team Leader, DPEII, OCPB

cc:
HFD-570 Div., Bosken, Syemor, Green
HFD-870 Malinowski, Hunt, Fadiran, Suarez-Sharp

General Information About the Submission

	Information		Information
NDA Number	21-730	**Brand Name**	Xoponex HFA
OCPB Division (I, II, III)	II	**Generic Name**	levalbuterol
Medical Division	DPADP	**Drug Class**	Beta agonist
OCPB Reviewer	Sandra Suarez-Sharp	**Indication(s)**	Treatment of bronchospasm
OCPB Team Leader	Emmanuel Fadiran	**Dosage Form**	MDI
PM Reviewer		**Dosing Regimen**	Adults and children 4 years of age and older: 2 inhalations (90 mcg) repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient.
Date of Submission	May 12, 2004	**Route of Administration**	Oral Inhalation
Estimated Due Date of OCPB Review	Feb 2005	**Sponsor**	Sepracor
PDUFA Due Date	March 12, 2005	**Priority Classification**	Standard
Division Due Date	Feb 26, 2005		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				

Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		
multiple dose:				
Patients-				
single dose:				
multiple dose:	x	8		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	5		
Phase 3 clinical trial:	x	3		
Population Analyses -				
Data rich:	x	2		
Data sparse:	x	2		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				

Total Number of Studies		**9**		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	**X**	**Comments have been sent to firm (or attachment included). FDA letter date if applicable.** • Provide data sets and NONMEM control stream files and output files generated from the population PK analysis for levalbuterol and S-albuterol.		
QBR questions (key issues to be considered)	1. Dose-response for safety 2. Relative BA to Proventil HFA 3. Covariate effects on the PK of the drug 4. Comparative systemic exposure in adults vs. children			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-658, HFD-870 (Electronic Entry or Lee), HFD-570 (Jackson), HFD-870 (Fadiran, Hunt, Malinowski)), CDR (B. Murphy)

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Sandra Suarez
6/29/04 08:02:41 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
6/29/04 08:32:55 AM
BIOPHARMACEUTICS
I concur