CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-730

MEDICAL REVIEW(S)

DIVISION DEPUTY DIRECTOR'S MEMORANDUM

Date: March 11, 2005

To: NDA 21-730

From: Eugene J. Sullivan, MD, FCCP
Deputy Director, Division of Pulmonary and Allergy Drug Products, HFD-570

Through: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug Products, HFD-570

Product: Xopenex HFA (levalbuterol tartrate) Inhalation Aerosol

Applicant: Sepracor, Inc.

Administrative and Introduction

Sepracor submitted NDA 21-730 for Xopenex HFA Inhalation Aerosol on May 11, 2004, under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The application was received by the Agency on May 12, 2004. The PDUFA due date for the application is March 12, 2005. The proposed indication is the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease. The proposed dose is 2 actuations every 4 to 6 hours. The drug product is a pressurized metered dose inhaler (MDI) containing the active drug substance levalbuterol tartrate. The MDI emits a dose of 45mcg levalbuterol per actuation (equivalent to 59mcg levalbuterol tartrate). Levalbuterol is the (R)-enantiomer of the beta$_2$-adrenergic receptor agonist albuterol. Albuterol is the active drug substance in several approved bronchodilator drug products, including products that are metered dose inhalers. The proposed indication, as well as much of the proposed labeling language mirrors the language from existing albuterol metered dose inhaler products. Levalbuterol is currently approved in an inhalation solution formulation (Xopenex [levalbuterol HCl] Inhalation Solution; Sepracor; NDA 20-837; Approved March 25, 1999). Xopenex HFA utilizes a non-ozone depleting propellant, hydrofluoroalkane. The clinical program was conducted under IND 62,906. The Applicant has obtained right of reference from 3M Pharmaceuticals, allowing the Agency to reference the long-term clinical safety data for Proventil HFA (albuterol sulfate) Inhalation Aerosol (NDA 20-503). In addition, the application is supported by various data previously submitted by the Applicant in support of the approved product, Xopenex Inhalation Solution. The Office of New Drugs, in consultation with the Office of Regulatory Policy, has reviewed the relevant materials and found that the 505(b)(2) regulatory pathway is appropriate for this application, and that all of the relevant patents have been appropriately certified.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation
A brief description of the drug product is included in the Administrative and Introduction section above. Manufacture and release testing of the drug substance, levalbuterol tartrate, is performed at several facilities in England, Canada, and the United States. The drug product is a suspension formulation containing levalbuterol tartrate and the following excipients: oleic acid, dehydrated alcohol, and HFA-134a in amounts necessary to achieve the labeled quantity of 200 actuations per canister. The primary packaging includes an 18mL — aluminum canister, a ⌒ metered valve, and a ⌣ orifice polypropylene actuator with dust cap. Manufacture and release testing of the drug product is performed by 3M Pharmaceuticals, in Northridge, CA. Appropriate establishment inspections have been performed and found to be acceptable. The CMC aspects of this application were reviewed by Dr. Suong Tran. The reader is referred to her Chemistry Review for a detailed discussion. Based on the data submitted, the CMC team has recommended a change to the proposed labeling language related to the need for re-priming after a period of non-use. The Applicant has proposed language that instructs patients to ⟶ This is based upon data that shows that loss of prime occurs after two weeks if the MDI is stored in the valve-down orientation. However, loss of prime occurred after 3 days when the device was stored in the valve-up orientation. The MDI is unlikely to be stored by patients in the valve-down orientation because it is prone to tipping over in this orientation. The re-priming instructions on the label should reflect the "worse case scenario" of loss of prime in 3 days.

The regulatory recommendation from the CMC review team is for an Approval action. The CMC team has also recommended that the Applicant pursue development of an integrated dose-counter after approval. This is consistent with the Agency's Guidance for Industry entitled "Integration of Dose-Counting Mechanisms into MDI Drug Products." The Applicant has agreed to pursue this.

Pharmacology and Toxicology
The Applicant states that the pharmacology and safety profile of levalbuterol have been previously characterized in support of the approved inhalation solution formulation. In support of the current application, the Applicant has performed new non-clinical studies examining aspects of the pharmacology and metabolism of levalbuterol, as well as comparative toxicology and safety studies, including qualification of impurities, leachables, and extractables. These studies did not identify any novel safety issues associated with this drug product. In addition to the Agency's prior finding of safety and effectiveness for the reference listed drug, Proventil Inhalation Solution (NDA 19-243), the Pharm/Tox review team relied on data from a variety of sources to support approval of this application. This includes data owned by the Applicant, data for which the applicant has obtained formal right of reference, and data in the published literature. Based on these data, the Pharm/Tox review team has recommended an Approval action. For further details regarding the supporting pharm/tox data, the reader is referred to Dr. Whitehurst's review document.

Clinical

The clinical program for this application consisted of 12 completed Phase 2 and Phase 3 studies, and one ongoing safety study. The Phase 2 program included two early studies using a CFC-containing product, two multiple-dose studies using an earlier actuator design, two dose-ranging studies, and three cumulative dose studies. The Phase 3 program consisted of three large, placebo- and active-controlled safety and efficacy studies, two in adults and adolescents (Studies 051-353, and 051-355), and one in children aged 4-11 years (Study 051-354). Given the similarities of the disease in adults and children, the Division has generally accepted this type of program for drugs intended to treat asthma. That is, if safety and efficacy is established in adults and adolescents, a single pediatric study can be sufficient to support a pediatric indication. The clinical safety and efficacy findings have been reviewed by the clinical reviewer, Dr. Seymour. The reader is referred to her excellent Medical Officer Review for details.

Dose-ranging

In general, the doses chosen for this product are based upon the approved doses of the albuterol MDI products. The Sponsor reasoned that the appropriate dose of the active enantiomer would be one-half of the dose of the approved racemic drug, as was the case for the approved levalbuterol inhalation solution product. The Sponsor utilized an exercise-induced bronchospasm (EIB) model to evaluate dose-response relationships in adults and children. Although EIB is a characteristic of asthma, the standardized protocols for eliciting the bronchospastic response are somewhat artificial, and may not be entirely representative of the natural, day-to-day bronchospasm associated with asthma. Therefore, it may not necessarily be the case that a specific dose that is effective in preventing EIB in such a model would be the most appropriate dose for clinical use. With that in mind, the most important aspect of these EIB dose-response studies may not be the absolute dose-response information, but rather the comparative data in regard to the approved active comparator, Proventil HFA. Unfortunately, the ability to compare the relative efficacy of Xopenex HFA and Proventil HFA was compromised in the adult dose-response study (Study 051-308) because study medication was administered using spacer devices. In vitro analyses performed subsequent to completion of Study 051-308 indicated that the effects of a spacer device on the fine particle dose differ between these two products. Therefore, observed pharmacodynamic differences may have been attributable to differential effects of the spacer devices, and may not represent differences that would be seen if the products were compared without the use of spacer devices. The results of the pediatric EIB dose-response study (Study 051-312), in which spacer devices were not used, suggest that the pharmacodynamic response of Xopenex HFA (45mcg levalbuterol /inhalation) is similar to that of Proventil HFA (90mcg albuterol/inhalation). This finding supports the proposed dose. In this study, one inhalation of study medication, both Xopenex HFA and Proventil HFA, provided protection from EIB similar to that provided by two inhalations. This might suggest that one inhalation could be an appropriate dose to explore in further clinical studies. However, as stated above, the most appropriate dose in this EIB model may not be the most appropriate clinical dose.

Efficacy

The efficacy of Xopenex HFA was established in three large, randomized, placebo- and active-controlled, parallel group studies of similar design. Two of these were performed in adults and adolescents 12 years of age and older (Studies 051-353 and 051-355), and one was performed in children aged 4 to 11 years (Study 051-354). The duration of randomized treatment was 8 weeks in the adult/adolescent studies, and 4 weeks in the pediatric study. While studies of 12 weeks duration are generally expected for most new drugs for asthma, these briefer studies were felt to be justified based on the vast clinical experience with albuterol. In these studies, patients with asthma, baseline $FEV_1 \geq 45\%$ and $\leq 75\%$ (adult/adolescent studies) or $\leq 80\%$ (pediatric study), and documented reversible airflow obstruction ($\geq 12\%$ improvement in FEV_1 following albuterol MDI 180mcg) were randomized to receive either Xopenex HFA 90mcg (two actuations, 45mcg/actuation)[1], placebo, or Proventil (albuterol sulfate) HFA 180mcg (two actuations, 90mcg/actuation). Randomization was performed in a 2:1:1 fashion. The primary measure of efficacy was the pulmonary function parameter, FEV_1, which the Agency has long accepted as a reasonable primary efficacy measure for bronchodilator drugs. The primary endpoint was the peak percent change from test day baseline FEV_1, averaged over the course of treatment. Three values contributed to the average as serial FEV_1 assessments were obtained three times during the studies (at Day 1, Week 4, and Week 8 in the adult/adolescent studies, and at Day 1, Week 2, and Week 4 for the pediatric studies). Secondary efficacy endpoints included other analyses of FEV_1 (peak change at each visit, AUC over the course of the serial spirometry, time to peak change, etc.), other pulmonary function parameters (FVC, $FEF_{25-75\%}$), rescue medication use, patient-reported outcomes (asthma symptom scores, Asthma Quality of Life Questionnaire, SF-36 Health Survey, and global evaluation), and a physician rated global evaluation.

In the two adult/adolescent studies (Studies 051-353 and 051-355), Xopenex HFA was demonstrated to be statistically superior to placebo on the pre-specified primary efficacy endpoint (Table 1). In addition, data reflecting the various secondary pulmonary function endpoints supported the conclusion that Xopenex HFA was superior to placebo. Although not statistically significant, analyses of rescue albuterol use and global evaluations generally supported efficacy, while the other patient-reported outcomes (asthma symptom scores, Asthma Quality of Life Questionnaire, and SF-36 Health Survey) did not differ between treatment groups, and did not provide support for efficacy. In both studies the active control, Proventil HFA, was also superior to placebo. Interestingly, Proventil HFA was numerically superior to Xopenex HFA in both studies, and the difference reached statistical significance ($p<0.05$) in one of the studies.

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[1]Because of a decision to change manufacturing facilities during the development program, the Xopenex HFA product used in the adult/adolescent studies was manufactured at two different facilities. However, the drug products manufactured at the two facilities have been determined by the appropriate Agency reviewers to be sufficiently similar in terms of CMC attributes and pharmacokinetics, such that they can be considered together for the purposes of interpretation of the clinical studies.

Table 1: Primary Endpoint: Peak Percent Change from Test Day Baseline, Averaged Over the Treatment Period (ITT population)			
Study 051-353			
	Xopenex HFA N=219	Proventil HFA N=119	Placebo N=107
LS Mean (SE)	25.63 (0.87)	28.98 (1.15)	13.94 (1.21)
Pairwise p-value vs. Placebo	<0.001	<0.001	
Pairwise p-value vs. Proventil HFA	0.018		
Study 051-355			
	Xopenex HFA* N=184	Proventil HFA N=60	Placebo N=59
LS Mean (SE)	A= 25.33 (1.05) B= 23.09 (1.05)	26.51 (1.49)	12.45 (1.49)
Pairwise p-value vs. Placebo	A= <0.001 B= <0.001	<0.001	
Pairwise p-value vs. Proventil HFA	A= 0.654 B= 0.132		
*Study 051-355 utilized Xopenex HFA manufactured at two facilities (see text above). The two formulations are reported separately here, as Formulation A (N=122), and Formulation B (N=62).			

In the pediatric study (Study 051-354), Xopenex HFA was demonstrated to be statistically superior to placebo on the pre-specified primary efficacy endpoint (Table 2). As in the adult/adolescent studies, the various secondary pulmonary function endpoints also support the efficacy of Xopenex, but the patient and physician reported outcomes did not provide evidence of efficacy. In this study, Xopenex HFA was numerically superior to the active comparator, although this difference was not statistically significant. The active comparator was not shown to be statistically superior to placebo (p=0.057), although this may in part relate to the small numbers of patients in these two groups, as well as a rather prominent placebo response.

Table 2: Primary Endpoint: Peak Percent Change from Test Day Baseline, Averaged Over the Treatment Period (ITT population)			
Study 051-354			
	Xopenex HFA N=74	Proventil HFA N=38	Placebo N=33
LS Mean (SE)	25.63 (1.34)	21.81 (1.83)	16.75 (1.94)
Pairwise p-value vs. Placebo	<0.001	0.057	
Pairwise p-value vs. Proventil HFA	0.086		

Safety

The safety monitoring performed in the program was typical of that expected for asthma drugs. In addition to adverse event reporting, labs, ECGs, and vital signs were monitored. Certain ECG and laboratory findings that are expected with beta-agonist drugs were identified in Phase 2 and Phase 3 studies, and are adequately described in the proposed product labeling, which is largely drawn from the labeling for other beta-agonist bronchodilators. One finding of note in the adult/adolescent Phase 3 studies was that the occurrence of asthma adverse events was slightly higher in the Xopenex HFA group (9.4%), than in the Proventil HFA group (7.3%) and the placebo group (6.0%). The occurrence of moderately severe asthma AEs was also higher in the Xopenex HFA

group (7.2%) than in the Proventil HFA group (4.6%) and the placebo group (2.9%). However, this pattern was not seen in the pediatric study, in which the occurrence asthma AEs was lower in the Xopenex HFA group than in the Proventil HFA and placebo groups. In addition to the safety data derived from the Xopenex HFA development program, the safety of this product is further supported by the Agency's previous determination of safety and efficacy of Xopenex Inhalation Solution and Proventil HFA, both of which are associated with greater systemic exposures to (R)-albuterol than Xopenex HFA.

Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology and biopharmaceutics aspects of this application were reviewed by Dr. Suarez. Based on her review, Dr. Suarez has recommended certain changes in the proposed product label to better describe the metabolic fate of levalbuterol, and to describe the extent of the existing pharmacokinetic data in patients with renal and hepatic impairment. In her review, Dr. Suarez has also pointed out the absence of a demonstrated dose-response in the pediatric dose-ranging study that was performed using a model of prevention of exercise-induced bronchospasm. This issue is discussed in further detail in the Clinical section of this document, above. The recommended regulatory action from the Office of Clinical Pharmacology and Biopharmaceutics is Approval.

Data Quality, Integrity, and Financial Disclosure

The Applicant indicates that all clinical studies were conducted in accordance with accepted ethical standards, and that it did not engage the services of any person who has been debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act. Six investigators who participated in clinical trials to support efficacy and/or safety claims were reported to have financial interests exceeding 25-50 thousand dollars; however, because of the relatively small numbers of subjects enrolled by these investigators, this potential conflict is unlikely to have affected the conclusions drawn. Review of the application did not raise questions regarding the quality or integrity of the data submitted. Early in the course of the review a consultation was placed with the Division of Scientific Investigation (DSI) for the purpose of initiating an audit of three study sites. These sites were chosen based on the numbers of subjects enrolled. At one of the three sites, DSI determined that the investigator had failed to maintain adequate and accurate records, and that she had not adhered to the investigational plan. Because of these findings, the biometrics reviewer re-analyzed the data from the study in which she participated, excluding the 10 subjects enrolled at that site. The exclusion of these subjects did not alter the conclusions of the study.

Pediatric Considerations

The clinical development program for Xopenex HFA included studies performed in children as young as 4 years of age. The Applicant has requested a waiver of the Pediatric Research Equity Act requirement to study patients younger than 4 years, stating that use of this product in patients younger than 4 years is not expected, and that studies in this population would be difficult to perform. However, the Division is aware that the use of bronchodilator MDIs, along with spacer and facemask devices is quite common,

even in very young patients. Further, in the context of a Written Request for Pediatric Studies, other Sponsors have explored dosing of similar drugs down to birth. Therefore, the request for a waiver will be denied. Rather, the requirement for pediatric studies under the Pediatric Research Equity Act will be deferred, and will be considered a required postmarketing study commitment.

Product Name
The proprietary product name has undergone appropriate review by the Division of Medication Errors and Technical Support, and by the Division of Drug Marketing, Advertising, and Communication, and has been found to be acceptable.

Labeling
The product labeling proposed by the Applicant is largely based on the product labeling for other beta-agonist bronchodilator MDI drugs, and is generally acceptable. The Division initiated discussions with the Applicant to gain mutual agreement on several modifications to the proposed label, which the Division felt were necessary to more appropriately convey the various findings. As a result of these discussions, a number of changes were made to the proposed label, including three significant modifications. First, the Applicant had originally proposed to

The approved product label will not contain this language. Second, the Applicant had originally proposed

. As discussed in the Clinical section of this document, the Division finds it reasonable to approve the drug for the 4-11 year old age group based on a single confirmatory study. The underlying assumption is that the disease is similar in adults and children, and therefore a single confirmatory study would be sufficient to conclude that the drug behaves similarly in the younger age group.

The approved product label will not include Finally, while much of the label is based on the product labeling for other beta-agonist bronchodilator MDI drugs, a new section on metabolism and elimination was added, in an effort to update and improve the label.

Action
Sepracor has submitted adequate data to support approval of Xopenex HFA (levalbuterol tartrate) Inhalation Aerosol for the proposed indication. Each of the review disciplines has recommended an approval action. Therefore, the action on this application will be APPROVAL.

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/s/

Eugene Sullivan
3/11/05 10:28:33 AM
MEDICAL OFFICER
Division Deputy Director Memo

Badrul Chowdhury
3/11/05 10:32:14 AM
MEDICAL OFFICER
I concur

CLINICAL REVIEW

Application Type	NDA
Submission Number	21730
Submission Code	N-000
Letter Date	May 11, 2004
Stamp Date	May 12, 2004
PDUFA Goal Date	March 12, 2005
Reviewer Name	Sally M. Seymour, M.D.
Review Completion Date	February 25, 2005
Established Name	Levalbuterol Tartrate HFA Inhalation Aerosol
(Proposed) Trade Name	Xopenex HFA Inhalation Aerosol
Therapeutic Class	β_2-adrenergic agonist
Applicant	Sepracor, Inc.
Priority Designation	S
Formulation	HFA Inhalation Aerosol
Dosing Regimen	Q 4-6 hours
Indication	Treatment or prevention of bronchospasm
Intended Population	Adults, adolescents, and children $\geq$ 4 years

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, the data submitted and referenced in this submission provide adequate support for Approval of this 505(b)(2) application. The adequate and controlled clinical studies demonstrated that 90mcg levalbuterol HFA provides a clinically meaningful degree of bronchodilation in patients with asthma. The primary assessment of the bronchodilator effect was based on a commonly used and accepted clinical endpoint, the forced expiratory volume in one second (FEV1) and was further supported by secondary endpoints.

The safety profile of levalbuterol HFA is acceptable. In the clinical studies conducted for this application, levalbuterol HFA was well-tolerated. Adverse events attributable to the drug were likely related to the systemic beta adrenergic effects of levalbuterol HFA. In this application, the safety of levalbuterol HFA is also supported by the Agency's previous finding of the safety of albuterol and the Agency's previous finding of the safety of Xopenex Inhalation Solution.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Because the long-term safety of albuterol is well-established, a postmarketing risk management plan is not recommended.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments for this application.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests for this application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The proposed drug in this application is levalbuterol tartrate. Levalbuterol is the (R)-enantiomer of albuterol and is a beta$_2$-adrenergic receptor agonist. The proposed trade name is Xopenex HFA Inhalation Aerosol. Xopenex HFA is a pressurized metered-dose aerosol inhaler (MDI),

which produces an aerosol for oral inhalation. The proposed drug is a new MDI formulation of levalbuterol, which does not contain chlorofluorocarbons (CFCs).

The Applicant's proposed indication is the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease. The proposed dosing regimen for adults and children 4 years of age and older is 2 inhalations (90 mcg) repeated every 4 to 6 hours.

This is a 505(b)(2) application, which relies in part upon the Agency's previous determination of safety and efficacy of an approved drug. The Agency's previous determination of the safety and efficacy of albuterol and Sepracor's Xopenex Inhalation Solution (levalbuterol HCl) provide support for this application.

The Applicant conducted three Phase 3 clinical studies, seven Phase 2 clinical studies, and one ongoing safety study to support the efficacy and safety of levalbuterol HFA. In the adult phase 3 studies, a total of 748 subjects were enrolled while in the pediatric phase 3 study, a total of 277 subjects aged 4 to 11 were enrolled. The total number of subjects in the multidose studies contributing to the safety database is greater than 1100, with over 600 treated with levalbuterol HFA. In the Phase 3 studies, levalbuterol HFA was administered 90mcg QID for 8 weeks in adults/adolescents and for 4 weeks in pediatric subjects. Reportedly, compliance was high in all of the Phase 3 studies. Overall, the number of patients and extent of exposure in the clinical studies were adequate.

In addition to the referenced data and the clinical studies, the Applicant submitted a literature review and postmarketing data for Xopenex Inhalation Solution to support the safety and efficacy of levalbuterol HFA.

Several issues are worth noting about the clinical development program for this application. First of all, the Applicant conducted clinical studies with two different manufacturers of levalbuterol HFA — and 3M. Second, the Applicant conducted some of the Phase 2 studies with spacers, which complicated interpretation of the study results. Third, the Applicant began the Phase 3 studies prior to completing the dose ranging studies. Finally, the Applicant failed to collect device performance data in the Phase 3 studies and amended an ongoing safety study to capture device performance data. These issues are addressed in detail in this review.

1.3.2 Efficacy

The three Phase 3 studies support the efficacy of levalbuterol HFA by demonstrating a clinically meaningful degree bronchodilation in patients with asthma. The studies were adequate, well-controlled and similar in design – multicenter, randomized, double-blind, placebo controlled, active controlled, and parallel group. The two adult studies enrolled subjects 12 years of age and older with asthma and FEV1 $\geq$ 45% and $\leq$ 75%. Subjects were treated with study medication for eight weeks duration. The pediatric study enrolled subjects 4 to 11 years of age with asthma and FEV1 $\geq$ 45% and $\leq$ 80%. Pediatric subjects were treated for four weeks duration. The study design, study population, and study duration are acceptable.

For the primary efficacy variable, the Applicant chose FEV1, which is a well-established efficacy variable to assess the treatment of bronchospasm. Serial spirometry (FEV1) was measured at specified clinic visits. The Applicant determined the peak percent change in FEV1 at each of the visits when serial spirometry was measured and then averaged the peak percent change in FEV1 over the double blind period. The average peak percent change in FEV1 over the double blind period was the primary endpoint in all three Phase 3 studies. Pertinent secondary endpoints included the peak percent change in FEV1 at each clinic visit, the percent change in FEV1, AUC percent change FEV1, FVC, and FEF25-75%. In addition to spirometry variables, asthma symptoms, quality of life, global evaluations, and rescue medication use were also evaluated.

The dose finding for this application was less than adequate because the Applicant started the Phase 3 studies prior to completing the dose ranging studies. The Applicant chose 90mcg levalbuterol HFA to study in both adult and pediatric subjects. The adult dose ranging study suggested that 90mcg levalbuterol HFA was the appropriate dose to further study in adults; however, the study was complicated by the use of spacers. The pediatric dose ranging study suggested that 45mcg levalbuterol HFA may be as effective as 90mcg levalbuterol HFA. Thus, the 45mcg levalbuterol HFA warrants further study in pediatric subjects.

The results of the clinical studies support the efficacy of levalbuterol for the treatment/prevention of bronchospasm. Efficacy was established by the demonstration of a clinically meaningful and statistically superior improvement in the peak percent change in FEV1 averaged over the double blind period (pre-specified primary endpoint) following administration of levalbuterol HFA as compared to placebo. Secondary endpoints, including percent change in FEV1, percent predicted FEV1, and peak percent change FVC further support the efficacy of levalbuterol HFA. The studies did not establish a significant improvement in physician or subject global assessment, asthma symptom scores, quality of life scores, or rescue medication use.

Although the Phase 3 studies were designed to compare the levalbuterol HFA group to placebo group, the Applicant included an active control group treated with racemic albuterol HFA. As expected, racemic albuterol HFA was also superior to placebo for key spirometry endpoints. In general, levalbuterol HFA produced results similar to racemic albuterol HFA. However, differences in efficacy variables were noted between levalbuterol HFA and racemic albuterol HFA in the individual studies. Occasionally the differences were statistically significant, but were not consistent across different studies. It is unclear if any differences noted would be clinically significant. Thus, in this reviewer's opinion, levalbuterol HFA generally produced results similar to racemic albuterol HFA.

1.3.3 Safety

The safety of levalbuterol HFA is supported by the Applicant's clinical studies, the Agency's previous determination of safety for albuterol and levalbuterol HCl, the Applicant's literature search, and the postmarketing safety data for levalbuterol HCl.

In the clinical program, the size of the safety database is approximately 1053 adults and 341 children. In addition, the Applicant provided interim safety data from an ongoing safety study in 547 patients. The majority of the subjects in the safety database participated in the multiple dose studies, which lasted 8 weeks in adults and 4 weeks in children.

The results of the clinical studies indicate that levalbuterol HFA was well-tolerated. Beta adrenergic agonists have been studied extensively and have the potential to produce certain beta-mediated adverse events, such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, dyspepsia, chest pain, arrhythmia, and worsening hypertension. Beta mediated adverse events were noted in the adult and pediatric clinical studies; however, the incidences were low. In adults, asthma-related adverse events tended to be more common in the active treatment groups than placebo, with a slightly higher incidence in the levalbuterol HFA treatment group than in the racemic albuterol HFA group. However this finding was not consistent with the pediatric study in which asthma-related AEs were more common in the placebo treatment group.

Hypokalemia and hyperglycemia are also considered systemic beta adrenergic effects. Minimal changes in the mean concentrations of glucose and potassium were noted in the clinical studies. However, a dose dependent increase in glucose concentration and decrease in potassium concentration were noted in the cumulative dose studies for both levalbuterol HFA and racemic albuterol HFA.

Beta agonists can also produce clinically significant cardiovascular effects including changes in heart rate, blood pressure, ECG changes, or cardiovascular symptoms. Clinically significant changes in heart rate and blood pressure were not noted in the clinical studies. Although there were no mean changes in ECG parameters across treatment groups, the cumulative dose studies showed an increase in QTc with cumulative dosing for both levalbuterol HFA and racemic albuterol HFA.

Device performance was not assessed in the Phase 3 clinical studies, but was incorporated into an ongoing safety study. In general, the device complaint rate was low with the most common complaints related to clogging. One limitation of the device performance data is that it does not provide device performance data for children age 4-11 years. The device complaints in the adult studies were generally clog-related, which leads this reviewer to believe device complaints in the pediatric population would also be clog related. Proper washing of the device appears to be important for reliable device performance.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen for adults and children 4 years of age and older is 2 inhalations (90 mcg) repeated every 4 to 6 hours. The adult dose ranging study showed that the dose selection of 90mcg levalbuterol HFA in adults appears to be appropriate. Although the Applicant also studied the 90mcg levalbuterol HFA dose in children, the pediatric dose ranging study suggested that 45mcg levalbuterol HFA may be just as effective in children. Therefore, in this reviewer's opinion, the 45mcg dose of levalbuterol HFA warrants further investigation in children. In terms

of the dosing frequency, the duration of effect of levalbuterol HFA ranges from 3-6 hours and thus, supports the dosing frequency.

1.3.5 Drug-Drug Interactions

The Applicant did not conduct formal drug-drug interaction studies as part of the levalbuterol HFA program, but referenced information regarding known drug-drug interactions with racemic albuterol. The Applicant included appropriate labeling regarding racemic albuterol drug interactions with beta blockers, diuretics, digoxin, monoamine oxidase inhibitors, and tricyclic antidepressants. The proposed label states that beta blockers can block the effect of beta adrenergic receptor agonists and can produce severe bronchospasm. For diuretics, the ECG changes and/or hypokalemia that may result from some diuretics could be worsened by beta agonists. Studies with racemic albuterol have shown that digoxin levels can decrease a mean 16-22% with racemic albuterol use. Finally, caution should be used when administering levalbuterol HFA with monoamine oxidase inhibitors or tricyclic antidepressants because the action of albuterol on the vascular system may be potentiated.

1.3.6 Special Populations

Special dosing is not recommended for levalbuterol HFA based upon race, gender, age, cardiac, endocrine, or respiratory disease. However, because of the potential beta mediated adverse effects, the proposed product label recommends cautious use in patients with cardiovascular disorders, convulsive disorder, hyperthyroidism, or diabetes mellitus.

There are no adequate and well-controlled studies in pregnant women; therefore, as with racemic albuterol, levalbuterol HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Similarly, it is not known if (R)-albuterol is excreted in human milk and, therefore, in nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The drug substance is levalbuterol tartrate. Levalbuterol is the (R)-enantiomer of albuterol and is a $beta_2$-adrenergic receptor agonist. The proposed trade name is Xopenex HFA Inhalation Aerosol. Xopenex HFA is a pressurized metered-dose aerosol inhaler (MDI), which produces an aerosol for oral inhalation. Levalbuterol HFA contains a microcrystalline suspension of levalbuterol tartrate in hydrofluoroalkane (HFA)-134a propellant, ethanol, and oleic acid. Thus, the proposed drug is a new MDI formulation of levalbuterol, which does not contain chlorofluorocarbons (CFCs).

The Applicant's proposed indication is the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.

The proposed dosing regimen for adults and children 4 years of age and older is 2 inhalations (90 mcg) repeated every 4 to 6 hours.

2.2 Currently Available Treatment for Indications

Currently, there are many $beta_2$-adrenergic receptor agonists available in a variety of formulations in the United States for the treatment of bronchospasm. Racemic albuterol, which is a mixture of both the (R) and (S)-enantiomers of albuterol, is available in inhalation solution, as an MDI (CFC), in tablet formulation, and as an HFA MDI. Levalbuterol, which is the R-enantiomer of albuterol, is currently available in the United States as an inhalation solution for nebulization. Currently, there are three other albuterol HFA MDIs approved for the treatment of bronchospasm: Proventil HFA, Ventolin HFA, and IVAX HFA Albuterol.

2.3 Availability of Proposed Active Ingredient in the United States

Levalbuterol tartrate is not currently marketed in the United States. Levalbuterol HCl inhalation solution was approved March 25, 1999, and is currently marketed as Xopenex Inhalation Solution. No major safety concerns or recent labeling changes due to safety concerns have been noted with levalbuterol hydrochloride.

2.4 Important Issues with Pharmacologically Related Products

Levalbuterol tartrate is a short acting $beta_2$-adrenergic agonist. No recent labeling changes, safety, or effectiveness concerns have been noted in members of the short-acting $beta_2$-adrenergic agonists. However, two issues with beta agonists are worth noting. First of all, the regularly scheduled use of a short acting inhaled beta agonist is controversial as some studies have shown an increase in adverse effects in some patients. The increase in adverse events may be related to asthma severity, tachyphylaxis, or polymorphisms of the beta adrenergic receptor. Second, within the last two years a large placebo-controlled safety study with salmeterol, which is a long acting beta agonist, showed a small increase in asthma related deaths in subjects in the salmeterol group versus subjects in the placebo group. Because of the results of this study, a Boxed Warning was placed on the product label of all salmeterol containing products.

One additional relevant issue is the CFC phase-out. The Montreal Protocol on Substances that Deplete the Ozone Layer is an international agreement designed to protect the ozone layer. The Montreal Protocol stipulates the phase out of CFCs, as these compounds could deplete the ozone layer. At some point, a decision will be made to phase out the currently marketed CFC MDIs. Levalbuterol HFA is a new MDI formulation of levalbuterol, which does not contain chlorofluorocarbons (CFCs) and would not be affected by the CFC phase out.

2.5 Presubmission Regulatory Activity

The following are pertinent regulatory milestones for the development of Xopenex HFA MDI. Although several meeting were held between the Division and the Applicant, an EOP-2 meeting was not requested.

- Sepracor submitted IND# 62,906 on July 11, 2001, for the Xopenex HFA MDI. Comments for the Sponsor included:
  - CFC data would not be acceptable to support dosing for HFA studies
  - Conduct dose ranging study
  - Conduct cumulative dose tolerability study
- Type C meeting on February 19, 2002, in which the Division provided the following guidance:
  - Device performance in actual clinical use needs to be addressed
  - A long-term safety study may not be required if the Applicant can cross-reference existing data on related products, such as racemic albuterol HFA and levalbuterol HCl. However, any differences between the products must be supported.
  - Define and support the proposed dose
  - Conduct PK/PD dose-ranging studies with 3 doses of Proventil HFA MDI and Xopenex HFA MDI in adults and children
    - If proceed to Phase 3 without dose ranging data, Sponsor enters Phase 3 at their own risk.
  - The Division stated that it is open to the length of the proposed study as long as the length could be justified.
    - 4 week study not long enough to look at life of device
    - 12 week study would provide adequate device exposure
    - 8 week study is possible provided device performance issue is adequately supported in the overall clinical program.
  - Perform a cumulative dose study comparing Proventil HFA MDI and Xopenex HFA MDI
- Special Protocol Assessment submitted March 18, 2002
  - SPA denied because appropriate dose not defined for Phase 3 studies
- Comments regarding protocols submitted May 22, 2002
  - Perform dose ranging studies
  - Perform cumulative dose study with Proventil HFA and Xopenex HFA
  - Discuss results with Division prior to Phase 3 study

Reviewer's Comment: The Applicant started one Phase 3 study in 5/02 and the other two in 12/02, but did not complete dose ranging studies until 2003.

- CMC/Clinical Meeting March 7, 2003
  - The Division noted that an EOP 2 meeting was not requested and the Division could not confirm the dose the Sponsor has chosen to pursue was appropriate.
- Type C Meeting October 29, 2003, in which the Division provided the following guidance:
  - Exercise challenge studies performed in dose ranging studies
  - The Division questioned whether the Applicant had acceptable data on device performance.
  - The Division indicated that all data the Applicant feels is necessary to support the safety of levalbuterol HFA should be submitted at the time of NDA submission.

- The Division indicated the Applicant's proposed dose selection of 90 mcg appeared appropriate.

- Type A Meeting (teleconference) January 5, 2004, in which device performance incorporation into 12 month safety study (051-356) was discussed.
  - The Division agreed with the plan for the Sponsor to test at least 100 non-complaint samples that have 35-50 actuations remaining.
  - The Division stated that the incidence of device malfunction should be the sum of all of the devices that malfunction on in-vitro testing divided by the number of devices used by patients in the study.
  - The Division stated if the entire device performance database is not submitted with the NDA, whether the data submitted is adequate to support the approval of the drug product will become a review issue.
- On May 11, 2004, Sepracor submitted NDA# 21-730 for Xopenex HFA Inhalation Aerosol.

2.6 Other Relevant Background Information

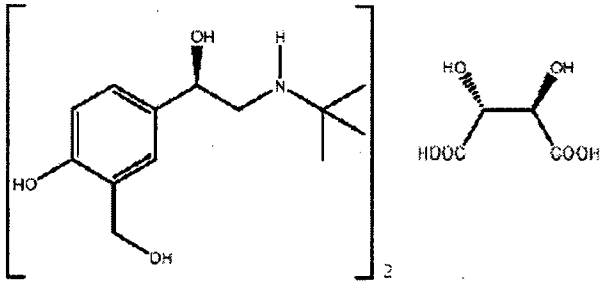
According to the Applicant, Xopenex HFA is not currently commercially marketed in any country and there have not been any foreign regulatory actions on Xopenex HFA.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

The drug substance is micronized levalbuterol tartrate. The chemical name is (R)-α^1-[[1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hemi-L-tartrate salt. The molecular weight is 628.71. The molecular structure of levalbuterol tartrate is shown in Figure 1.

Figure 1 Molecular Structure of Levalbuterol Tartrate



The drug product contains a microcrystalline suspension of levalbuterol tartrate in hydrofluoroalkane (HFA)-134a propellant, ethanol, and oleic acid. Xopenex HFA is a pressurized metered-dose aerosol inhaler (MDI), which produces an aerosol for oral inhalation. Thus, the proposed drug is a new MDI formulation of levalbuterol, which does not contain chlorofluorocarbons (CFCs).

For the Phase 3 clinical trials, the Applicant utilized levalbuterol HFA produced by two different manufacturers. The two different manufactured levalbuterols are referred throughout this review as levalbuterol HFA-A, which was manufactured at 3M and levalbuterol HFA-B, which was manufactured at — The proposed commercial manufacturer for levalbuterol HFA is 3M. The Applicant compared the following pertinent CMC attributes of the — and 3M product: actuator size/design, dose content uniformity, aerodynamic particle size, assay, ethanol, enantiomeric purity, water content, weight loss, microscopy, and impurities. The Applicant determined the products from the two manufacturers are comparable [N21730\N_000\2004-05-11\cmc\product.pdf, p 1877]. The Division's CMC Reviewer, Dr. Suong Tran agreed with the Applicant's conclusion.

Spacer Use

The Applicant conducted additional in vitro testing with spacers because the results of Phase 2 studies conduced with spacers indicated racemic albuterol HFA was more potent than levalbuterol HFA. The Applicant evaluated the impact of spacers and conditioning of spacers on the fine particle dose (FPD) of (R)-albuterol. The Applicant considers 'conditioning' to be the initial cleaning of the spacer according to manufacturer recommendations prior to initial use. According to the Applicant, conditioning a spacer minimizes potential electrostatic interactions between the plastic of the spacer and the aerosol cloud of some MDI products.

In vitro testing was performed using an Andersen Cascade Impactor. As shown below in Table 1, the mean FPD delivered with levalbuterol HFA and racemic albuterol HFA is increased with a conditioned spacer compared to no spacer. However, if levalbuterol HFA is delivered with an unconditioned spacer, the mean FPD actually decreases slightly compared to without a spacer. The FPD of racemic albuterol HFA is not significantly affected by the conditioning of the spacer. However, the conditioning of the spacer has an impact on the FPD delivered with levalbuterol HFA.

Table 1 The Impact of the Use of a Spacer on Fine Particle Dose						
	No Spacer		Unconditioned Spacer		Conditioned Spacer	
	Levalbuterol HFA	Proventil HFA	Levalbuterol HFA	Proventil HFA	Levalbuterol HFA	Proventil HFA
Mean emitted dose (mcg of (R) albuterol)	43.10	42.87	21.00	31.51	28.97	33.20
Mean Fine Particle Dose (FPD, mcg of (R) albuterol)*	23.09	23.19	20.40	30.05	28.19	31.66
Mean Fine Particle Fraction (%)**	53.6	54.1	97.2	95.4	97.3	95.4

* Fine Particle Dose is the mass of drug (expressed as free base) collected on Stages 3 and higher using the Andersen Cascade Impactor.
**Fine Particle Fraction is the fraction of the recovered emitted dose collected on Stages 3 and higher using Andersen Cascade Impactor.
Source: [N21730\N_000\2004-05-11\cmc\product.pdf, p 1885]

Reviewer's Comment: An interesting observation in the above table is the larger increase in FPD of (R)-albuterol with Proventil HFA delivered with an unconditioned spacer compared to levalbuterol HFA. This increase in FPD with Proventil HFA relative to levalbuterol HFA could impact the results of studies conducted with unconditioned spacers.

At the time of finalization of this review, Dr. Suong Tran, the Division's CMC reviewer, recommends an Approvable action for this application pending a satisfactory response to chemistry issues communicated to the Applicant during the review period.
Reviewer's Comment: Refer to Dr. Tran's CMC review for further details.

3.2 Animal Pharmacology/Toxicology

No pharmacology/toxicology studies were required for this NDA as (R)-albuterol is approved in many drug products, including levalbuterol HCl and racemic albuterol HFA. The pharmacology/toxicology reviewer, Dr. Virgil Whitehurst found no new pharmacology/toxicology issues with this application and recommends Approval.

3.3 DMETS and DDMAC

A DMETS and DDMAC consult provided no objection to the proposed tradename of Xopenex HFA. Both DMETS and DDMAC also provided labeling comments.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

All the clinical data for this review were obtained from clinical trials conducted by the Applicant. This is a 505(b)(2) application, which allows approval of the proposed drug to rely on the Agency's previous finding of safety and/or effectiveness for an approved drug, coupled with the information needed to support the change from the approved product. Thus, the Agency's

previous determination of the safety and efficacy of albuterol and Xopenex Inhalation Solution (NDA# 20-837, Sepracor, Inc.) support this application.

4.2 Tables of Clinical Studies

Table 2 provides a summary of the pivotal clinical studies in this application. Of note, Studies 051-355 and 051-354 were conducted with the levalbuterol HFA product produced by the proposed commercial manufacturer, 3M. Study 051-353 was conducted with the levalbuterol HFA product produced by [redacted]. Study 051-355 provided a comparison between the levalbuterol product produced by [redacted] (denoted by HFA-B) and the product produced by the proposed commercial manufacturer, 3M (denoted by HFA-A).

Table 2 Pivotal Studies for NDA# 21-730

Study #	Study Purpose/Relevance	Subjects	Design	Treatment Groups
051-353	Efficacy & Safety Adults/Adolescents	445 subjects 12 years and older with asthma	R, DB, PC, AC, MC, // 8 weeks	Levalbuterol HFA-B 90 mcg QID Proventil HFA180 mcg QID Placebo 2 actuations QID
051-355	Efficacy & Safety Adults/Adolescents	303 subjects 12 years and older with asthma	R, DB, PC, AC, MC, // 8 weeks	Levalbuterol HFA-A 90 mcg QID Levalbuterol HFA-B 90 mcg QID Proventil HFA 180 mcg QID Placebo 2 actuations QID
051-354	Efficacy & Safety Pediatric	150 subjects 4-11 years of age with asthma	R, DB, PC, AC, MC, // 4 weeks	Levalbuterol HFA-A 90 mcg QID Proventil HFA 180 mcg QID Placebo 2 actuations QID

R = randomized, DB = double blind, PC = placebo controlled, AC = active controlled, MC = multicenter, // = parallel group
Levalbuterol HFA-A: proposed commercial manufacturer, 3M
Levalbuterol HFA-B: early manufacturer [redacted]

Table 3 provides a summary of supportive clinical studies in this application.

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Table 3 Supportive Studies for NDA# 21-730

Study #	Study Purpose	Subjects	Design	Treatment Groups	Relevance to Review
051-305	Efficacy, Safety, Tolerability Adults/Adolescent	Males and females 12 years or older with asthma N = 162	R, MC, DB, PC, AC, // 4 weeks	Levalbuterol HFA-**B** 90 mcg Levalbuterol HFA-**B** 180 mcg Ventolin CFC 180 mcg Placebo	-Safety only -No efficacy b/c **early actuator design**
051-306	Efficacy, Safety, Tolerability Pediatric	Males and females 4 to 11 years of age with asthma N=127	R, DB, PC, AC, MC, // 4 weeks	Levalbuterol HFA-**B** 90 mcg Levalbuterol HFA-**B** 180 mcg Ventolin CFC 180 mcg Placebo	-Safety only -No efficacy b/c **early actuator design**
051-308	Dose Ranging EIB Adults/Adolescent	Males or females 12 years or older with asthma N=62	R, Modified-blind, AC, MC, //, 3x3 CO (5 +/- 2 day w/o) 3 weeks	Levalbuterol HFA-**A** 45 mcg Levalbuterol HFA-**A** 90 mcg Levalbuterol HFA-**A** 180 mcg Proventil HFA 90 mcg Proventil HFA 180 mcg Proventil HFA 360 mcg	-Safety -Dose response -No efficacy b/c all subjects used **spacers** and **not placebo-controlled**
051-309	Cumulative Dose Safety/Tolerability Adults/Adolescent	Males or females 12 years or older with asthma N=49	R, Modified-blind, AC, MC, 2 way CO 3 weeks	Levalbuterol HFA-**A** 16 cumulative actuations then Proventil HFA 16 cumulative actuations Proventil HFA 16 cumulative actuations then Levalbuterol HFA-**A** 16 cumulative actuations	-Safety
051-310	Cumulative Dose Safety/Tolerability Adults/Adolescent	Males or females 12 years or older with asthma N=32	R, Modified-blind, AC, MC, 2 way CO 3 weeks	Levalbuterol HFA-**A** 16 cumulative actuations then Proventil HFA 16 cumulative actuations Proventil HFA 16 cumulative actuations then Levalbuterol HFA-**A** 16 cumulative actuations	-Safety - No efficacy b/c all subjects used **spacers**
051-311	Cumulative Dose Safety/Tolerability Pediatric	Males and females 4 to 11 years of age with asthma N=31	R, DB, AC, MC, two treatment, two period CO 3 weeks	Spacer Cohort and No Spacer Cohort Levalbuterol HFA-**A** 8 cumulative actuations then Proventil HFA 8 cumulative actuations Proventil HFA 8 cumulative actuations then Levalbuterol HFA-**A** 8 cumulative actuations	-Safety -Comparison of spacer and non-spacer user
051-312	Dose Ranging EIB Pediatric	Males and females 4 to 11 years of age with asthma N=33	R, DB, AC, MC, //, 3x3 CO (5 +/- 2 day w/o) 4 weeks	Levalbuterol HFA-**A** 45 mcg Levalbuterol HFA-**A** 90 mcg Levalbuterol HFA-**A** 180 mcg Proventil HFA 90 mcg Proventil HFA 180 mcg Proventil HFA 360 mcg	-Safety -Dose response -Limited efficacy b/c **not placebo-controlled**
051-356	Safety Study Device Performance	Males or females 12 years or older with asthma N=547 (As of July 1, 2004) N= 650 (goal)	R, open-label, AC, MC, // 12 months	Levalbuterol HFA-**A** 90mcg Proventil HFA 180 mcg	-Safety **-Device performance**

R = randomized; DB = double blind; PC = placebo controlled; AC = active controlled; MC = multicenter; // = parallel group; CO = crossover; EIB = exercise induced bronchospasm; w/o = washout
Levalbuterol HFA-A: proposed commercial manufacturer, 3M
Levalbuterol HFA-B: early manufacturer, [redacted]

Several points are worth noting from the above table. First of all, all the studies will contribute to the safety database for levalbuterol HFA. Second, Studies 051-305 and 051-306 were conducted with an early actuator design and thus, will not contribute to the evidence of efficacy of levalbuterol HFA. Next, because Studies 051-308 and 051-310 were conducted with spacers, the studies can provide evidence of a dose response relationship, but because of the confounding effect of the spacers, Studies 051-308 and 051-310 cannot contribute to evidence of efficacy of levalbuterol HFA. Study 051-312 provides dose response data and some limited efficacy data. Studies 051-309 and 051-311 were primarily safety studies and do not contribute significantly to the efficacy analyses. Finally, Study 051-356 is an ongoing safety study, which provides the only data on device performance.

4.3 Review Strategy

The pivotal Phase 3 studies shown in Table 2 are the primary basis in this review to support the efficacy of levalbuterol HFA. Each of the pivotal studies is reviewed in detail in Section 10 - Appendices. In Section 6 – Integrated Review of Efficacy, the relevant efficacy results for the adult studies (051-355 and 051-353) are discussed together, while the relevant efficacy results for the pediatric population from Study 051-354 are presented separately. Although the Phase 2 studies primarily provide information on the dose response relationship of levalbuterol HFA and safety data, data supporting the efficacy of levalbuterol is included in the Integrated Review of Efficacy, where appropriate.

The following is a summary of the review strategy for the supporting studies listed in Table 3:

- Studies 051-305 and 051-306 are omitted from the efficacy analysis because the studies were conducted with an earlier actuator design. The results contribute to safety only.
- Studies 051-308 and 051-310 are summarized in Section 10 – Appendices. Because spacers were used, the studies do not contribute to the efficacy of levalbuterol HFA. Relevant dose-response information from Studies 051-308 and 051-310 are discussed in Section 5.2.1 – Dose-Response Relationship.
- Studies 051-309 and 051-311 were primarily safety studies and, thus, were not included in the efficacy analysis. The results are summarized in Section 10- Appendices and in the Integrated Review of Safety.
- Study 051-312 is summarized in Section 10- Appendices and provides dose-response information, which is discussed in Section 5.3 – Exposure Response Relationship.
- Study 051-356 is an ongoing safety study, which interim results are summarized in Section 10-Appendices and pertinent details are discussed in the Integrated Review of Safety.

Although safety data from all the studies is included in the safety analyses, the primary sources of safety data are the multidose clinical studies. Additional sources of safety include the postmarketing safety database of levalbuterol HCl, a literature review, and the safety of racemic albuterol, which is described in the labeling of approved albuterol products.

4.4 Data Quality and Integrity

A DSI audit was requested for this new formulation of levalbuterol. The following sites were selected based upon the number of subjects the investigators enrolled in the pivotal clinical studies.

- Study Center 0201, Dr. William C. Rees; Burke,Virginia
- Study Center 0017, Dr. Andrew J. Pedinoff; Princeton, New Jersey
- Study Center 1000, Dr. Angelique Barreto; Oklahoma City, Oklahoma

The DSI audit found no significant findings at Study Center 0201 and 0017. However, at Study Center 1000, several issues were noted. The inspectors noted a lack of calibration of the spirometer according to ATS guidelines. In addition, duplicate spirometry printouts were found for two or three spirometry attempts. Duplicate printouts were found in subsequent visits also. According to the report, Dr. Barreto did not maintain adequate and accurate recordkeeping and did not adhere to the investigational plan.
Reviewer's Comment: Dr. Barreto enrolled 10 subjects in Study 051-354. Due to the findings of the DSI audit, the Division's statistician analyzed the primary endpoint for Study 051-354 without the data from site 1000. The results of the study were not significantly affected by the deletion of the data from site 1000.

As noted in the following section, the Applicant conducted quality assurance audits of selected clinical sites and noted several sites to be non-compliant with GCP. Depending on the deficiencies noted, the Applicant adjusted the dataset to exclude data collected at certain non-compliant sites.

4.5 Compliance with Good Clinical Practices

The Applicant stated that the clinical studies for this application were conducted in compliance with Good Clinical Practices. The Applicant conducted GCP quality assurance audits of 61 sites out of a total of 223 clinical study sites that enrolled subjects. Of the sites audited, the Applicant noted the sites to be compliant with the exception of 8 investigational sites [N21730\N_000\2004-05-11\clinstat\clinsum.pdf, p 51]. Of the 61 sites audited, 8 sites were found to have deficiencies. Five sites in the pivotal studies were noted to be noncompliant with GCP. One site in Study 051-355 was found to have falsified data; however, this site only enrolled one subject. In Study 051-354, four sites were found to have data collection and reporting that did not meet minimum standards as well as other deficiencies. Collectively these sites enrolled 33 subjects (19%) in Study 051-354. The Applicant modified the dataset for analyses for Study 051-354 to adjust for some of the discovered deficiencies. However, the Applicant also conducted analyses on the ITT population.
Reviewer's Comment: The Applicant modified the dataset for Study 051-354 to exclude the data of 5 subjects (3 with implausible data, 2 with data collected by unqualified personnel). The Applicant's Modified ITT is acceptable. The Division's statistician performed an analysis of the primary endpoint for Study 051-354 without all of the data from the sites found to be non-compliant with GCP. The analysis without the data from the four sites did not significantly change the results of the primary endpoint analysis.

The clinical studies reviewed for this application specified obtaining informed consent from subjects prior to participation in the study. Protocol violations during the study appeared to be appropriately noted in the clinical study reports.

4.6 Financial Disclosures

The Applicant provided financial disclosure for the clinical investigators and indicated six investigators with financial ties to the Applicant [N21730\N_000\2004-05-11\other\financial.pdf, p 3]. Three of the six identified investigators enrolled 1 or no subjects in clinical studies. The other three investigators enrolled 5 – 15 subjects in the clinical studies. The investigator with financial ties to Sepracor who enrolled the most subjects was . He enrolled 15 subjects in and 10 subjects in . The small number of subjects enrolled by investigators with financial ties to the Applicant is unlikely to affect the results of the submitted studies.

5 CLINICAL PHARMACOLOGY

Several important clinical pharmacology conclusions can be made from the PK data submitted by the Applicant. First of all, the Applicant used population pharmacokinetics to show that for the same 90mcg dose of levalbuterol HFA, children have less exposure to (R)-albuterol than adults. Population pharmacokinetic parameters also demonstrated that in adults and children, exposure to (R)-albuterol was slightly less in the levalbuterol 90mcg HFA group compared to the racemic albuterol HFA 180mcg group.

Because some of the Phase 2 studies were conducted with spacers, the effect of spacer use on (R)-albuterol exposure was evaluated. In general, spacers increased the exposure of (R)-albuterol for both levalbuterol HFA and racemic albuterol HFA. However, even with the increased (R)-albuterol exposure with a spacer, the exposure of (R)-albuterol in the levalbuterol HFA group remained less than in the racemic albuterol HFA group.

Because the Applicant used two different manufacturers in the Phase 2 and 3 studies, the PK of the two different manufactured levalbuterol HFA products was compared in Study 051-355. The results indicate that the two different manufactured levalbuterol HFA products. and 3M, produced similar exposure to (R)-albuterol.

The Applicant chose 90mcg levalbuterol HFA as the appropriate dose for both adults and children. The Phase 2 dose ranging study, utilizing an exercise-induced bronchospasm model, suggests that 90mcg levalbuterol HFA is an appropriate dose in adults. However, the dose ranging study in the pediatric population, utilizing an exercise-induced bronchospasm model, suggests that the 45 mcg levalbuterol HFA dose may be effective in children.

The relationship between (R)-albuterol exposure and safety suggests that an increase in exposure to (R)-albuterol is associated with an increase in glucose, a decrease in potassium, and a prolongation of the QT interval. The lesser (R)-albuterol exposure with 90mcg levalbuterol HFA compared to the approved 180mcg racemic albuterol HFA dose supports the safety of 90mcg

levalbuterol HFA. It should be noted that this relies on the assumption that the presence of (S)-albuterol does not impact the safety of (R)-albuterol.

Details regarding the aforementioned pharmacology conclusions are addressed in the following sections.
Reviewer's Comment: For a detailed review of the clinical pharmacology data, refer to the review by Dr. Sandra Suarez of the Office of Clinical Pharmacology and Biopharmaceutics.

5.1 Pharmacokinetics

The Applicant did not conduct studies to investigate the absorption, distribution, metabolism, and excretion (ADME) of levalbuterol HFA, but did reference ADME studies in the Xopenex Inhalation Solution NDA. To summarize, (R)-albuterol is rapidly absorbed in the systemic circulation following an inhaled dose of levalbuterol. (R)-albuterol is primarily bound to α_1-glycoprotein in the circulation and is primarily metabolized by sulphotransferase (SULTIA3). A large first pass effect impacts the swallowed fraction of the inhaled dose. The primary route of elimination of albuterol enantiomers is through renal excretion [N21730\N_000\2004-05-11\hpbio\hpsum.pdf, p 10-11].

The Applicant did measure key pharmacokinetic parameters during the clinical studies, which are discussed in the following sections.

5.1.1 Adults and Children

The Applicant used population pharmacokinetics to show that for the same 90mcg dose of levalbuterol HFA, children have less exposure to (R)-albuterol than adults, as shown below in Table 4.

Table 4 Model Predicted Non-Compartmental PK Parameters for (R)-albuterol

Study Population	Parameter	Randomized Treatment	
		Levalbuterol 90mcg HFA	Proventil 180mcg HFA
Adults (≥ 12 years) Studies 051-353 and 051-355	C_{max} (ng/mL)	0.199	0.236
	t_{max} (hr)	0.54	0.53
	$AUC_{(0-6)}$ (ng·hr/mL)	0.695	0.798
Pediatrics (<12 years) Study 051-354	C_{max} (ng/mL)	0.163	0.238
	t_{max} (hr)	0.76	0.78
	$AUC_{(0-6)}$ (ng·hr/mL)	0.579	0.828

Source: [N21730\N_000\2004-05-11\hpbio\hpsum.pdf, p 44]

Reviewer's Comment : Interestingly, the PK assessments in the individual studies did detect (S)-albuterol in the levalbuterol treatment groups. The mean concentrations in the levalbuterol treatment groups were significantly lower than the (S)-albuterol concentrations in the racemic albuterol group. However, given that levalbuterol is only (R)-albuterol, it is not clear why any (S)-albuterol would be detected in the levalbuterol group. Possible theories include:1) the (S)-albuterol may have been residual from rescue medication use prior to the clinic visit as the highest concentrations were noted at Visit 2; 2) conversion from (R) to (S)-albuterol in vitro; or 3) conversion from (R) to (S)-albuterol in vivo.

5.1.2 Levalbuterol HFA versus Racemic Albuterol HFA

The same population pharmacokinetic parameters shown above in Table 4 demonstrate that exposure to (R)-albuterol was slightly less in the levalbuterol 90mcg HFA group compared to the racemic albuterol HFA 180mcg group. However, overall the PK parameters were quite similar between the two treatment groups, with the exception of a slightly smaller AUC with levalbuterol HFA. The decreased exposure to (R)-albuterol with levalbuterol HFA compared with racemic albuterol HFA is important for the racemic albuterol safety database to be applicable to levalbuterol HFA.

5.1.3 — versus 3M

The two different manufactured levalbuterol HFA products, — (B) and 3M (A), were compared in Study 051-355 and produced similar exposure to (R)-albuterol as shown below in Table 5.

Table 5 PK Parameters for (R)-albuterol and (S)-albuterol for Study 051-355

	Levalbuterol A			Levalbuterol B			Racemic Albuterol					
	(R) -albuterol			(R) -albuterol			(R) -albuterol			(S) -albuterol		
	n	Mean (SD)	Median (min-max)	n	Mean (SD)	Median (min-max)	n	Mean (SD)	Median (min-max)	n	Mean (SD)	Median (min-max)
C_{max} (ng/mL)	104	0.27 (0.24)	0.18 (0.02-1.23)	52	0.25 (0.22)	0.19 (0.03-1.19)	50	0.34 (0.50)	0.20 (0.04-3.46)	50	0.79 (0.62)	0.60 (0.06-3.93)
t_{max} (hr)	104	1.02 (1.50)	0.53 (0-8.0)	52	0.77 (0.82)	0.51 (0.2-8.0)	50	0.90 (1.35)	0.49 (0-8.0)	50	1.73 (1.72)	1.04 (0-8.0)
AUC $_{(0\text{-last})}$ (ng·hr/mL)	104	0.89 (0.41)	0.70 (0.08-3.40)	52	0.82 (0.61)	0.65 (0.22-3.39)	50	1.05 (1.30)	0.81 (0.09-9.34)	50	3.54 (1.99)	3.00 (0.29-9.05)
AUC $_{(0\text{-}4)}$ (ng·hr/mL)	97	0.57 (0.41)	0.50 (0.06-2.78)	51	0.54 (0.35)	0.46 (0.12-1.82)	48	0.69 (0.65)	0.54 (0.06-4.36)	48	2.28 (1.31)	2.00 (0.14-7.86)

Source: [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 110]

Reviewer's comment : From a CMC standpoint and from a PK exposure standpoint, the — and 3M levalbuterol HFA products are similar.

5.1.4 Additional PK Factors

The Applicant determined that gender and race had no impact on pharmacokinetics. In addition, according to the Applicant once body weight was taken into account, age did not have a significant impact on (R)-albuterol exposure. Drug-drug interaction studies were not conducted

for this application because the Applicant references the levalbuterol inhalation solution NDA for information regarding drug-drug interaction [N21730\N_000\2004-05-11\hpbio\hpsum.pdf, p 45-46].

5.2 Pharmacodynamics

The adult dose ranging study conducted by the Applicant suggests that the 90mcg levalbuterol HFA dose is a reasonable dose in adults; however, the adult dose ranging study was conducted with spacers, which confounds the results. The pediatric dose ranging study suggests that the 45mcg dose may provide the same degree of bronchoprotection as the 90mcg levalbuterol HFA dose. The Applicant preceded with the Phase 3 studies prior to completing the dose ranging studies. The Applicant's rationale for choosing the 90mcg levalbuterol HFA dose for children was based upon PK parameters and the similarity between adults and children in disease course and pathophysiology. Although the Applicant's rationale for 90mcg levalbuterol HFA in children is noted, the 45 mcg dose of levalbuterol HFA warrants further investigation in children.
Reviewer's Comment: In a meeting with the Applicant on October 29, 2003, the Division indicated that the Applicant's dose selection of 90mcg Xopenex HFA appeared appropriate.

5.2.1 Dose-Response Relationship

A review of the pre-submission regulatory activity indicates that the Division was concerned about the Applicant proceeding to Phase 3 without adequate dose ranging studies to confirm the appropriate dose selected for Phase 3. The Applicant did conduct two dose ranging studies; however, neither dose ranging study was completed prior to commencement of the Phase 3 studies.

The Applicant conducted two dose ranging studies, Study 051-308 in adults and Study 051-312 in children. Both dose ranging studies were randomized, double-blind, active controlled exercise challenge studies. Subjects underwent baseline exercise challenges and the degree of bronchospasm induced by the exercise challenge was measured by spirometry. Subjects were then treated with levalbuterol HFA or racemic albuterol HFA followed by an exercise challenge. The degree of bronchospasm induced by exercise challenge following medication use was measured by spirometry. The adult study was confounded by the use of spacers and thus, provides limited information.
Reviewer's Comment:

Reviewer's Comment: The dose ranging studies utilized an exercise induced bronchospasm (EIB) model. The dose that prevents EIB might not necessarily be the optimum clinical dose. However, these studies can be used to compare the study drug to an approved product. Unfortunately, this comparison was compromised in the adult studies because spacers were used.

Neither study showed a clear dose response for each dose of levalbuterol HFA. As shown below in Table 6, in the adult dose ranging study (051-308) both the 90mcg and 180mcg levalbuterol

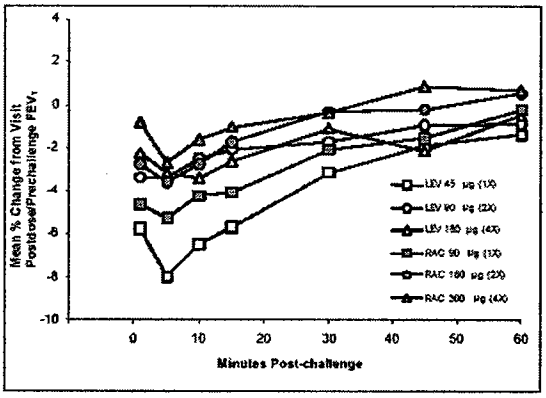
HFA were more bronchoprotective than 45mcg levalbuterol HFA; however, the difference was not statistically significant. The responses to the 90mcg and 180mcg levalbuterol HFA dose were similar, suggesting a plateau in the effect of levalbuterol above 90mcg. Key secondary endpoints in Study 051-308 suggested that 90mcg and 180mcg produced similar results and were more bronchoprotective than 45mcg levalbuterol HFA; however, the difference between the 45mcg and 180mcg levalbuterol HFA dose was not statistically significant. As shown below in Figure 2, the effect of levalbuterol appears to plateau after two actuations (90mcg).

Table 6 Dose Response - Study 051-308
Correctly Randomized Population Excluding Site 621

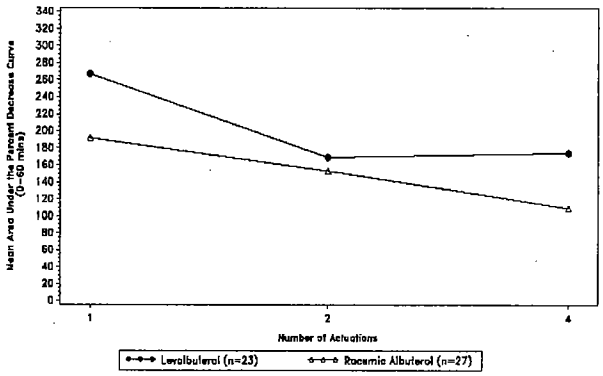
	Levalbuterol			Racemic Albuterol		
	45 mcg (n=23)	**90mcg (n=23)**	**180mcg (n=22)**	**90mcg (n=25)**	**180mcg (n=27)**	**360mcg (n=25)**
Percent Decrease from Visit Post-dose/Pre-challenge FEV1 AUC (Primary EP)						
Mean (SD)	267 (296)	169 (270)	174 (280)	192 (249)	153 (249)	109 (201)
LS Mean (±)	264 ± 66		171 ± 67	184 ± 48		109 ± 48
	Lev 45mcg vs. Lev 180mcg p=0.164			Rac 90mcg versus Rac 360mcg p=0.07		
	Point estimate of relative potency (90% CI) 0.491 (0.028, 2.836)					
Maximum Percent Decrease from Visit Post-dose/Pre-challenge FEV1 (Secondary EP)						
Mean (SD)	9.75 (8.7)	5.95 (6.7)	5.57 (6.7)	7.64 (8.6)	5.73 (7.0)	3.90 (5.1)
LS Mean (±)	9.45 ± 1.8		5.46 ± 1.9	7.54 ± 1.5		3.92 ± 1.5
	Lev 45mcg vs. Lev 180mcg p=0.055			Rac 90mcg versus Rac 360mcg p=0.026		
	Point estimate of relative potency (90% CI) 0.684 (0.211, 1.801)					

[N21730\N_000\2004-05-11\clinstat\adultasthma\051-308.pdf, p 76-78]

Figure 2 Dose Response in Study 051-308



NOTE: All doses of levalbuterol were produced at manufacturing site A (3M). The racemic albuterol comparator was Proventil® HFA



Source : [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 107 ; 051-308.pdf, p 486]

The choice of 90mcg levalbuterol HFA appears to be an appropriate dose in adults. Racemic albuterol HFA demonstrated a clear dose response relationship even above the currently approved dose of 180mcg. It should be noted, however, that Study 051-308 was conducted with spacers and therefore provides limited information.

In general, an increase in adverse events was not noted with increasing doses in the levalbuterol treatment group. A larger change in the potassium concentration was noted with increasing doses of levalbuterol HFA. The change in glucose did not show a consistent dose response relationship.

The second dose ranging study using an exercise challenge model (Study 051-312) was conducted in children and did not demonstrate a clear dose response relationship for either levalbuterol HFA or racemic albuterol HFA. Table 7 displays the results for the primary endpoint, the maximum percent decrease in FEV1 from visit post-dose/pre-challenge.

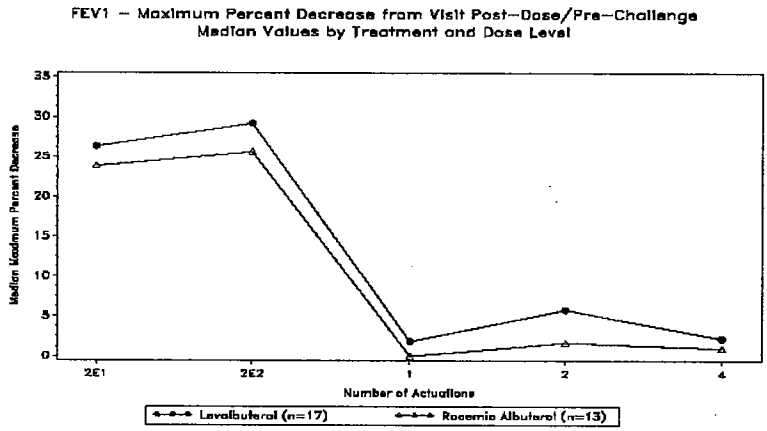
Table 7 Study 051-312 Maximum percent decrease in FEV1 from visit post-dose/pre-challenge (Primary EP) EVAL population

	Levalbuterol HFA			Racemic Albuterol HFA		
	45 mcg (n=16)	90mcg (n=16)	180mcg (n=16)	90mcg (n=16)	180mcg (n=16)	360mcg (n=16)
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	0.92, 6.70	2.81, 12.33	1.35, 9.13	0.69, 8.37	1.13, 4.25	0.78, 6.65

Source : [N21730\N_000\2004-05-11\clinstat\adultasthma\051-312.pdf, p 71]

As shown below in Figure 3, one actuation of levalbuterol HFA provided protection from bronchospasm in children.

Figure 3 Maximum % Decrease in FEV1 in Study 051-312



Reviewer's Comment: The above figure does not exactly match the Table 7 because the table displays the mean maximum percent decrease in FEV1 from visit post-dose/prechallenge, while the figure displays the median maximum percent decrease in FEV1 from visit post-dose/prechallenge.

At baseline following exercise challenge in this subject population the average decrease in FEV1 was approximately 27%. Thus, as shown above, one actuation of levalbuterol HFA (45mcg) and one actuation of racemic albuterol (180mcg) were bronchoprotective. Since the baseline average decrease in FEV1 following exercise challenge was 27%, all treatment groups appear to be effective in preventing bronchospasm. However, the 45 mcg dose of levalbuterol HFA appears to be as effective as the 90mcg or 180mcg dose. In general, no dose related increase in AEs was noted in either treatment group. Because of limited laboratory assessments, change in glucose and potassium with each dosing group was not assessed.

The Applicant suggested that because the disease course, pathophysiology, and drug effect are likely to be similar in adults and pediatrics subjects, comparable (R)-albuterol exposure supports the 90mcg levalbuterol HFA dose in children age 4-11. In addition, the Applicant stated that 90mcg levalbuterol HFA did not demonstrate any safety concerns indicating that a lower dose would not be required to address safety issues. That being said, the Applicant does state that 45mcg levalbuterol HFA may be effective in some patients.
Reviewer's Comment: The Applicant's rationale for 90mcg levalbuterol HFA in children is noted. However, the Division discourages exploring the exposure- efficacy relationship because plasma concentrations do not represent the drug concentration at the site of action. Although the 90mcg levalbuterol HFA dose did not appear to have additional safety concerns, the dose ranging study suggests 45 mcg dose of levalbuterol HFA may be effective in children. The Applicant includes language in the Dosage and Administration section of the proposed product label, which states that in some patients, 1 inhalation every 4 hour may be sufficient. This

language is consistent with other racemic albuterol products. However, the 45mcg dose of levalbuterol in children 4-11 years of age warrants further investigation.

5.3 Exposure-Response Relationships

This section will focus on the relationship between exposure and safety. The relationship between exposure and efficacy will not be explored because in meetings with the Applicant, the Division discouraged the exploration of the exposure of (R)-albuterol and key efficacy outcomes. The rationale for not exploring the exposure-efficacy relationship is that plasma concentrations do not represent the drug concentration at the site of action.

5.3.1 Exposure-Safety Relationship

Through analyses of the PK data and the glucose and potassium levels, the Applicant determined that serum glucose levels tended to increase with increasing (R)-albuterol levels and serum potassium levels tended to decrease with increasing (R)-albuterol levels. However, no consistent trend was noted with heart rate and (R)-albuterol levels. In addition, the Division's OCPB reviewer, Dr. Sandra Suarez noted a potential relationship between an increase in (R)-albuterol exposure and QT prolongation. As discussed above in Section 5.1 the PK data indicates that 90mcg levalbuterol HFA produces less exposure to (R)-albuterol than the currently marketed 180mcg racemic albuterol HFA. The slight decrease in (R)-albuterol exposure with 90mcg levalbuterol HFA compared to the approved 180mcg racemic albuterol HFA dose supports the safety of 90mcg levalbuterol [N21730\N_000\2004-05-11\hpbio\hpsum.pdf, p 33].

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication – Treatment or Prevention of Bronchospasm

The proposed indication for Xopenex HFA Inhalation Aerosol is for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease. This is consistent with the labeled indication for the currently approved albuterol products.

6.1.1 Methods

Studies 051-355 and 051-353 were the Phase 3 studies in adults and thus, are the primary basis in this review to support the efficacy of levalbuterol HFA in adults. Study 051-354 is the primary basis of support for the efficacy of levalbuterol HFA in the pediatric population. Given the presumed similarity of the disease in adults and children, the Division determined that a single Phase 3 study would be adequate to establish efficacy in children, provided that the two adult studies established efficacy in that population. Each of the pivotal studies is reviewed in detail in Section 10 - Appendices. The efficacy results for Studies 051-355 and 051-353 are discussed together, while the efficacy results for the pediatric population, Study 051-354, are presented separately. Phase 2 studies, which provide information regarding the dose response of

levalbuterol HFA, were discussed in detail in Section 5.2.1 Dose Response Relationship. Relevant efficacy data from supporting Phase 2 studies are included in the Integrated Review of Efficacy, where appropriate.

6.1.2 General Discussion of Endpoints

For the development of a drug to treat/prevent bronchospasm, FEV_1 is the most appropriate primary outcome variable. Typically, for a bronchodilator the Division looks at the change in FEV1 from predose or baseline, which is a well-established clinically meaningful endpoint. The degree of change in FEV1 that is clinically meaningful is less well-established. However, to assess an acute bronchodilator response, the American Thoracic Society recommends a 12% increase from baseline FEV1 and an absolute change in FEV1 of at least 200mL.

The Applicant chose to determine the peak percent change in FEV1 at each of the visits when serial spirometry was measured and then average the peak percent change as the primary efficacy endpoint. Although the primary endpoint chosen by the Applicant is acceptable, averaging the peak percent change in FEV1 from several visits could obscure the results from each individual visit. Thus, the peak percent change in FEV1 at each clinic visit, a secondary endpoint, is also reviewed. Additional FEV1 variables discussed in the review include: peak percent change in FEV1 from study baseline, AUC percent change FEV1, percent predicted FEV1, percent change in FEV1from visit predose, time to onset of a 15% increase in FEV1, time to peak effect in FEV1, and the duration of 15% increase in FEV1.

Although endpoints involving FEV1 are the primary basis to support efficacy, other pulmonary function tests variables, such as FVC and FEF25-75%, are reviewed to support the efficacy of levalbuterol HFA. Finally, asthma symptoms, quality of life, global evaluations, and rescue medication use are analyzed.

Another important issue is the clinical comparison between the two different manufactured levalbuterol HFA products utilized in the pivotal studies: levalbuterol HFA-A (3M), the proposed commercial manufacturer and levalbuterol HFA-B [redacted]. Study 051-355 is the only clinical study comparing the efficacy of both manufacturers of levalbuterol HFA. A comparison of the CMC and PK exposure to (R)-albuterol from both manufactured levalbuterol products demonstrates the products are comparable. A clinical comparison of the two manufactured levalbuterol HFA products is discussed in Section 6.1.4.1.7.

Finally, a secondary objective of each of the studies is a comparison between levalbuterol HFA and racemic albuterol HFA. Although the studies were not designed/powered for a formal comparison between the products, a brief discussion of the comparison between levalbuterol HFA and racemic albuterol HFA is provided. A more detailed discussion of the comparison between levalbuterol HFA and racemic albuterol HFA in each Phase 3 study is located in the Appendices.

6.1.3 Study Design

The three pivotal studies (Study 051-353, Study 051-355, and Study 051-354) were adequate and well-controlled studies and provide a reasonable assessment of the degree of bronchodilation provided by levalbuterol HFA in patients with asthma. As shown below in Table 8, the pivotal studies were similar in design – multicenter, randomized, double-blind, placebo-controlled, active-controlled, parallel group studies in subjects with asthma. The adult studies were 8 weeks in duration, while the pediatric study was 4 weeks in duration.

Reviewer's Comment: The phase 3 clinical studies did not evaluate the prevention or treatment of acute bronchospasm. The clinical studies evaluated the bronchodilator effects of levalbuterol HFA in patients with asthma. Because of the Agency's previous determination of efficacy of racemic albuterol and levalbuterol HCl for the prevention and treatment of bronchospasm, the design of the studies is adequate to support the prevention and treatment of acute bronchospasm indication.

Reviewer's Comment: Typically, the Agency recommends clinical trials evaluating the efficacy of bronchodilators be approximately 12 weeks in duration to assess the durability of the treatment effect and the drug-device-patient interaction [Guidance to Industry: Clinical Development of MDI and DPI for Pulmonary Indications]. However, the length of the pivotal studies was discussed with the Applicant in a meeting on February 19, 2002. In that meeting, the Division indicated it was open to a shorter duration study, such as 8-weeks, provided device performance was adequately addressed in the overall clinical program.

The pediatric study was only 4 weeks duration. According to the Agency's Guidance for MDI/DPI development, the duration of pediatric trials for bronchodilators is dependent upon the prior knowledge about the product in the pediatric population and the characterization of the product in the adult population. Given the fact that levalbuterol is the (R)-enantiomer of racemic albuterol, racemic albuterol has been studied extensively in children, and a related medication (levalbuterol HCl) was determined to be safe and effective in children by the Division, a 4-week clinical trial in children is acceptable.

Table 8 Summary of the Phase 3 Studies for Levalbuterol HFA (NDA# 21-730)

Study #	Study Purpose/Relevance	Subjects	Design	Treatment Groups
051-353	Efficacy & Safety Adults/Adolescents	445 subjects 12 years and older with asthma	R, DB, PC, AC, MC, // 8 weeks	Levalbuterol HFA-B 90 mcg QID Proventil HFA180 mcg QID Placebo 2 actuations QID
051-355	Efficacy & Safety Adults/Adolescents	303 subjects 12 years and older with asthma	R, DB, PC, AC, MC, // 8 weeks	Levalbuterol HFA-A 90 mcg QID Levalbuterol HFA-B 90 mcg QID Proventil HFA 180 mcg QID Placebo 2 actuations QID
051-354	Efficacy & Safety Pediatric	150 subjects 4-11 years of age with asthma	R, DB, PC, AC, MC, // 4 weeks	Levalbuterol HFA-A 90 mcg QID Proventil HFA 180 mcg QID Placebo 2 actuations QID

Levalbuterol HFA-A: proposed commercial manufacturer, 3M
Levalbuterol HFA-B: early manufacturer, —

Reviewer's Response: Study 051-355 was the only study to provide a comparison between levalbuterol HFA-A and levalbuterol HFA-B.

In the three pivotal studies, following a one week run-in period, a total of 748 adult subjects with asthma and 150 subjects aged 4-11 years with asthma were randomized to receive levalbuterol HFA, Proventil HFA (racemic albuterol HFA), or placebo QID. Eligible subjects had a history of asthma with an FEV1 $\geq$ 45% and $\leq$ 75% (adults) or $\leq$ 80% (pediatric), airway reversibility of $\geq$12%, and otherwise in good health. The entry criteria for the Phase 3 studies were reasonable. Serial spirometry was measured at baseline (Visit 2), at four weeks (Visit 4), and at 8 weeks (Visit 6) in the adult studies, while serial spirometry was measured at baseline (Visit 2), two weeks (Visit 4), and four weeks (Visit 6) in the pediatric study. On those clinic days, spirometry was measured at the following times: pre-dose, immediately post-dose, 0.25, 0.50, 0.75, 1.0, 1.25, 1.50, 1.75, 2, 3 hours, then hourly up to 8 hours. Additional efficacy endpoints, such as asthma symptoms, quality of life, global assessments, and rescue medication use were collected at various times during the studies.

The Applicant chose 90mcg of levalbuterol HFA for the Phase 3 studies. The Phase 2 dose ranging study was conducted with spacers and thus provides limited support for the choice of the 90mcg levalbuterol HFA dose. Although the pediatric dose ranging study suggested that the 90mcg levalbuterol HFA would be effective in children, the study also suggested that the 45mcg levalbuterol HFA dose may also be effective in children. Details regarding the dose-response relationship are discussed in Section 5.2.1, Dose-Response Relationship.
Reviewer's Comment: The Division indicated the Applicant's proposed 90mcg dose of levalbuterol HFA appeared appropriate in the October 29, 2003, meeting with the Applicant.

6.1.4 Efficacy Findings

6.1.4.1 Adult Studies (Study 051-353 and Study 051-355)

6.1.4.1.1 Demographics and Baseline Characteristics

The demographics and baseline characteristics of the subjects in Studies 051-353 and 051-355 were quite similar. The average age of the subjects was between 35 and 37 years. Approximately 50% of the subjects were males. Around seventy percent of the subjects were white, 18% were black, 2-3% were Asian, and 7-8% were Hispanic. At screening, the average FEV1 was 2.2L (64-65% predicted)
[N21730\N_000\2004-05-11\clinstat\ise.pdf, page 72-73].

6.1.4.1.2 Primary Endpoint

Both of the adult studies demonstrated that levalbuterol HFA was superior to placebo on the pre-specified primary endpoint, the peak percent change in FEV1from visit predose average over the double blind period. As shown in Table 9, the peak percent change for levalbuterol HFA averaged over the double blind period was between 23-26% versus 12-14% in the placebo group. In assessing an acute bronchodilator response, the ATS recommended criteria are a 12% increase from baseline FEV1 and an absolute change of at least 200mL. Thus, a peak percent change in FEV1 of 23-26% is not only statistically significant, but is also clinically significant.

Table 9 Primary Endpoint: Peak Percent Change FEV1 from Visit Predose Averaged over the Double-Blind Period - Study 051-353 and Study 051-355			
	Levalbuterol HFA-A* 90 mcg	**Levalbuterol HFA- B* 90 mcg**	**Placebo** HFA-134a
Study 051-353 (N)	--	219	107
LS Mean ± SE		25.63 ± 0.87	13.94 ± 1.21
Pairwise p-value vs. placebo**		**<0.001**	
Study 051-355 (N)	122	62	59
LS Mean ± SE	25.33 ± 1.05	23.01 ± 1.46	12.45 ±1.49
Pairwise p-value vs. placebo**	**<0.001**	**<0.001**	

* Levalbuterol HFA-A was manufactured at 3M; Levalbuterol HFA-B was manufactured at —
**Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. Tests were performed using a one degree of freedom contrast.
Source : [N21730\N_000\2004-05-11\clinstat\ise.pdf, page 79]

The mean treatment effect size produced by levalbuterol is likely clinically meaningful. The treatment effect size is the peak percent change in FEV1 in the levalbuterol group minus the peak percent change in FEV1 in the placebo group. For levalbuterol, the treatment effect size averaged over the double-blind period ranged from 10.56%-12.88%. The treatment effect size is not consistently greater than 12% and thus, does not satisfy the ATS criteria for a bronchodilator. However, the average treatment effect of 10.56-12.88% is likely clinically meaningful. In addition, in assessing a clinically meaningful degree of bronchodilation, it is not customary to consider placebo responses.
Reviewer's Comment: It is unclear to this reviewer why the placebo group had a 12-13% response. The large placebo response negatively affects the treatment effect size.

Reviewer's Comment: The Division's Statistician analyzed the data for the primary endpoint and agrees with the Applicant's analysis.

6.1.4.1.3 Secondary FEV1 Endpoints

Levalbuterol HFA was superior to placebo for the peak percent change in FEV1 from visit predose at each study visit. Because averaging the peak percent change at each visit combines the response at each visit , Table 10 displays the peak percent change FEV1 from visit predose for Day 1 (Visit 2) and Day 56 (Visit 6). The data below indicates a decrease in the peak percent change in FEV1 from Visit 2 to Visit 6, for levalbuterol HFA-B and placebo.

Table 10 Peak Percent Change FEV1 from Visit Predose for Visit 2 and Visit 6 Study 051-353 and Study 051-355

	Levalbuterol HFA-A* 90 mcg	Levalbuterol HFA-B* 90 mcg	Placebo HFA-134a
Study 051-353 (N)	--	219	107
Visit 2 - LS Mean ± SE		30.94 ± 1.19	19.67 ± 1.67
Pairwise p-value vs. placebo**		<0.001	
Visit 6- LS Mean ± SE		22.25 ± 1.19	10.70 ±1.61
Pairwise p-value vs. placebo**		<0.001	
Study 051-355 (N)	122	62	59
Visit 2 - LS Mean ± SE	24.86 ± 1.32	26.24 ± 1.83	13.87 ± 1.88
Pairwise p-value vs. placebo**	<0.001	<0.001	
Visit 6- LS Mean ± SE	24.99 ± 1.43	19.90 ± 2.00	12.43 ± 2.05
Pairwise p-value vs. placebo**	<0.001	0.010	

* Levalbuterol HFA-A was manufactured at 3M; Levalbuterol HFA-B was manufactured at —
**Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and visit predose FEV1 as the covariate. Tests were performed using a one degree of freedom contrast.
Source : [N21730\N_000\2004-05-11\clinstat\051-355.pdf p 235-237 ; 051-353.pdf, p 121].

A closer examination of the data indicates the decrease in response from Visit 2 to Visit 6 for levalbuterol HFA-B was primarily due to an increase in visit predose FEV1 values. A review of the results of the peak percent change FEV1 from study baseline for Visit 2 and Visit 6 for levalbuterol HFA-B showed a decline of 1-3% from Visit 2 to Visit 6, versus a 7-8% decline noted for levalbuterol HFA-B when using the visit predose FEV1. Thus, the visit predose FEV1 increased from Visit 2 to Visit 6 for the levalbuterol HFA-B treatment group. In Study 051-353, from Visit 2 to Visit 6 the predose FEV1 increased 6.33% for the levalbuterol HFA-B group and 6% for the placebo group, while in Study 051-355, the predose FEV1 increased 5.3% in the levalbuterol HFA-B and 5.65% in the placebo group while the levalbuterol HFA-A group actually had a decrease in predose FEV1 by 1% [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 90].

Reviewer's Comment: In Study 051-355, it is unclear why the visit predose FEV1 increased from Visit 2 to Visit 6 primarily in the levalbuterol HFA-B treatment group and decreased in the levalbuterol HFA-A group. The decline in visit predose FEV1 of 1% with levalbuterol HFA-A is likely not clinically significant. The peak percent change in FEV1 for levalbuterol HFA-A remained constant during the study.

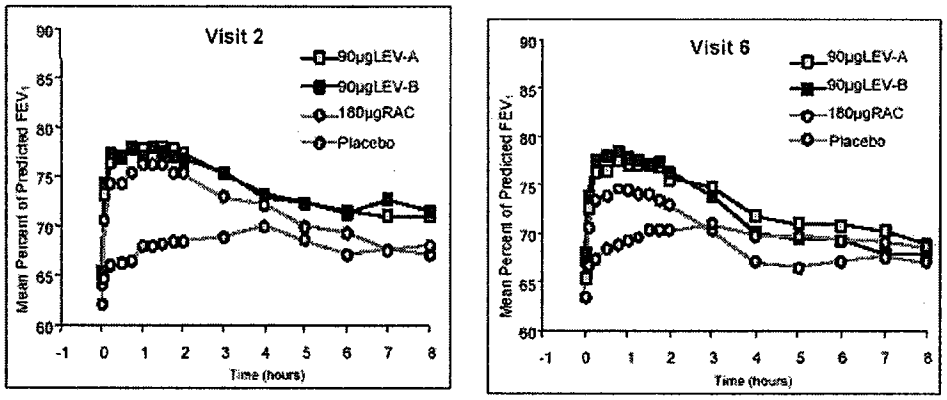
Additional FEV1-related secondary endpoints support the efficacy of levalbuterol HFA. Levalbuterol HFA was superior to placebo for the following endpoints: the area under the FEV1 percent change from visit predose curve, percent predicted FEV1, percent change in FEV1 from visit predose, time to onset of a 15% increase in FEV1, time to peak effect, and the duration of 15% increase in FEV1.

In both adult studies, levalbuterol HFA was superior to placebo for the area under the FEV1 percent change from visit predose curve. The 90mcg levalbuterol HFA treatment group in both studies were significantly better than placebo ($p < 0.001$) for the AUC FEV1 percent change from visit predose curve averaged over the double blind treatment period as well as at Visit 2 and 6,

with the exception of levalbuterol HFA-B in Study 051-355. At Visit 6 in Study 051-355, 90 mcg levalbuterol HFA-B was not significantly different from placebo (p=0.204) for the area under FEV1 percent change curve. The Applicant suggested the increase in visit predose FEV1 partially explains the failure to observe a statistical significance at Visit 6 for levalbuterol HFA-B [N21730\N_000\2004-05-11\clinstat\ise.pdf, table 11.1].

Levalbuterol HFA was superior to placebo in the peak percent predicted FEV1 and percent predicted FEV1. The Applicant included the following graphs in the proposed product label from Study 051-355 displaying the mean percent predicted FEV1 at Day 1 (Visit 2) and Day 56 (Visit 6).

Figure 4 Study 051-355 Mean Percent of Predicted FEV1 Visit 2 and Visit 6



Source: [N21730\N_000\2004-05-11\clinstat\ise.pdf, figure 11.1.2.3-1, p 87]

The percent of predicted FEV1 in both adult studies increased immediately after dosing in the levalbuterol groups and improvement continued for at least three to four hours after dosing.

Reviewer's Comment

For completeness, the percent predicted FEV1 versus time from Study 051-353 is shown below in Figure 5.

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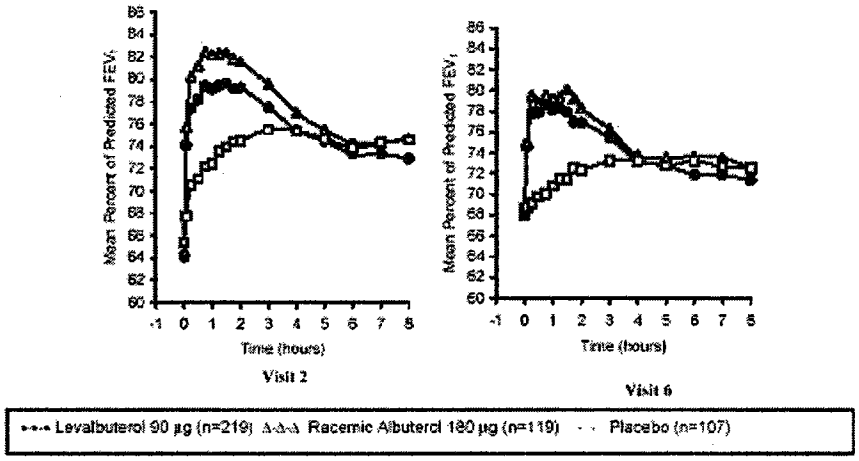
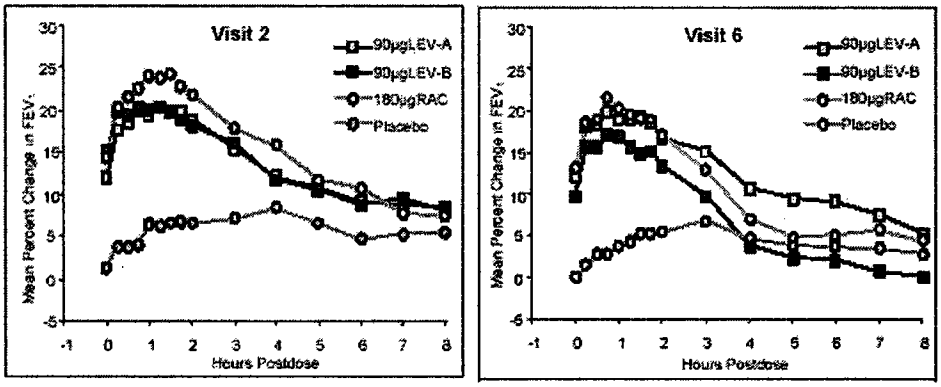
Figure 5 Study 051-353- Mean Percent Predicted FEV1at Visits 2 and 6



Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, page 98]

Another secondary endpoint, the percent change in FEV1 from visit predose for levalbuterol HFA was greater than placebo in both studies at most time points.
following graphs in Figure 6 which show the percent change in FEV1 for Visit 2 and Visit 6 for Study 051-355 [N21730\N_000\2004-05-11\clinstat\ise.pdf, figure 11.1.2.4-1, p 89].

Figure 6 Study 051-355 Mean Percent Change from Visit predose in FEV1 Visit 2 and Visit 6



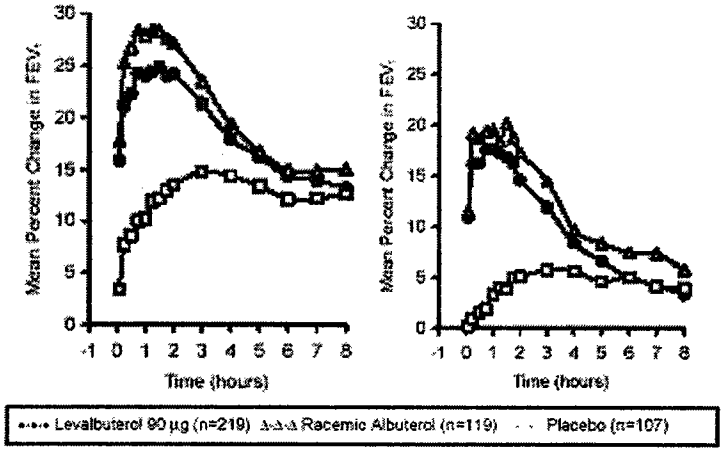
Source: [N21730\N_000\2004-05-11\clinstat\ise.pdf, figure 11.1.2.3-1, p 89]

Reviewer's Comment:

Study 051-353 had the largest number of subjects in the

levalbuterol treatment group. Although not conducted with the product manufactured by 3M, the product is similar from a CMC standpoint.

Figure 7 Study 051-353 Mean Percent Change from Visit predose in FEV1 Visit 2 and Visit 6



Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, page 95]

In terms of responder analyses, Studies 051-353 and 051-355 showed that at each visit, there were more responders in the levalbuterol HFA group than in the placebo group. Responders were defined as subjects with at least one post-dose FEV1 value ≥15% above the visit predose value. As shown in Table 11, the studies showed the time to onset of 15% response was faster in the active treatment groups and the duration of response was longer in the active treatment groups compared to the placebo group. In the active treatment groups, the time to onset increased from Visit 2 to Visit 6. The duration of response decreased from Visit 2 to Visit 6. In general, the duration of response of racemic albuterol was longer than levalbuterol HFA.

APPEARS THIS WAY ON ORIGINAL

Table 11 Time to Onset and Duration of 15% Increase in FEV1 from Predose for Visit 2 and Visit 6 for Study 051-353 and Study 051-355
(Responders and Non-Responders)

median time (minutes)	**Levalbuterol HFA- A* 90 mcg**	**Levalbuterol HFA-B* 90 mcg**	**Racemic Albuterol HFA 180mcg**	**Placebo** HFA-134a
Study 051-353				
Time to onset of 15% response-Visit 2	--	6.3	4.0	224.7
Time to onset of 15% response-Visit 6	--	50.7	29.8	UTD
Duration of response Visit 2 (responders & non resp)	--	184	260	2
Duration of response Visit 6 (responders & non resp)	--	33	64	0
Duration of response Visit 2 (responders only)		252	292	113
Duration of response Visit 6 (responders only)		149	164	99
Study 051-355				
Time to onset of 15% response-Visit 2	10.2	5.5	6.7	UTD
Time to onset of 15% response-Visit 6	16.3	41.5	37.9	UTD
Duration of response Visit 2 (responders & non resp)	118	168	228	0
Duration of response Visit 6 (responders & non resp)	103	53	72	0
Duration of response Visit 2 (responders only)	176	202	255	147
Duration of response Visit 6 (responders only)	178	164	178	34

* Levalbuterol HFA-A was manufactured at 3M; Levalbuterol HFA-B was manufactured at [redacted]
UTD – unable to determine because less than 50% of the subjects responded

Reviewer's Comment: The Applicant's proposed product label states that for Xopenex HFA the median time to onset of a 15% increase in FEV1 ranged from 5.5 to 10.2 minutes, [redacted]

[redacted] The Applicant's proposed product label states that for Xopenex HFA, the median duration of a 15% increase in FEV1 was 3 to 4 hours, with a duration of effect in some patients up to 6 hours. This duration of effect is for responders only and should be clarified in the product label.

Both studies showed the time to peak FEV1 observed post-dose was shorter in the levalbuterol HFA treatment group than in the placebo treatment group. In Study 051-353, the median time to peak change in FEV1 in the levalbuterol HFA-B group ranged from 73-77 minutes whereas in the placebo group the median time to peak change in FEV1 ranged from 106-178 minutes and in the racemic albuterol group the median time to peak change in FEV1 ranged from 70-76 minutes [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 290]. In Study 051-355, the median time to peak change in FEV1 in the levalbuterol HFA-A, levalbuterol HFA- B, racemic albuterol, and placebo groups was 71-76 minutes, 48-78 minutes, 67-84 minutes, and 122-180 minutes, respectively [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 283].
Reviewer's Comment: The Applicant's proposed product label states the median time to peak effect for Xopenex HFA ranged from 76 to 78 minutes. The proposed language is acceptable.

6.1.4.1.4 Additional Secondary Endpoints

Other spirometric endpoints, such as FVC and FEF25-75% support the efficacy of levalbuterol HFA. Levalbuterol HFA was statistically superior to placebo for peak percent change FVC averaged over the double blind treatment period as well as at Visit 2 and 6, with the exception of levalbuterol B in Study 051-355. At Visit 6 in Study 051-355, the peak percent change in FVC with 90 mcg levalbuterol HFA-B was not significantly different from placebo (p=0.069) [N21730\N_000\2004-05-11\clinstat\ise.pdf, table 25.1]. Finally, both studies showed the peak percent change in FEF25-75% averaged over the double blind treatment period as well as at Visit 2 and Visit 6 were statistically superior to placebo [N21730\N_000\2004-05-11\clinstat\ise.pdf, tables 26.1 and 27.1].

Although not statistically significant, additional secondary endpoints provide some support of the efficacy of levalbuterol HFA. Physician and subject global assessment of asthma symptoms at Visit 6 in both studies showed an improvement in over half the patients in the levalbuterol HFA treatment group compared to 36% in the placebo group. At the end of the study, rescue medication use was generally less in the levalbuterol HFA treatment groups (1.02 puffs per day, 2.23 days per week) than in the placebo group (1.43 puff per day, 2.77 days per week) in the adult multiple dose studies [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 94-95; iss.pdf p112]. However, asthma symptom scores and quality of life measured with questionnaires did not show any notable differences between treatment groups.

6.1.4.1.4.1 Secondary Endpoints– Comparison with Racemic Albuterol

As a secondary objective, both studies investigated the efficacy of levalbuterol HFA versus racemic albuterol HFA. The adult studies demonstrated that levalbuterol HFA and racemic albuterol produce similar clinical responses. In both studies, racemic albuterol HFA showed a larger peak percent change FEV1 averaged over the double blind period (primary endpoint) than levalbuterol HFA. As shown in Table 12, the difference between the two products was statistically significant in Study 051-353 (p=0.018).

For several secondary endpoints in Study 051-353, such as AUC for FEV1 percent change averaged over the double blind period, peak percent predicted FEV1 averaged over the double blind period, and peak percent change FEF 25-75% averaged over the double blind period, racemic albuterol HFA produced a greater (statistically significant $p<0.05$) response than levalbuterol HFA. In contrast, levalbuterol HFA produced a greater (but not statistically significant) response for several secondary endpoints in Study 051-355. For other pertinent endpoints, the results for levalbuterol HFA and racemic albuterol HFA were similar. Therefore, although there were statistically significant differences in the adult studies between levalbuterol HFA and racemic albuterol HFA, the results were not consistent across studies.

Table 12 Levalbuterol HFA Compared to Racemic Albuterol HFA Primary Efficacy Variable - Study 051-353 and Study 051-355			
	Levalbuterol HFA-A*	**Levalbuterol HFA-B***	**Racemic Albuterol HFA**
Study 051-353 (N)		219	107
Peak percent change FEV1 from visit predose averaged over the double blind period - LS Mean ± SE		25.63 ± 0.87	28.98 ± 1.15
Pairwise p-value vs. racemic albuterol**		0.018	
Study 051-355 (N)	122	62	59
Peak percent change FEV1 from visit predose averaged over the double blind period - LS Mean ± SE	25.33 ± 1.05	23.01 ± 1.46	26.14 ±1.49
Pairwise p-value vs. racemic albuterol **	0.654	0.132	

* Levalbuterol HFA-A was manufactured at 3M; Levalbuterol HFA-B was manufactured at —
**Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. Tests were performed using a one degree of freedom contrast.
Source : [N21730\N_000\2004-05-11\clinstat\ise.pdf, page 79].

Reviewer's Comment: In the proposed product label, the Applicant states —

. Thus, the language in the proposed label —

— *is not recommended.* —

6.1.4.1.5 Subgroup Analyses of Studies 051-353 and 051-355

Subgroup analyses showed the only consistent pattern of response was that subjects with more severe disease appeared to have a greater response to levalbuterol HFA than subjects with mild/moderate asthma. Otherwise, subgroup analyses showed no consistent pattern for age, gender, race, or steroid use. In terms of age, only 25 subjects greater than 65 years of age were enrolled in the two studies and the peak percent change in FEV1 did not show any significant pattern with respect to age. A similar proportion of males and females were enrolled in each study arm and the results for the primary endpoint were similar across genders. Although steroid users who used levalbuterol HFA-B in Study 051-355 demonstrated a smaller improvement in peak percent change in FEV1, this was not consistent with the results of Study 051-353. Thus, no clear pattern of response with regard to steroid use was noted [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 96, 98-99].

For the primary endpoint, subgroup analyses did not suggest a consistent pattern with respect to race. In Study 051-355, Hispanics and others demonstrated a smaller response with levalbuterol HFA-A, while blacks demonstrated a smaller response with levalbuterol HFA-B. The Applicant appropriately states that the results in Hispanics and other racial categories should be interpreted with caution due to the small number of subjects. In addition, the smaller response in blacks

with levalbuterol HFA-B in Study 051-355 was not consistent with the results in blacks in Study 051-353. Finally, although a smaller response for Hispanics and blacks was noted with levalbuterol HFA in Study 051-355, the response with levalbuterol HFA in Hispanics and blacks was still greater than the response with placebo [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 97].

6.1.4.1.6 Support of Efficacy from Phase 2 Study

The use of spacers in Study 051-308 (adult dose ranging study) and lack of placebo control limits the contribution of Study 051-308 to the efficacy of levalbuterol HFA.

6.1.4.1.7 — and 3M Manufacturers

Based upon the efficacy data from Studies 051-353 and 051-355, levalbuterol HFA-A demonstrated a greater response than levalbuterol HFA-B. The Division's CMC reviewer, Dr. Suong Tran, analyzed the pertinent CMC attributes of the two different manufactured products and determined the — and 3M product are comparable. A pharmacokinetic comparison of the two products indicates the (R)-albuterol exposure produced by both manufactured products is similar (Table 5). Study 051-355 provides a direct comparison of the pharmacodynamic effect of the two different manufactured products and is described in detail in the Appendices. A comparison of the primary efficacy variable(Table 65) and key secondary efficacy variables (Table 66) indicates that levalbuterol HFA-A produced numerically greater responses for many endpoints than levalbuterol HFA-B. It is unclear why the levalbuterol HFA products produced by different manufacturers with similar CMC attributes would demonstrate a difference in responses. However, the fact that levalbuterol HFA-A, which was manufactured by 3M (the to-be-marketed manufacturer) demonstrated a numerically greater response is reassuring.

6.1.4.2 Pediatric Study (Study 051-354)

Study 051-354 was the single pediatric Phase 3 study with levalbuterol HFA and provides the primary basis for the efficacy of levalbuterol HFA in children. A detailed review of Study 051-354 is located in the Appendices; however, pertinent efficacy variables are discussed in the following sections. In addition, a Phase 2 dose ranging study (051-312) provides some supportive efficacy data and will be summarized briefly.

For Study 051-354, the Applicant performed analyses on a Modified ITT population, which excluded data from two subjects who had PFTs collected by an unqualified staff member and three subjects who had clinically implausible spirometry values (FEV1 >200%).
Reviewer's Comment: The modification of the analysis population is acceptable. The Applicant also analyzed the data utilizing the ITT population.

6.1.4.2.1 Demographics and Baseline Characteristics

The average age of the subjects was 8.4 years and the study enrolled a predominance of males (63%). Approximately 51% were white, 32% black, 15% Hispanic, and 2% Asian. At screening, the average FEV1 was 1.35L or 70% predicted. The mean duration of treatment during the four weeks of double blind dosing was 27.3 days [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 124].

6.1.4.2.2 Primary Endpoint

Study 051-354 demonstrated that levalbuterol HFA was superior to placebo for the pre-specified primary endpoint, the peak percent change FEV1 from visit predose averaged over the double blind period. The peak percent change for levalbuterol HFA averaged over the double blind period was 26% versus 17% in the placebo group, which was statistically significant (P<0.001) as shown below in Table 13. The peak percent change in FEV1 of 25-26% is also considered clinically significant.

Table 13 Primary Endpoint: Peak Percent Change FEV1 from Visit Predose Averaged over the Double-Blind Period - Study 051-354 (Modified ITT)

	Levalbuterol HFA-A* 90 mcg	Racemic Albuterol HFA 180 mcg	Placebo HFA-134a
Study 051-354 (N)	74	38	33
LS Mean ± SE	25.63 ± 1.34	21.81 ± 1.83	16.75 ± 1.94
Pairwise p-value vs. placebo**	**<0.001**		

*Levalbuterol HFA-A was manufactured at 3M

**Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. Tests were performed using a one degree of freedom contrast.

Source : [N21730\N_000\2004-05-11\clinstat\ise.pdf, page 129].

Reviewer's Comment: The Division's Statistician agrees with the Applicant's analysis of the primary endpoint. The Applicant's analysis of the primary endpoint using the ITT population did not show any significant difference between any of the treatment groups. This can be explained by the fact that in the Modified ITT population, the data from three subjects was removed because of implausible values (FEV1>200%). Two of the subjects were in the placebo group while one of the subjects was in the racemic albuterol group. Because the study had a small number of subjects, the inclusion of two subjects with FEV1 values greater 200% significantly changes the LS Mean of the placebo group to 29.56. Thus, in the ITT population, neither levalbuterol HFA nor racemic albuterol HFA demonstrated a significant response over placebo.

6.1.4.2.3 Secondary FEV1 Endpoints

Levalbuterol HFA was superior to placebo for the peak percent change in FEV1 from visit predose at Visit 2 and Visit 6. Table 14 displays the peak percent change FEV1 from visit predose for Day 1 (Visit 2) and Day 28 (Visit 6). As noted in the adult studies, the data below shows a decrease in the peak percent change in FEV1 from Visit 2 to Visit 6.

Reviewer's Comment: Of note, neither levalbuterol HFA nor racemic albuterol HFA were superior to placebo at Visit 4.

Table 14 Peak Percent Change FEV1 from Visit Predose for Visit 2 and Visit 6 Study 051-354 (Modified ITT)

	Levalbuterol HFA- A* 90 mcg	Racemic Albuterol HFA 180 mcg	Placebo HFA-134a
Study 051-354 (N)	74	38	33
Visit 2 - LS Mean ± SE	33.14 ± 2.51	29.56 ± 3.43	17.77 ± 3.64
Pairwise p-value vs. placebo**	<0.001		
Visit 6- LS Mean ± SE	22.41 ± 1.53	19.25 ± 2.02	11.30 ± 2.19
Pairwise p-value vs. placebo**	<0.001		

*Levalbuterol HFA-A was manufactured at 3M
**Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. Tests were performed using a one degree of freedom contrast.
Source: [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p95].

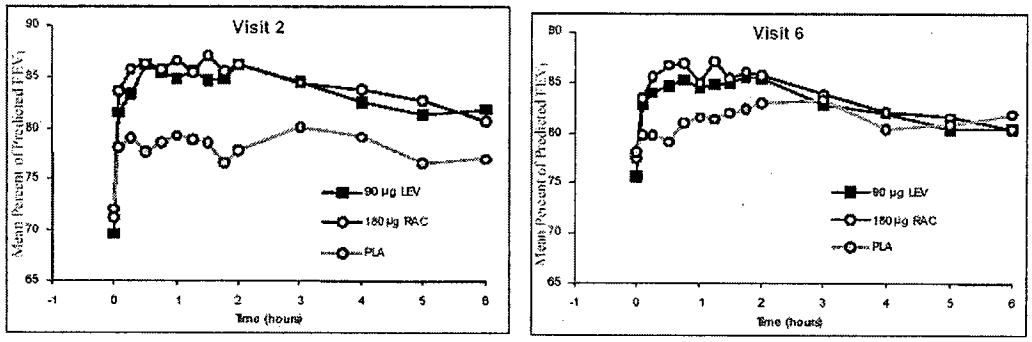
The decrease in response from Visit 2 to Visit 6 noted in all three treatment groups was primarily due to an increase in visit predose FEV1 values. A review of the results of the peak percent change FEV1 from study baseline for Visit 2 and Visit 6 showed no significant decline in response from Visit 2 to Visit 6. The peak percent change in FEV1 from study baseline declined less than <1% from Visit 2 to Visit 6, versus a decline of 8-10% noted for each of the treatment groups when using the visit predose FEV1. The mean increase in visit predose FEV1 from Visit 2 to Visit 6 was 8.96%, 9.69%, and 8.18% in the levalbuterol HFA, racemic albuterol HFA, and placebo groups, respectively [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 889].
Reviewer's Comment: It is unclear why the study baseline FEV1 increased in all the treatment groups during the four week treatment period. Contributing factors could be inappropriate washout from previous dose or a regression to the mean.

Additional FEV1 related secondary endpoints support the efficacy of levalbuterol HFA in children. Levalbuterol HFA was superior to placebo for the following endpoints: the AUC for FEV1 percent change from visit predose, peak percent predicted FEV1, and percent change FEV1 from visit predose. These endpoints are discussed in the following section.

Levalbuterol HFA was superior to placebo for the AUC FEV1 percent change from visit predose averaged over the double blind treatment period as well as at Visits 2 and 6. A decrease in the AUC FEV1 percent change was again noted from Visit 2 to Visit 6. The decrease from Visit 2 to Visit 6 is likely secondary to the increase in the visit predose FEV1 [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 131].

Levalbuterol HFA was superior to placebo in the peak percent predicted FEV1 and percent predicted FEV1.

Figure 8 Percent Predicted FEV1 at Visits 2 and 6 by Treatment in Study 051-354 (Modified ITT)

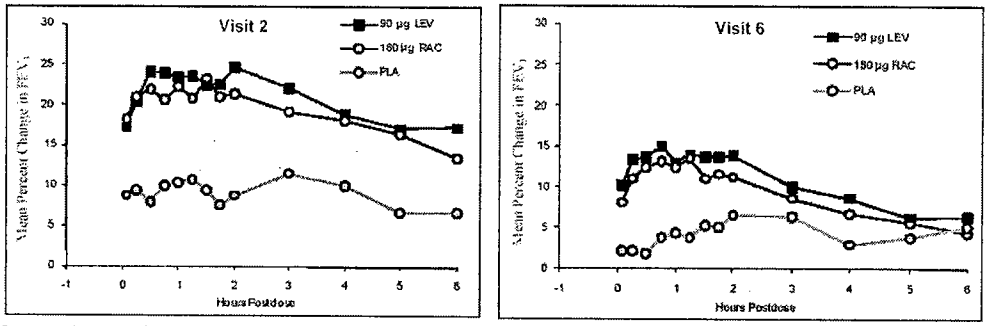


Source: [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 133]

As shown above in Figure 8, the percent predicted FEV1 in Study 051-354 increased immediately after dosing in the levalbuterol HFA group and improvement continued for at least 6 hours at Visit 2 and 3 hours at Visit 6.

The percent change in FEV1 from visit predose for levalbuterol HFA was greater than placebo at most time points. The Applicant chose the following graphs for the product label, which show the percent change in FEV1 for Visit 2 and Visit 6 in Study 051-354. The percent change in FEV1 increased immediately after dosing with levalbuterol HFA and racemic albuterol HFA. At Visit 2, the improvement was noted for at least 6 hours, while the duration of improvement at Visit 6 was 3 to 6 hours. [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 135].

Figure 9 Percent Change in FEV1 from Visit Predose at Visit 2 and 6 for Study 051-354 (Modified ITT)



Source: [N21730\N_000\2004-05-11\clinstat\ise.pdf, p135]

Reviewer's Comment: —

—

Study 051-354 showed that at each visit, there were more responders in the levalbuterol HFA group than in the placebo group. Responders were defined as subjects with at least one post-dose FEV1 value ≥ 15% above the visit predose value. Table 15 displays the responder data for Study 051-354. Study 051-354 also showed that the time to onset of response was lower in the levalbuterol HFA group than in the placebo group. Also, the duration of response was longer in the levalbuterol HFA group than in the placebo group. Finally, Study 051-354 demonstrated the time to peak change FEV1 was shorter in the levalbuterol treatment group than in the placebo treatment group [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 136-138].

Table 15 Time to Onset and Duration of 15% Increase in FEV1 , Time to Peak Change from Predose for Visit 2 and Visit 6 for Study 051-354 (Modified ITT)

Median time (minutes)	**Levalbuterol HFA-A* 90 mcg**	**Racemic Albuterol HFA 180mcg**	**Placebo** HFA-134a
Study 051-354 (N)	74	38	33
Responders Visit 2 (%)	82.4	81.6	51.5
Responders Visit 6 (%)	66.2	54.3	27.6
Time to onset of 15% response-Visit 2	4.5	4.9	272
Time to onset of 15% response-Visit 6	40	102	UTD
Duration of response Visit 2 (responders & non- resp)	147	213	3
Duration of response Visit 6 (responders & non- resp)	33	17	0
Duration of response Visit 2 (responders only)	186	261	70
Duration of response Visit 6 (responders only)	76	103	54
Time to peak change Visit 2	77	77	90
Time to peak change visit 6	78	62	123

*Levalbuterol HFA-A was manufactured at 3M
UTD – unable to determine because less than 50% subjects were responders
[N21730\N_000\2004-05-11\clinstat\051-354.pdf, p 297; N21730\N_000\2004-05-11\clinstat\ise.pdf, p 137-138]

Reviewer's Comment: As noted in the adult studies, the time to onset of response increased from Visit 2 to Visit 6 and the duration of response decreased from Visit 2 to Visit 6. The time to onset

at Visit 6 was shorter in the levalbuterol HFA group than in the racemic albuterol HFA group. In responders, the duration of response with levalbuterol HFA was shorter than racemic albuterol HFA.

Reviewer's Comment: The proposed product label states ' —— *This statement is not entirely correct and is not recommended for the product label.*

Reviewer's Comment: The Applicant stated the following in the product label: 'For Xopenex HFA, the median time to onset of a 15% increase in FEV1 was 4.5 minutes and the median time to peak effect was 77 minutes. The median duration of effect as measured by a 15% increase in FEV1 was 3 hours, with a duration of effect in some pediatric patients up to 6 hours.' The median time to onset of a 15% increase in FEV1 quoted by the applicant was for Visit 2 only. In addition, the median duration of effect of 3 hours quoted by the Applicant was for Visit 2 only. This should be clarified in the product label.

6.1.4.2.4 Additional Secondary Endpoints

$FEF_{25-75\%}$ supports the efficacy of levalbuterol HFA in children. Levalbuterol HFA was statistically superior to placebo for peak percent change $FEF_{25-75\%}$averaged over the double blind period and at Visit 2 and Visit 6. In addition, the change in FVC at each visit was measured and, in general, was greater in the levalbuterol HFA treatment group than the placebo treatment group [N21730\N_000\2004-05-11\clinstat\051-354.pdf, p 417-427].

Subjects in the active treatment groups demonstrated a greater decrease in rescue medication use (when compared to the single-blind run-in period) compared to the placebo group. The largest decrease in rescue medication use was noted in the last two weeks of the study (-0.72 days in the levalbuterol HFA, -0.62 days in racemic albuterol HFA and +0.35 days in the placebo group) [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 164-165].

Additional secondary endpoints do not show any significant difference between treatment groups and thus, do not provide support of the efficacy of levalbuterol HFA in children. Physician and subject global assessment of asthma symptoms at Visit 6 showed an improvement in approximately two thirds of the subjects in all the treatment groups. In addition, asthma symptom scores collected with questionnaires improved in all treatment groups. Finally, the quality of life responses as measured by the Pediatric Asthma Quality of Life Questionnaire remained stable during the course of the study [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 138-139].

6.1.4.2.5 Secondary Endpoints- Comparison with Racemic Albuterol

Study 051-354 demonstrated that in children levalbuterol HFA produced numerically higher results compared to racemic albuterol HFA. As shown below in Table 16, for the primary efficacy variable, levalbuterol HFA showed a larger peak percent change FEV1 than racemic albuterol HFA; however, the difference was not statistically significant. As shown in Table 74 and Table 75 in the Appendices, for many secondary endpoints, including peak percent change

FEV1 at each visit, AUC FEV1 percent change, peak change FEF25-75%, and peak percent predicted FEV1, levalbuterol HFA produced slighter greater response than racemic albuterol HFA; however, the difference was not statistically significant.

Table 16 Primary Endpoint: Peak Percent Change FEV1 from Visit Predose Averaged over the Double-Blind Period - Study 051-354 (Modified ITT)

	Levalbuterol-HFA-A* 90 mcg	Racemic Albuterol HFA 180 mcg	Placebo HFA-134a
Study 051-354 (N)	74	38	33
LS Mean ± SE	25.63 ± 1.34	21.81 ± 1.83	16.75 ± 1.94
Pairwise p-value vs. racemic albuterol**	0.086		

*Levalbuterol HFA-A was manufactured at 3M
**Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. Tests were performed using one degree of freedom contrast.
Source: [N21730\N_000\2004-05-11\clinstat\ise.pdf, page 129].

One difference noted between levalbuterol HFA and racemic albuterol HFA in Table 15 is the median duration of 15% increase FEV1. In responders, the median duration of 15% response with levalbuterol HFA was less than racemic albuterol HFA.
Reviewer's Comment: In the proposed product label, the Applicant states —

—

—

— *Thus, this language is not recommended for the product label.*

6.1.4.2.6 — and 3M Manufacturers

The levalbuterol HFA utilized in all the pediatric studies, including Study 051-354, was manufactured at 3M, the proposed commercial manufacturer. Thus, the Applicant could not perform a comparison between the manufacturers of levalbuterol HFA.

6.1.4.2.7 Subgroup Analyses

Because there was only one Phase 3 pediatric study, it is difficult to make any significant conclusions from subgroup analyses. The following were noted from the subgroup analyses: subjects 4-5 years demonstrated a larger peak percent change in FEV1 from visit predose averaged over the double blind period than children age 6-11. Hispanics (11 subjects) and Asian (1) pediatric subjects in the levalbuterol HFA treatment group did not demonstrate any significant change in FEV1 from visit predose averaged over the double blind period compared to Hispanic (6) and Asian (1) pediatric subjects in the placebo group. There was no significant pattern of response across genders. Steroid non users in the levalbuterol HFA and placebo group had greater improvements in FEV1 from visit predose averaged over the double blind period than steroid users. The opposite was noted in the racemic albuterol HFA group. Subgroup analyses indicated subjects with a greater percent reversibility at screening had a better response to all treatments [N21730\N_000\2004-05-11\clinstat\ise.pdf, p 140-141].

6.1.4.2.8 Support of Efficacy from Phase 2 Study

Study 051-312 provides some support for the efficacy of levalbuterol HFA in pediatric subjects. Study 051-312 was an active controlled, dose ranging study utilizing exercise to induce

bronchospasm in children aged 4-11 years. The primary efficacy variable was FEV1, which was obtained pre-dose, post dose, and serially post exercise challenge. The primary endpoint was the maximum percent decrease in FEV1 from visit post-dose/pre-challenge FEV1 (the smaller the percent decrease, the better protection from exercise induced bronchoconstriction). At baseline following exercise challenge the decrease in FEV1 was on average approximately 27%. As shown below in Table 17, the lowest dose of levalbuterol HFA and racemic albuterol HFA were bronchoprotective.

Table 17 Study 051-312 Maximum percent decrease in FEV1 from visit post-dose/pre-challenge (Primary EP) EVAL population

	Levalbuterol HFA			Racemic Albuterol HFA		
	45 mcg (n=16)	90mcg (n=16)	180mcg (n=16)	90mcg (n=16)	180mcg (n=16)	360mcg (n=16)
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	0.92, 6.70	2.81, 12.33	1.35, 9.13	0.69, 8.37	1.13, 4.25	0.78, 6.65

Reviewer's Comment: Although both levalbuterol HFA and racemic albuterol HFA showed some protection from exercise induced bronchospasm, no dose response was noted with either treatment. A more detailed discussion of the exposure response relationship is located in Section 5.2.1. Additional details of Study 051-312 are located in the Appendices.

Study 051-312 was not placebo controlled and thus, provides only limited support of the efficacy of levalbuterol HFA.

No dose response relationship was noted with either levalbuterol HFA or racemic albuterol HFA. The results of Study 051-312 suggest that 45 mcg levalbuterol HFA may be effective in children.

6.1.5 Clinical Microbiology

This section is not applicable since levalbuterol is not an antimicrobial.

6.1.6 Efficacy Conclusions

Studies 051-353 and 051-355 were two adequate and well controlled studies that demonstrated levalbuterol HFA is superior to placebo and support the proposed indication of the treatment and prevention of bronchospasm in adults and adolescents. The peak percent change for levalbuterol HFA averaged over the double blind period (pre-specified primary endpoint) was between 23-26% versus 12-17% in the placebo group. The peak percent change in FEV1 in the levalbuterol HFA treatment group is both statistically and clinically significant. Levalbuterol HFA is also superior to placebo for key secondary endpoints (percent change FEV1, percent predicted FEV1, AUC FEV1 percent change, FVC, FEF25-75%). Although not statistically significant, additional endpoints such as physician and subject global assessments and rescue medication use, provide support of the efficacy of levalbuterol HFA.

Study 051-354 was an adequate and well controlled study that demonstrated levalbuterol HFA is superior to placebo supporting the proposed indication of the treatment and prevention of

bronchospasm in children age 4-11 years. The peak percent change for levalbuterol HFA averaged over the double blind period (pre-specified primary endpoint) was between 25.6% versus 16.8% in the placebo group. The peak percent change in FEV1 in the levalbuterol HFA treatment group is both statistically and clinically significant. Levalbuterol HFA is also superior to placebo for key secondary endpoints (percent change FEV1, percent predicted FEV1, AUC FEV1 percent change, FEF25-75%).

All three Phase 3 clinical studies (051-353, 051-355, 051-354) demonstrated that levalbuterol HFA and racemic albuterol HFA produce similar clinical responses in adults, adolescents, and children age 4-11. Generally, the differences noted between levalbuterol HFA and racemic albuterol HFA were not statistically significant. Although an occasional statistically significant difference was noted, usually the differences were not consistent from study to study.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The sources of data reviewed to support the efficacy of levalbuterol HFA included the following: the safety data from the Applicant's Phase 3 studies, the safety data from the supporting Phase 2 studies, postmarketing safety data for Xopenex Inhalation Solution, a literature review provided by the Applicant, and the safety update, which includes interim data from on ongoing safety study (Study 051-356). For the purposes of the safety review, safety data from both manufacturers of levalbuterol (levalbuterol HFA-A and levalbuterol HFA-B) as well as safety data using an earlier actuator design are combined.

The adult/adolescent data and the pediatric safety data will be addressed separately. The Applicant presented the safety data for adults/adolescents as follows:

- Pooled multidose studies
    - Study 051-353 and Study 051-355 (Phase 3 studies)
    - Study 051-305 (multidose study with earlier actuator design)

Reviewer's Comment : Study 051-305 was a multidose study in adults utilizing levalbuterol HFA 90mcg and 180mcg with an earlier actuator design. Although the Applicant pooled Study 051-305 with the Phase 3 adult studies, the two Phase 3 adult studies data were pooled without Study 051-305, where appropriate.

Reviewer's Comment: The ECG data from Study 051-305 was <u>not</u> pooled with Studies 051-353 and 051-355. The ECGs in Study 051-305 were investigator read only and were not over-read by a central ECG facility as in Studies 051-353 and 051-355.

- Cumulative dose safety studies presented separately
    - Study 051-309
    - Study 051-310

Reviewer's Comment: The Applicant separated the two cumulative dose studies because Study 051-309 was conducted without the use of spacers and Study 051-310 was conducted with the use of spacers. Spacer use increased the (R)-albuterol exposure when used with racemic albuterol HFA and thus, the Applicant stated pooling the two studies was not appropriate.

Although, the Applicant's rationale for separating the two cumulative dose safety studies is reasonable, this review will combine the cumulative dose safety study data, when appropriate.

- Dose ranging study
  - Study 051-308

Similarly, the Applicant presented the safety data from the pediatric studies as follows:

- Pooled multidose studies
  - Study 051-354 (Phase 3 study)
  - Study 051-306 (Phase 2 study with earlier actuator design)

Reviewer's Comment : Study 051-306 was a multidose study in children utilizing levalbuterol HFA 90mcg and 180mcg with an earlier actuator design. Although the Applicant pooled Study 051-306 with the Phase 3 pediatric study, the pediatric Phase 3 study data is reviewed without Study 051-306, where appropriate.
Reviewer's Comment: The ECG data from Study 051-306 was not pooled with Study 051-354. The ECGs in Study 051-306 were investigator read only and were not over-read by a central ECG facility as in Study 051-354.

- Cumulative dose safety studies
  - Study 051-311 (Phase 2 study)
- Dose ranging study
  - Study 051-312

In general, the Applicant's pooling of data within study types is reasonable. The majority of the safety data for this review comes from the multidose studies because the multidose studies have more subjects, provide more exposure to the study medication, and are placebo-controlled. The dose-ranging studies and cumulative dose studies provide additional safety data, but this review emphasizes the multiple dose studies. Thus, the approach taken in the following review will follow the Applicant's pooling of safety data as outlined above. Deviation from this approach will be indicated and explained, where appropriate.

7.1.1 Deaths

No deaths were noted in any adult or pediatric study conducted for this application.

7.1.2 Other Serious Adverse Events

A review of the SAEs in both the adult and pediatric Phase 2-3 studies does not suggest a safety signal. In this reviewer's opinion only one SAE reported may be related to levalbuterol HFA. The potentially related SAE was asthma, which was reported in the levalbuterol HFA treatment group in one of the adult studies. Although the asthma exacerbation may be related to levalbuterol HFA, the report was complicated by concomitant drug abuse. A more detailed discussion of the SAEs reported in the adult and pediatric studies follows.

Overall, 12 SAEs were noted in the adult clinical studies. SAEs were noted in the Phase 3 studies only, while none were noted in the Phase 2 studies. The reported SAEs in the adult

studies are listed in Table 18 below. The Applicant utilized the following definition for a serious adverse event: an SAE is any event that is fatal or life-threatening, is permanently disabling, requires or prolongs hospitalization, is a congenital anomaly, or requires intervention to prevent permanent damage. This definition is consistent with the definition in FDA regulations referring to NDA post-marketing reports [21 CFR 314.80(a)].

Table 18 Serious Adverse Events for Adult Studies

	Levalbuterol HFA 90 mcg n=445	Racemic Albuterol HFA 180 mcg n=218	Placebo n=206
	n(%) / # events	n(%)/ # events	n(%)/ # events
Any SAE	4 (0.9) / 7	2 (0.9) / 2	3 (1.5) / 3
Accidental Injury	2 (0.4) / 4	0	0
Chest Pain	0	1 (0.5) / 1	0
Cyst	1 (0.2) / 1	0	0
Appendicitis	0	0	1 (0.5) / 1
Herniated C5/C6 Disc	0	1 (0.5) / 1	0
Hypertension	1 (0.2) / 1	0	0
Asthma	1 (0.2) / 1	0	1 (0.5) / 1
Prostatic disorder	0	0	1 (0.5) / 1

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 67-70]

Reviewer's Comment: The percentage of subjects reporting SAEs was slightly less in the active treatment groups than in the placebo group.

In the pediatric studies, only two SAEs were noted after randomization. Both SAEs were GI related – one case of gastroenteritis in the racemic albuterol HFA group and one case of constipation in the racemic albuterol HFA washout group.

The Applicant's narratives and CRFs were reviewed for the SAEs noted in the levalbuterol HFA group. In this reviewer's opinion, most of the SAEs are clearly not related to levalbuterol HFA. The accidental injuries (ACL ligament tear, medial meniscus injury, concussion, lumbar fracture) were either pre-existing conditions or secondary to a fall. The ovarian cyst is likely unrelated. The hypertension and asthma SAE were noted in the same individual. The asthma SAE may be related to levalbuterol use. However, the case was complicated by drug use (cocaine and opioids), which could also explain the elevated blood pressure and wheezing.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Generally, greater than 88% of the subjects in both the adult and pediatric studies completed the Phase 2- 3 studies. In the adult multidose studies, the drop out rate was similar among the treatment groups. In the adult multidose studies, discontinuation due to AEs was similar in the levalbuterol HFA 90mcg and racemic albuterol HFA treatment groups. In the pediatric multidose studies, the drop out rate was slightly higher in the levalbuterol 90mcg treatment group than in the placebo group; however, discontinuation due to AEs was highest in the placebo

group. The most common reason for discontinuation in both the adult and pediatric studies was adverse events, which is discussed in the next section, 7.1.3.2. A more detailed discussion of the disposition of subjects in the adult and pediatric studies follows.

Table 19 summarizes the disposition of subjects in the adult/adolescent multiple dose studies. In general, the percentage of subjects terminating the study early was similar among the treatment groups, except the 180mcg levalbuterol HFA treatment group, which had a slightly lower percentage of subjects terminating the study early. The most common reason for adults terminating the study early was AEs. The percentage of subjects discontinuing due to AEs was similar among the active treatment groups, but was slightly higher than the placebo group.

Table 19 Subject Disposition for the Adult Multiple Dose Studies Study 051-353, Study 051-355, Study 051-305

	Levalbuterol HFA 90mcg	Levalbuterol HFA 180mcg	Racemic Albuterol HFA 180mcg	Placebo HFA-134a	Total
Randomized	445	41	218	206	910
Completed Study	391 (87.9%)	38 (92.7%)	191 (87.6%)	185 (89.8%)	805 (88.5%)
Terminated Study	54 (12.1%)	3 (7.3%)	27 (12.4%)	21 (10.2%)	105 (11.5%)
Adverse Event	**25 (5.6%)**	**1 (2.4%)**	**12 (5.5%)**	**9 (4.4%)**	**47 (5.2%)**
Protocol Violation	4 (0.9%)	0	2 (0.9%)	1 (0.5%)	7 (0.8%)
Voluntary Withdrawal	13 (2.9%)	2 (4.9%)	8 (3.7%)	5 (2.4%)	28 (3.1%)
Lost to Follow-up	2 (0.4%)	0	3 (1.4%)	1 (0.5%)	6 (0.7%)
Didn't meet entry criteria	3 (0.7%)	0	1 (0.5%)	1 (0.5%)	5 (0.5%)
Other	7 (1.6%)	0	1 (0.5%)	4 (1.9%)	12 (1.3%)

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 56]

Reviewer's Comment : Many of the tables in the ISS include a 180mcg levalbuterol HFA group. Study 051-305 was a multidose study in adults utilizing levalbuterol HFA 90mcg and 180mcg with an earlier actuator design.

Reviewer's Comment: The discontinuation rate due to AEs was similar among the treatment groups (5.4%-5.5%)when Studies 051-353 and 051-355 were pooled.

Table 20 is included for completeness and summarizes the subject disposition for the supporting adult Phase 2 studies. Of note, more subjects discontinued due to AEs in the levalbuterol HFA group in the cumulative dose studies than in the racemic albuterol HFA group.

Table 20 Subject Disposition for the Adult Cumulative Dose and Dose Ranging Studies Study 051-309, Study 051-310, Study 051-308

Cumulative Dose Studies 051-309 and 051-310		
	Levalbuterol HFA n (%)	Racemic Albuterol HFA n (%)
Randomized	78	76
Discontinued due to AE	5 (6.4%)	2 (2.6%)
Discontinued due to Protocol Violation	0	1 (1.3%)
Dose Ranging Study 051-308		
	Levalbuterol HFA n (%)	Racemic Albuterol HFA n (%)
Randomized	27	35
Discontinued due to AE	1 (3.7%)	1 (2.9%)
Discontinued due to Protocol Violation	0	1 (2.9%)
Voluntary Withdrawal	0	1 (2.9%)

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 56]

Table 21 summarizes the disposition of subjects in the pediatric multiple dose studies. In general, the percentage of subjects terminating the study early was slightly higher in the levalbuterol HFA group compared to the placebo group. The most common reasons for children leaving the study early were AEs and protocol violations. The percentage of subjects discontinuing due to AEs was highest in the placebo group

Table 21 Subject Disposition for the Pediatric Multiple Dose Studies Study 051-354, Study 051-306

	Levalbuterol HFA 90mcg	Levalbuterol HFA 180mcg	Racemic Albuterol HFA 180mcg	Placebo HFA-134a	Total
Randomized	104	34	70	69	277
Completed Study	94 (90.4%)	33 (97.1%)	66 (94.3%)	63 (91.3%)	256 (92.4%)
Terminated Study	10 (9.6%)	1 (2.9%)	4 (5.7%)	6 (8.7%)	21 (7.6%)
Adverse Event	**2 (1.9%)**	**0**	**2 (2.9%)**	**4 (5.8%)**	**8 (2.9%)**
Protocol Violation	4 (3.8%)	1 (2.9%)	1 (1.4%)	1 (1.4%)	7 (2.5%)
Voluntary Withdrawal	1 (1.0%)	0	0	0	1 (0.4%)
Lost to Follow-up	1 (1.0%)	0	0	0	1 (0.4%)
Didn't meet entry criteria	0	0	1 (1.4%)	0	1 (0.4%)
Other	2 (1.9%)	0	0	1 (1.4%)	3 (1.1%)

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 154]

Reviewer's Comment: The percentage of subjects discontinuing secondary to AEs in Study 051-354 was 1.3%, 2.6%, and 8.6% in the levalbuterol HFA, racemic albuterol HFA, and placebo groups, respectively.

Table 22 is included for completeness and summarizes the subject disposition for the dose ranging pediatric study (Study 051-312). All subjects completed the cumulative dose study, Study 051-311. As in the multiple dose studies, the most common reasons for discontinuation were AEs and protocol violations.

Table 22 Subject Disposition for the Pediatric Dose Ranging Study 051-312

Dose Ranging Study 051-312		
	Levalbuterol HFA n (%)	Racemic Albuterol HFA n (%)
Randomized	19	14
Discontinued due to AE	1 (5.3%)	1 (7.1%)
Discontinued due to protocol violation	1 (5.3%)	1 (7.1%)
Didn't meet entry criteria	1 (5.3%)	0

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 154-155]

7.1.3.2 Adverse events associated with dropouts

The most common adverse event leading to discontinuation in both adults and children was asthma. In the adult studies, discontinuation due to asthma was twice as common in the levalbuterol HFA 90mcg group as in the placebo group. However, the percentage of adult subjects discontinuing secondary to asthma was similar in the levalbuterol HFA 90mcg and racemic albuterol HFA group. A different pattern was noted in the pediatric studies, in which the placebo group had three times the percentage of subjects discontinuing due to asthma as compared to the levalbuterol HFA group. A detailed discussion of AEs leading to discontinuation follows.

Adverse events leading to discontinuation in the adult multiple dose studies were slightly more common in the levalbuterol HFA 90mcg group than in the placebo group, as shown in Table 23. However, the percentage of subjects discontinuing secondary to AEs was similar between the levalbuterol HFA 90mcg group and the racemic albuterol HFA group. The most common AE leading to discontinuation was asthma. Although the percentage of subjects discontinuing secondary to asthma was similar between the levalbuterol HFA 90mcg group (4.0%) and the racemic albuterol HFA group (4.1%), both treatment groups had a higher percentage of dropouts secondary to asthma adverse events compared to the placebo group (1.9%).

Table 23 Adverse Events Leading to Discontinuation in the Adult Multiple Dose Studies Study 051-353, Study 051-355, Study 051-305

n (%) / # events	Levalbuterol HFA 90mcg n=445	Levalbuterol HFA 180mcg n=41	Racemic Albuterol HFA 180mcg n=218	Placebo HFA-134a n=206
Any Adverse Event	25 (5.6%) / 40	1 (2.4%) / 1	12 (5.5%) / 15	9 (4.4%) / 11
Asthma	**18 (4.0) / 18**	**0 / 0**	**9 (4.1) / 9**	**4 (1.9) / 4**
Viral Infection	4 (0.9) / 4	0 / 0	0 / 0	1 (0.5) / 1
Accidental injury	3 (0.7) / 7	0 / 0	0 / 0	0 / 0
Chest pain	2 (0.4) / 2	0 / 0	2 (0.9) / 2	1 (0.5) / 1
Fever	1 (0.2) / 1	0 / 0	0 / 0	0 /0
Flu syndrome	1 (0.2) / 1	0 / 0	0 / 0	0 / 0
Pain	1 (0.2) / 1	0 / 0	0 / 0	0 / 0
Nausea/ Vomiting	2 (0.4) / 2	0 / 0	0 / 0	0 / 0
Hypertension	1 (0.2) / 1	0 / 0	0 / 0	0 / 0
Pneumonia	1 (0.2) / 1	0 / 0	0 / 0	0 / 0
Hematuria	1 (0.2) / 1	0 / 0	0 / 0	0 / 0
Abnormal Vision	1 (0.2) / 1	0 / 0	0 / 0	0 / 0
Pharyngitis	0 / 0	1 (2.4) / 1	0 / 0	0 / 0

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 73-74]

For the supportive adult Phase 2 studies, one subject in the levalbuterol group (asthma) and one subject in the racemic albuterol group (asthma, sinusitis, viral infection) discontinued the adult dose-ranging study (051-308) secondary to an AE. Table 20 shows that in the pooled cumulative dose studies 5 (6.4%) subjects in the levalbuterol HFA treatment group discontinued the study secondary to an AE versus 2 (2.6%) in the racemic albuterol HFA treatment group. The AEs in the levalbuterol group were viral infection and asthma, hypertension, and ECG abnormalities (3), while the AEs in the racemic albuterol group were ECG abnormalities (2).
Reviewer's Comment: The ECG abnormalities were primarily QTc prolongations that were noted by the investigator, but not confirmed by central overread.
Reviewer's Comment: A more detailed discussion of the ECG findings is located in Section 7.1.9.

In the pediatric studies, adverse events leading to discontinuation were more common in the placebo group as shown below in Table 24. As in the adult studies, the most common AE leading to discontinuation was asthma. The percentage of subjects discontinuing secondary to asthma in the placebo group was three times the percentage of discontinuation secondary to asthma in the levalbuterol HFA or racemic albuterol HFA treatment groups.

Table 24 Adverse Events Leading to Discontinuation in the Pediatric Multiple Dose Studies - Study 051-354 & Study 051-306

n (%) / # events	Levalbuterol HFA 90mcg n=104	Levalbuterol HFA 180mcg n=74	Racemic Albuterol HFA 180mcg n=70	Placebo HFA-134a n=69
Any Adverse Event	2 (1.9) / 3	0 / 0	2 (1.9) / 3	5 (7.2) / 6
Asthma	**2 (1.9) / 2**	**0 / 0**	**2 (1.9) / 2**	**4 (5.8) / 4**
Bronchitis	1 (1.0) / 1	0 / 0	0 / 0	0 / 0
Rhinitis	0 / 0	0 / 0	0 / 0	1 (1.4) / 1
Viral infection	0 / 0	0 / 0	0 / 0	1 (1.4) / 1

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 166]

For the supportive pediatric Phase 2 studies, there were no discontinuations secondary to AEs in the cumulative dose study (Study 051-311). In the pediatric dose ranging study one subject in the levalbuterol HFA group (otitis media and sinusitis) and one subject in the racemic albuterol HFA group (sinusitis) discontinued due to an AE.

7.1.3.3 Other significant adverse events

This section is not applicable as marked laboratory abnormalities were not noted and an expansion of the dropouts due to adverse events is not warranted.

7.1.4 Other Search Strategies

This section is not as applicable as new safety signals were not identified by postmarketing or literature reports and special safety studies were not conducted for this application.

7.1.5 Common Adverse Events

For the purpose of discussing the common adverse events, only the placebo controlled multidose studies will be discussed. Although the Applicant pooled data from studies with an earlier actuator design (Studies 051-305 and 051-306) with data from the Phase 3 studies, the common adverse events will also be reviewed based upon the Phase 3 studies only as the adverse events from the Phase 3 studies are most appropriate for the product label. A discussion of the Applicant's Adverse Reactions section of the proposed product label will be incorporated, where appropriate.

7.1.5.1 Eliciting adverse events data in the development program

In the adult multidose studies, subjects were instructed to record adverse events in medical event calendars throughout the study period. At each clinic visit, diary cards and event calendars were reviewed by study personnel and recorded on the CRF. Subjects were evaluated at clinic visits every two weeks, except in Study 051-305, in which subjects were evaluated at clinic visits every week.

The approach was similar in the pediatric multiple dose studies, in which the parent/guardian was instructed to record adverse events in medical event calendars. At each clinic visit, diary cards and event calendars were reviewed by study personnel and recorded on the CRF. Subjects in both pediatric multidose studies were evaluated at clinic visits every week.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Applicant utilized COSTART to classify and report adverse events. A sample of some CRFs from subjects who discontinued secondary to AEs was reviewed. The review suggests that the description of the AEs recorded on the CRFs were consistent with the AE terms used by the Applicant.

7.1.5.3 Incidence of common adverse events

7.1.5.3.1 Adult Studies

The adverse event reports from the adult studies demonstrate that asthma AEs, rhinitis, and pharyngitis were more common in the levalbuterol HFA treatment group than in the other treatment groups. Rhinitis and pharyngitis are currently listed as Adverse Reactions in the product labels for Proventil HFA and Xopenex Inhalation Solution, while asthma is listed in the Adverse Reactions section of the Xopenex Inhalation Solution product label. When looking at the three adult multiple dose studies, the percentage of subjects with asthma AEs in the levalbuterol HFA group (9.4%) is similar to the percentage of subjects with asthma AEs in the racemic albuterol HFA group (8.7%). This finding is not consistent with the pediatric studies in which the levalbuterol HFA 90mcg had the lowest percentage of subjects with asthma AEs. Since the finding of asthma AEs was not consistent in the adult and pediatric studies and the percentage of subjects with asthma AEs in the levalbuterol HFA group was similar to the percentage of subjects with asthma AEs in the racemic albuterol HFA group, the increased asthma AE reports in the adult clinical studies should not preclude approval, but should be included in the product label. A detailed discussion of AEs reported in the clinical studies follows.

Reviewer's Comment: If Studies 051-353 and 051-355 are pooled, asthma AEs were 9.4%, 7.3%, and 6.0% in the levalbuterol HFA, racemic albuterol HFA, and placebo groups, respectively.

Reviewer's Comment: The safety of levalbuterol HFA is also supported by the Agency's previous determination of the safety of albuterol and levalbuterol HCl. Because the exposure to (R)-albuterol with levalbuterol HFA is less than the (R)-albuterol exposure with racemic albuterol HFA and Xopenex Inhalation Solution, the Agency's previous finding of the safety of racemic albuterol HFA and Xopenex Inhalation Solution supports this application. Although the Division considers the Proventil HFA database to be generally supportive, it is possible that the (S)-albuterol in Proventil HFA could affect the safety profile of (R)-albuterol.

Adverse events reported in ≥2% of the subjects in the adult multidose studies receiving levalbuterol HFA or racemic albuterol HFA and more frequently in the active treatment groups than in patients receiving placebo are shown below in Table 25.

Table 25 Adverse Events Reported in ≥ 2% Subjects and Greater than Placebo in the Adult Multiple Dose Studies: Study 051-353, Study 051-355, Study 051-305

n (%)	Levalbuterol HFA 90mcg n=445	Levalbuterol HFA 180mcg n=41	Racemic Albuterol HFA 180mcg n=218	Placebo HFA-134a n=206
Any Adverse Event	225 (50.6)	20 (48.8)	114 (52.3)	113 (54.9)
BODY AS A WHOLE	110 (24.7)	10 (24.4)	51 (23.4)	62 (30.1)
Abdominal Pain	7 (1.6)	2 (4.9)	4 (1.8)	8 (3.9)
Accidental Injury	20 (4.5)	1 (2.4)	11 (5.0)	12 (5.8)
Chest Pain	3 (0.7)	0	5 (2.3)	3 (1.5)
Fever	6 (1.3)	1 (2.4)	2 (0.9)	3 (1.5)
Headache	50 (11.2)	5 (12.2)	18 (8.3)	22 (10.7)
Infection	1 (0.2)	1 (2.4)	0	1 (0.5)
Pain	19 (4.3)	2 (4.9)	8 (3.7)	8 (3.9)
Viral Infection	3 (0.7)	1 (2.4)	0	1 (0.5)
DIGESTIVE SYSTEM	38 (8.5)	5 (12.2)	10 (4.6)	24 (11.7)
Diarrhea	8 (1.8)	1 (2.4)	1 (0.5)	4 (1.9)
Eructation/ Belching	0	1 (2.4)	0	0
Nausea	11 (2.5)	1 (2.4)	4 (1.8)	4 (1.9)
Oral moniliasis	0	1 (2.4)	0	0
MUSCULOSKELETAL SYSTEM	9 (2.0)	2 (4.9)	5 (2.3)	4 (1.9)
Leg Cramps	0	1 (2.4)	1 (0.5)	2 (1.0)
Myalgias	6 (1.3)	1 (2.4)	2 (0.9)	1 (0.5)
NERVOUS SYSTEM	29 (6.5)	1 (2.4)	13 (6.0)	15 (7.3)
Dizziness	13 (2.9)	1 (2.4)	2 (0.9)	3 (1.5)
RESPIRATORY SYSTEM	125 (28.1)	10 (24.4)	55 (25.2)	51 (24.8)
Asthma	**42 (9.4)**	**1 (2.4)**	**19 (8.7)**	**12 (5.8)**
Dyspnea	2 (0.4)	1 (2.4)	0	1 (0.5)
Pharyngitis	**35 (7.9)**	**4 (9.8)**	**7 (3.2)**	**8 (3.9)**
Rhinitis	**32 (7.2)**	**1 (2.4)**	**4 (1.8)**	**7 (3.4)**
Viral Infection	43 (9.7)	3 (7.3)	24 (11.0)	20 (9.7)
SKIN & APPENDAGES	12 (2.7)	1 (2.4)	7 (3.2)	4 (1.9)
Herpes Zoster	0	1 (2.4)	0	0
SPECIAL SENSES	12 (2.7)	2 (4.9)	5 (2.3)	2 (1.0)
Ear Disorder	0	1 (2.4)	1 (0.5)	0
Ear Pain	4 (0.9)	1 (2.4)	1 (0.5)	1 (0.5)
UROGENITAL SYSTEM	16 (3.6)	1 (2.4)	4 (1.8)	10 (4.9)
Dysmenorrhea	3 (0.7)	1 (2.4)	3 (1.4)	0

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 88-90]

Reviewer's Comment:

In general, rates of adverse events were similar across all treatment groups, ranging from 54.9% in the placebo group to 48.8% in the levalbuterol 180mcg HFA treatment group. The most commonly reported AEs were headache, respiratory viral infection, asthma, pharyngitis, rhinitis,

treatment groups, the Applicant determined there was a slightly higher percentage of subjects with severe asthma (FEV1 <60%) in the levalbuterol HFA treatment group (31.5%) than in the placebo group (27.7%). In addition, more subjects in the levalbuterol HFA groups used asthma controller medications [N21730\N_000\2004-05-11\clinstat\iss.pdf p 100].
Reviewer's Comment: It is unclear if the small increase in subjects with severe asthma in the levalbuterol HFA group could account for the increase in asthma AEs noted with levalbuterol HFA. The Applicant indicated that subjects with severe asthma at baseline experienced a higher rate of asthma events during the study.

Reviewer's Comment: Both Studies 051-353 and 051-355 showed an increased incidence of asthma AEs in the levalbuterol HFA treatment group compared to the other treatment groups. The increase was more compelling in Study 051-353. A review of the demographics of the subjects in Study 051-353 shows a slightly higher percentage of Blacks in the levalbuterol HFA (19.2%) and racemic albuterol HFA (18.5%) treatment groups than in the placebo group (14%). However, it is doubtful the difference contributes to the asthma AEs, because in Study 051-353 the incidence in asthma AEs was similar between the racemic albuterol HFA and placebo groups.

One third of subjects with asthma AEs in the levalbuterol HFA treatment group in Study 051-353 had a respiratory infection compared to no subjects in the placebo group. However, in Study 051-355, all treatment groups had a similar incidence of respiratory infection.
Reviewer's Comment: Although respiratory infection can predispose to asthma exacerbation, in Study 051-353 a similar percentage of subjects in the levalbuterol HFA (10.5%) and placebo treatment groups (9.3%) had a respiratory viral infection. Thus, although a similar percentage of subjects reported respiratory viral infections in all groups, more subjects in the levalbuterol HFA treatment group reported asthma AEs.

Of the asthma AEs reported in the adult multiple dose studies, most were mild to moderate in severity. The levalbuterol HFA 90mcg treatment group (7.2%) did have more moderate severity cases compared to placebo (2.9%) and racemic albuterol (4.6%) [N21730\N_000\2004-05-11\clinstat\iss.pdf p 543]. Rates of discontinuation due to asthma were higher (but similar) in both active treatment groups (4.0-4.1%) than in placebo (1.9%) [N21730\N_000\2004-05-11\clinstat\iss.pdf p 100].
Reviewer's comment: The levalbuterol HFA treatment group did have more moderate severity asthma AEs compared to the other treatment groups.

The Applicant also performed further analyses to investigate the increased reports of pharyngitis and rhinitis with levalbuterol HFA. The increased reports of pharyngitis and rhinitis were mostly driven by the levalbuterol HFA-B [redacted] treatment group in Study 051-355. For example, in Study 051-355, 19% and 22% of the subjects in the levalbuterol HFA-B treatment group reported rhinitis and pharyngitis, respectively, compared to 7% and 5% of subjects in the levalbuterol HFA-A treatment group. In the same study, the placebo group reported 1.7% and 0%, respectively. The Applicant suggested a worsening of allergy symptoms or viral syndrome in subjects who reported rhinitis and pharyngitis in the [redacted] treatment group.
Reviewer's Comment: The [redacted] and 3M product are similar from a CMC standpoint. It is unclear why the [redacted] treatment group demonstrated such a large proportion of subjects with

rhinitis and pharyngitis compared to the other treatment groups. This large increase in percentage of subjects with rhinitis and pharyngitis was not noted in the other Phase 3 studies. The increased incidence of rhinitis and pharyngitis is included in the table in the proposed product label, which is appropriate.
Reviewer's Comment: Refer to Table 70 for a detailed listing of AEs in Study 051-355.

Overall, in the adult Phase 2 studies (active-controlled, not placebo-controlled), more AEs were reported in the racemic albuterol HFA treatment groups than in the levalbuterol HFA treatment groups. The reported AEs in the dose ranging and cumulative dose studies were reviewed. No consistent pattern of AEs was noted in the dose ranging study. Of note, one subject in the levalbuterol HFA and one subject in the racemic albuterol HFA group experienced an asthma adverse event. The cumulative dose studies demonstrate that overall AEs increased with dose accumulation. Dizziness and nervousness appeared to have a dose response. Dizziness and nervousness are known beta adrenergic agonist effects. In the two cumulative dose studies, one subject experienced asthma during the washout period five days after dosing with levalbuterol HFA. Thus, the limited AE data from the adult Phase 2 studies does not suggest a new safety signal for levalbuterol HFA.

To summarize, the adverse event reports from the adult studies demonstrate that asthma AEs, rhinitis, and pharyngitis were more common in the levalbuterol HFA treatment groups than in the other treatment groups. Although the Applicant provided further analyses and some explanation for the increase in AEs, the subgroup analyses was interpreted with caution due to the post hoc nature and small number of subjects.

Rhinitis and pharyngitis are currently listed as Adverse Reactions in the product labels for Proventil HFA and Xopenex Inhalation Solution; while asthma is currently listed as an Adverse Reaction in the Xopenex Inhalation Solution product label. When the two pivotal Phase 3 adult studies are pooled, the percentage of subjects with asthma AEs in the levalbuterol HFA group (9.4%) is slightly higher than the percentage of subjects with asthma AEs in the racemic albuterol HFA group (7.3%) and placebo group (6.0%). This finding is not consistent with the pediatric studies in which the levalbuterol HFA 90mcg had the lowest percentage of subjects with asthma AEs, as will be discussed in the next section. Since the finding of asthma AEs was not consistent in the adult and pediatric studies, the increased asthma AE reports in the adult clinical studies should not preclude approval, but should be included in the product label.

Reviewer's Comment: The Adverse Reactions section of the Applicant's proposed product label needs some revisions. The number of subjects in the adult studies should be 748, not — The sentence "

should be removed.

Table 2 in the proposed product label has an incorrect number of placebo subjects and should be 166, not — The sentence

should also be removed.

7.1.5.3.2 Pediatric Studies

The adverse event data for the pediatric studies demonstrate that AEs were more common in the placebo group than the active treatment groups. In contrast to the adult studies an increase in asthma and rhinitis in the levalbuterol HFA group compared to placebo was not noted in the pediatric studies. The AEs which were more common in the levalbuterol HFA group than the placebo group included: accidental injury, vomiting, bronchitis, pharyngitis, rash, and otitis media and should be noted in the product label. A detailed discussion of AEs reported in the clinical studies follows.

Adverse events reported in ≥2% of the subjects in the pediatric multidose studies receiving levalbuterol HFA or racemic albuterol HFA and more frequently than in patients receiving placebo are shown below in Table 27.

Table 27 Adverse Events Reported in ≥ 2% Subjects and Greater than Placebo in the Pediatric Multiple Dose Studies: Study 051-354 and Study 051-306

n (%)	Levalbuterol HFA 90mcg n=104	Levalbuterol HFA 180mcg n=34	Racemic Albuterol HFA 180mcg n=70	Placebo HFA-134a n=69
Any Adverse Event	44 (42.3)	17 (50)	36 (51.4)	37 (53.6)
BODY AS A WHOLE	28 (26.9)	12 (35.5)	19 (27.1)	21 (30.4)
Abdominal Pain	3 (2.9)	3 (8.8)	3 (4.3)	4 (5.8)
Accidental Injury	**8 (7.7)**	**1 (2.9)**	**6 (8.6)**	**3 (4.3)**
Asthenia	1 (1.0)	1 (2.9)	1 (1.4)	1(1.4)
Fever	6 (5.8)	4 (11.8)	4 (5.7)	5 (7.2)
Headache	9 (8.7)	4 (11.8)	6 (8.6)	7 (10.1)
Viral Infection	1 (1.0)	1 (2.9)	0	0
DIGESTIVE SYSTEM	11 (10.6)	2 (5.9)	8 (11.4)	7 (10.1)
Diarrhea	3 (2.9)	1 (2.9)	3 (4.3)	3 (4.3)
Dyspepsia	1 (1.0)	1 (2.9)	2 (2.9)	0
Vomiting	**9 (8.7)**	**0**	**4 (5.7)**	**4 (5.8)**
METABOLIC DISORDER	0	1 (2.9)	0	0
	0	1 (2.9)	0	0
MUSCULOSKELETAL SYSTEM	0	1 (2.9)	1 (1.4)	1 (1.4)
Myalgias	0	1 (2.9)	1 (1.4)	1 (1.4)
RESPIRATORY SYSTEM	27 (26.0)	11 (32.4)	21 (30.0)	21 (30.4)
Asthma*	9 (8.7)	2 (5.9)	7 (10.0)	10 (14.5)
Epistaxis	0	1 (2.9)	2 (2.9)	2 (2.9)
Pharyngitis	**6 (5.8)**	**5 (14.7)**	**7 (10.0)**	**2 (2.9)**
Rhinitis*	2 (1.9)	2 (5.9)	3 (4.3)	5 (7.2)
Viral Infection	6 (5.8)	3 (8.8)	9 (12.9)	6 (8.7)
SKIN & APPENDAGES	3 (2.9)	0	4 (5.7)	1 (1.4)
Rash	1 (1.0)	0	2 (2.9)	0
SPECIAL SENSES	2 (1.9)	1 (2.9)	4 (5.7)	3 (4.3)
Ear Pain	0	1 (2.9)	2 (2.9)	2 (2.9)

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 172-173]
*Asthma and rhinitis are included because of the findings in the adult studies. However, asthma and rhinitis were more common in the placebo group.

Reviewer's Comment:

AEs were more common in the placebo group than in any of the active treatment groups. In Table 27, asthma and rhinitis are included because of the findings in the adult studies; however, unlike in the adult studies, asthma AEs and rhinitis were more common in the placebo group than in the active treatment groups. AEs more common in the levalbuterol HFA 90mcg group than the placebo group include: pharyngitis, accidental injury, and vomiting.

Table 28 displays the AEs reported in ≥2% of subjects and with a greater incidence in the levalbuterol HFA group than placebo for the Phase 3 pediatric Study 051-354. Asthma AEs and rhinitis were more common in the placebo group than in the active treatment groups, and therefore, are not listed in Table 28. Subjects in the racemic albuterol HFA had the greatest incidence of AEs.

Table 28 Adverse Events Reported in ≥ 2% Subjects and Greater than Placebo in the Pediatric Multiple Dose Study 051-354

n (%)	Levalbuterol HFA 90mcg n=76	Racemic Albuterol HFA 180mcg n=39	Placebo HFA-134a n=635
Any Adverse Event	33 (43.4)	22 (56.4)	18 (51.4)
BODY AS A WHOLE			
Accidental Injury	7 (9.2)	4 (10.3)	2 (5.7)
DIGESTIVE SYSTEM			
Vomiting	8 (10.5)	3 (7.7)	2 (5.7)
RESPIRATORY SYSTEM			
Bronchitis	2 (2.6)	0	0
Pharyngitis	5 (6.6)	5 (12.8)	2 (5.7)
SKIN & APPENDAGES			
Rash	1 (1.3)	1 (2.6)	0
SPECIAL SENSES			
Otitis media	1 (1.3)	1 (2.6)	0

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 182]

Reviewer's Comment: The above table is appropriate for the product label; however, otitis media and rash should be removed as the incidence in the levalbuterol group was <2%.

In Study 051-354, the AEs which were more common in the levalbuterol HFA group than the placebo group included: accidental injury, vomiting, bronchitis, pharyngitis, rash, and otitis media. These AEs should be included in the product label. Of note, only vomiting, bronchitis, and rash were greater in the levalbuterol HFA group than racemic albuterol HFA group.

The AEs reported in reported in ≥ 2% of pediatric subjects and greater in the levalbuterol group than placebo are different than in the adult studies. The only shared AE is pharyngitis. While asthma AEs and rhinitis were common AEs in the pediatric studies, they were more common in the placebo group than the levalbuterol HFA group.

Overall, in the pediatric Phase 2 studies (active-controlled, not placebo-controlled), few AEs were reported. No consistent pattern of AEs was noted in either study. In the dose ranging study, the most common AEs were viral infection in the levalbuterol HFA group (2) and headache in the racemic albuterol group (2). Only four subjects reported AEs during the cumulative dose study and all were reported during the washout period after cumulative dosing. Thus, the limited AE data from the pediatric Phase 2 studies does not suggest a new safety signal for levalbuterol HFA.

To summarize the adverse event data for the pediatric studies, AEs were more common in the placebo group than the active treatment groups. In contrast to the adult studies an increase in asthma and rhinitis in the levalbuterol HFA group compared to placebo was not noted in the pediatric studies. The AEs which were more common in the levalbuterol group than the placebo group included: accidental injury, vomiting, bronchitis, pharyngitis, rash, and otitis media and should be noted in the product label.

Reviewer's Comment: The Adverse Reactions section of the Applicant's proposed product label needs some revisions. Table 3 should not include the information about because it is confusing.

7.1.5.4 Common adverse event tables

Table 29 and Table 30 display the adverse events reported in ≥2% of subjects and greater in the levalbuterol HFA group than placebo group for the adult Phase 3 studies and pediatric Phase 3 study, respectively. These tables are the basis for the Adverse Reactions section of the product label.

Table 29 Adverse Events Reported in ≥ 2% Subjects and Greater than Placebo in the Adult Multiple Dose Studies: Study 051-353 and Study 051-355

n (%)	Levalbuterol HFA 90mcg n=403	Racemic Albuterol HFA 180mcg n=179	Placebo HFA-134a n=166
Any Adverse Event	102 (25.3)	31 (17.3)	27 (16.3)
BODY AS A WHOLE	19 (4.7)	11 (6.1)	8 (4.8)
Chest Pain	3 (0.7)	5 (2.8)	3 (1.8)
Pain	16 (4.0)	6 (3.4)	6 (3.6)
NERVOUS SYSTEM	11 (2.7)	1 (0.6)	3 (1.8)
Dizziness	11 (2.7)	1 (0.6)	3 (1.8)
RESPIRATORY SYSTEM	81 (20.1)	21 (11.7)	18 (10.8)
Asthma	38 (9.4)	13 (7.3)	10 (6.0)
Pharyngitis	32 (7.9)	4 (2.2)	4 (2.4)
Rhinitis	30 (7.4)	4 (2.2)	5 (3.0)

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 663]

Table 30 Adverse Events Reported in ≥ 2% Subjects and Greater than Placebo in the Pediatric Multiple Dose Study 051-354

n (%)	Levalbuterol HFA 90mcg n=76	Racemic Albuterol HFA 180mcg n=39	Placebo HFA-134a n=635
Any Adverse Event	33 (43.4)	22 (56.4)	18 (51.4)
BODY AS A WHOLE	7 (9.2)	6 (15.4)	2 (5.7)
Accidental Injury	7 (9.2)	4 (10.3)	2 (5.7)
DIGESTIVE SYSTEM	8 (10.5)	3 (7.7)	2 (5.7)
Vomiting	8 (10.5)	3 (7.7)	2 (5.7)
RESPIRATORY SYSTEM	10 (13.2)	13 (33.3)	4 (11.4)
Bronchitis	2 (2.6)	0	0
Pharyngitis	5 (6.6)	5 (12.8)	2 (5.7)
SKIN & APPENDAGES	1 (1.3)	2 (5.1)	0
Rash	1 (1.3)	1 (2.6)	0
SPECIAL SENSES	1 (1.3)	2 (5.1)	0
Otitis media	1 (1.3)	1 (2.6)	0

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 182]

7.1.5.5 Identifying common and drug-related adverse events

7.1.5.5.1 Beta Mediated Adverse Events

Beta adrenergic agonists have been studied extensively and have the potential to produce certain beta-mediated adverse events, such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, dyspepsia, chest pain, arrhythmia, worsening hypertension, hyperglycemia, hypokalemia, and ECG changes. Beta mediated adverse events were noted in the adult and pediatric clinical studies; however, the incidences were low.

Beta-mediated adverse events for the adult multiple dose studies are shown in Table 31. Other beta-mediated adverse events, such as hyperglycemia, hypokalemia, and ECG changes (including QTc prolongation) are discussed in Sections 7.1.7 - Laboratory Findings and 7.1.9 - ECGs.

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Table 31 Beta-Mediated Adverse Events in the Adult Multiple Dose Studies Study 051-353, Study 051-355, and Study 051-305

n (%)	Levalbuterol HFA 90mcg n=445	Levalbuterol HFA 180mcg n=41	Racemic Albuterol HFA 180mcg n=218	Placebo HFA-134a n=206
BODY AS A WHOLE				
Chest Pain	3 (0.7)	0	5 (2.3)	3 (1.5)
CARDIOVASCULAR SYSTEM				
Palpitation	0	0	1 (0.5)	0
Tachycardia	1 (0.2)	0	0	0
DIGESTIVE SYSTEM				
Dyspepsia	9 (2.0)	1 (2.4)	1 (0.5)	12 (5.8)
Nausea	11 (2.5)	1 (2.4)	4 (1.8)	4 (1.9)
MUSCULOSKELETAL SYSTEM				
Leg cramps	0	1 (2.4)	1 (0.5)	2 (1.0)
NERVOUS SYSTEM				
Dizziness	13 (2.9)	1 (2.4)	2 (0.9)	3 (1.5)
Hypertension	3 (0.7)	0	1 (0.5)	0
Insomnia	4 (0.9)	0	2 (0.9)	5 (2.4)
Nervousness	3 (0.7)	0	3 (1.4)	2 (1.0)
Tremor	1 (0.2)	0	0	0

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 104]

In general, the incidence of beta mediated adverse events in the multidose studies was low. Dizziness and hypertension were slightly more common in the levalbuterol 90mcg HFA group compared to placebo. The Phase 2 supportive studies also demonstrated a low incidence of beta mediated adverse events. Dizziness, nervousness, and tachycardia appeared to be the most commonly reported beta mediated adverse events. No convincing dose related AEs were noted [N21730\N_000\2004-05-11\clinstat\iss.pdf p 104].

Beta-mediated adverse events for the multiple dose pediatric studies are shown in Table 32. As in adults, rates of beta mediated adverse events were low. Dyspepsia was slightly more common in the levalbuterol HFA treatment groups than in the placebo group, but was similar to the racemic albuterol HFA group. As in the adult studies, the beta mediated adverse events in the Phase 2 pediatric studies were infrequent and did not demonstrate a dose response relationship [N21730\N_000\2004-05-11\clinstat\iss.pdf p 181].

Table 32 Beta-Mediated Adverse Events in the Pediatric Multiple Dose Studies Study 051-354 and Study 051-306

n (%)	Levalbuterol HFA 90mcg n=104	Levalbuterol HFA 180mcg n=34	Racemic Albuterol HFA 180mcg n=70	Placebo HFA-134a n=69
BODY AS A WHOLE				
Chest Pain	1 (1.0)	0	1 (1.4)	2 (2.9)
DIGESTIVE SYSTEM				
Dyspepsia	1 (1.0)	1 (2.9)	2 (2.9)	0

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 181]

7.1.5.5.2 Potentially Related Adverse Events

A review of the adverse events for the adult multiple dose studies indicates the following adverse events (reported in <2% of the subjects) were more common in the levalbuterol HFA treatment group than placebo and judged possibly related to study medication: back pain, fever, viral infection, tachycardia, atrial fibrillation, vomiting, tremor, epistaxis, and rash [N21730\N_000\2004-05-11\clinstat\iss.pdf p 580-615].

7.1.5.6 Additional analyses and explorations

Additional analyses provided by the Applicant did not suggest a dose response relationship with the reported AEs or an association with age, race, and gender. The Applicant analyzed the adverse events for the adult multiple dose studies by age, race, and gender. A review of the analyses does not suggest a consistent relationship between the reported AEs with levalbuterol HFA and gender, age, or racial subgroups.

In terms of a dose response relationship, the beta mediated adverse effects noted in the clinical studies did not demonstrate a dose response relationship. The Applicant determined there was a significantly shorter time to onset of dyspepsia with placebo than with levalbuterol HFA 90mcg or racemic albuterol HFA.

7.1.6 Less Common Adverse Events

The total number of subjects enrolled in the adult multiple dose studies was 910. Adverse events reported by more than one subject more often in the levalbuterol HFA group than the placebo group, but in < 2% of the subjects included: gastroenteritis, flu syndrome, epistaxis, lung disorder, acne, herpes simplex, rash, conjunctivitis, hematuria, and vaginal moniliasis [N21730\N_000\2004-05-11\clinstat\iss.pdf p 439-445].

The pediatric multiple dose studies only enrolled 277 subjects total. Thus, the database is likely not large enough to provide meaningful information regarding less common adverse events.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In the multiple dose clinical studies, laboratory testing was conducted at baseline, during the treatment period, and at the end of the treatment period. Laboratory tests included: hematology, chemistry, urinalysis, alkaline phosphatase, AST, ALT, albumin, total bilirubin, total protein, uric acid, calcium, magnesium, and phosphorus. Because beta agonists are known to have potential effects on glucose and potassium levels, glucose and potassium levels were collected more frequently: screening, pre and post-dose (1-2 hours) on the first day of dosing as well as pre and post dose (1-2 hours) on the final clinic visit (last day of dosing). This section of the review concentrates on the glucose and potassium levels.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

As in other sections of the review, the adult and pediatric laboratory data will be discussed separately. The laboratory data from the multiple dose studies was pooled because the studies incorporated a placebo comparison and were of longer duration than the dose ranging and cumulative dose studies. The dose ranging and cumulative dose studies were reviewed for a dose response relationship.

7.1.7.3 Standard analyses and explorations of laboratory data

Adult Studies
Overall, minimal changes in the mean potassium level were noted in all treatment groups as shown in Table 33. Minimum and maximum changes in potassium concentration were similar across all treatment groups.

Table 33 Change in Potassium Level (mEq/L) from Visit Pre-dose in the Adult Multiple-Dose Studies Study 051-353, Study 051-355, Study 051-305

		Levalbuterol HFA 90mcg n=445	Levalbuterol HFA 180 mcg n=41	Racemic Albuterol 180mcg n=218	Placebo n=206
Week 0*	n	431	41	214	196
	Mean	0.02	-0.06	-0.02	0.07
	Min, Max	-1.1, 1.2	-0.7, 0.7	-1.1, 1.3	-0.9, 1.1
Week 4** (end of Study 051-305)	n	36	37	28	36
	Mean (SD)	0.04	0.03	0.04	0.03
	Min, Max	-0.6, 0.6	-0.8, 1.6	-0.5, 1.1	-1.0, 1.0
Week 8**	n	329	-	147	132
	Mean (SD)	0.04	-	-0.01	0.06
	Min, Max	-1.3, 1.8	-	-1.0, 1.6	-0.9, 0.8

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 114]
*Post 1-2 hour data
**Post 60 minute data

Minimal changes in the mean glucose level were noted in all treatment groups as shown in Table 34. The active treatment groups demonstrated a similar increase in mean glucose concentration compared to the placebo group. Minimum and maximum changes were similar across all treatment groups, with the exception of the minimum of -115mg/dL in the levalbuterol HFA 90mcg group, which the Applicant stated occurred in a 66-year old subject with diabetes mellitus.

Table 34 Change in Glucose Level (mg/dL) from Visit Pre-dose in the Adult Multiple-Dose Studies Study 051-353, Study 051-355, Study 051-305					
		Levalbuterol HFA 90mcg n=445	Levalbuterol HFA 180 mcg n=41	Racemic Albuterol 180mcg n=218	Placebo n=206
Week 0*	n	431	41	214	199
	Mean (SD)	3.17	4.51	5.38	-0.24
	Min, Max	-90, 85	-60, 56	-89, 87	-63, 55
Week 4** (end of Study 051-305)	n	37	37	30	36
	Mean (SD)	4.81	-0.11	4.47	-2.36
	Min, Max	-26, 36	-40, 32	-25, 29	-37, 40
Week 8**	n	336	-	153	133
	Mean (SD)	2.00	-	2.00	-1.00
	Min, Max	-115, 69	-	-46, 77	-55, 60

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 115]
*Post 1-2 hour data
**Post 60 minute data

The Applicant also conducted a shift table analysis for the potassium and glucose shifts from normal in the adult multidose studies, which showed there were more subjects who shifted from normal to low potassium in the active treatment groups compared the placebo group. No consistent pattern was noted with the glucose concentrations [N21730\N_000\2004-05-11\clinstat\iss.pdf p 116].

Potentially significant changes in glucose (≥160mg/dL) and potassium (< 3mEq/L and >6 mEq/L) were determined by the Applicant. More potentially significant increases in glucose were noted with levalbuterol HFA (8, 3.6%) and racemic albuterol HFA (3, 2.5%) compared to placebo (1, 0.9%). Three potentially significant changes in potassium were noted: two elevations in the levalbuterol HFA group and one elevation in the placebo group. In the levalbuterol HFA group, one subject's potassium went from 5.3mEq/L pre-dose to 6.0mEq/L post-dose (Study 051-355), while another subject's potassium increased from 5.1mEq/L at baseline to 6.5mEq/L prior to dosing at Visit 2 (Study 051-353).
Reviewer's Comment: It is unusual to see an increase in potassium as a decrease in potassium is expected with beta adrenergic agonists.

The mean changes in other laboratory parameters (hematology, chemistry) were similar across treatment groups during the study. Only one clinically significant change was noted in the adult multidose studies. One subject in the placebo group demonstrated clinically significant abnormal elevation of the liver function tests [N21730\N_000\2004-05-11\clinstat\iss.pdf p 117, 122-126].

Pediatric Studies

Overall, minimal changes in the mean potassium level were noted in all treatment groups as shown in Table 35. The minimum changes in potassium concentration were slightly lower in the levalbuterol HFA group at Week 0, but were similar across the treatment groups for the remainder of the study.

Table 35 Change in Potassium Level (mEq/L) from Visit Pre-dose in the Pediatric Multiple-Dose Studies Study 051-354 and Study 051-306					
		Levalbuterol HFA 90mcg n=104	Levalbuterol HFA 180 mcg n=34	Racemic Albuterol 180mcg n=70	Placebo n=69
Week 0*	n	92	31	63	63
	Mean	-0.14	-0.17	-0.19	0.01
	Min, Max	-1.9, 0.9	-1.9, 1.3	-1.2, 0.4	-0.8, 1.6
Week 3**	n	27	32	26	30
	Mean (SD)	-0.11	-0.33	-0.22	-0.18
	Min, Max	-1.0, 0.5	-1.3, 0.4	-1.2, 0.9	-1.0, 0.6
Week 4***	n	58	0	31	28
	Mean (SD)	-0.16	-	-0.19	-0.05
	Min, Max	-1.3, 0.8	-	-1.1, 0.9	-1.0, 0.9

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 187]
*Post 1-2 hour data **Post 2-4 hour data ***Post 1 hour data

Minimal changes in the mean glucose level were noted in all treatment groups as shown in Table 36 except at Week 8 in which the placebo group had a decrease in mean glucose levels.

Table 36 Change in Glucose Level (mg/dL) from Visit Pre-dose in the Pediatric Multiple-Dose Studies Study 051-354 and Study 051-306					
		Levalbuterol HFA 90mcg n=104	Levalbuterol HFA 180 mcg n=32	Racemic Albuterol 180mcg n=70	Placebo n=69
Week 0*	n	94	33	63	64
	Mean (SD)	5.24	3.73	8.02	4.67
	Min, Max	-36, 52	-14, 37	-18, 43	-15, 79
Week 4** (end of Study 051-305)	n	27	32	27	30
	Mean (SD)	2.85	5.03	2.70	2.17
	Min, Max	-45, 57	039, 48	-33, 43	-39, 40
Week 8**	n	59	-	31	29
	Mean (SD)	4.95	-	7.55	-2.69
	Min, Max	-68, 33	-	-31, 53	-33, 20

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 188]
*Post 1-2 hour data
**Post 60 minute data

The Applicant also conducted a shift table analysis for the potassium and glucose shifts from normal in the pediatric multidose studies. Only one subject shifted from normal to low for potassium levels (racemic albuterol HFA group). [N21730\N_000\2004-05-11\clinstat\iss.pdf p 189].

The mean changes in other laboratory parameters (hematology, chemistry) were similar across treatment groups during the study [N21730\N_000\2004-05-11\clinstat\iss.pdf p 197].

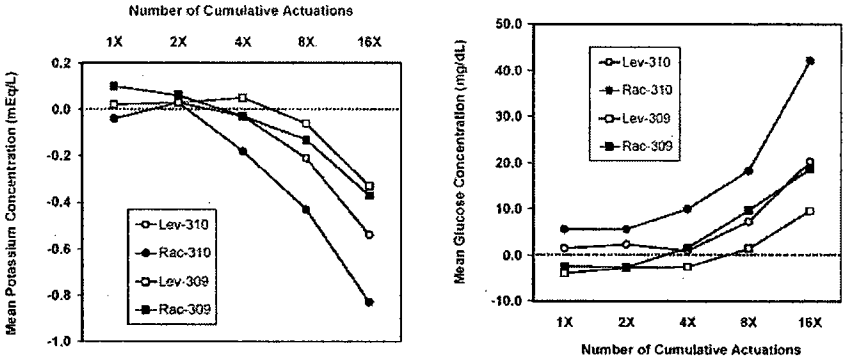
7.1.7.4 Additional analyses and explorations

Adult Studies

The dose ranging and cumulative dose studies were reviewed for potential information regarding a dose response relationship between levalbuterol HFA and glucose and potassium levels. In the cumulative dose studies, there appears to be a clear dose response for potassium and glucose. Figure 10 shows that with additional dosing after 2-4 actuations, both racemic albuterol HFA and levalbuterol HFA demonstrate a dose-related decrease in potassium concentration and increase in glucose concentration.

Reviewer's Comment: The cumulative dose studies were randomized, double blind, active-controlled, multicenter crossover studies in subjects with asthma. Subjects were dosed up to 16 cumulative actuations of study medication as follows: 1 puff at 0 and 30 minutes, two puffs at 60 minutes, four puffs at 90 minutes, and eight puffs at 120 minutes. Spirometry and safety parameters were measured

Figure 10 Mean change in serum potassium and glucose concentrations following cumulative doses in Study 051-310 and 051-309



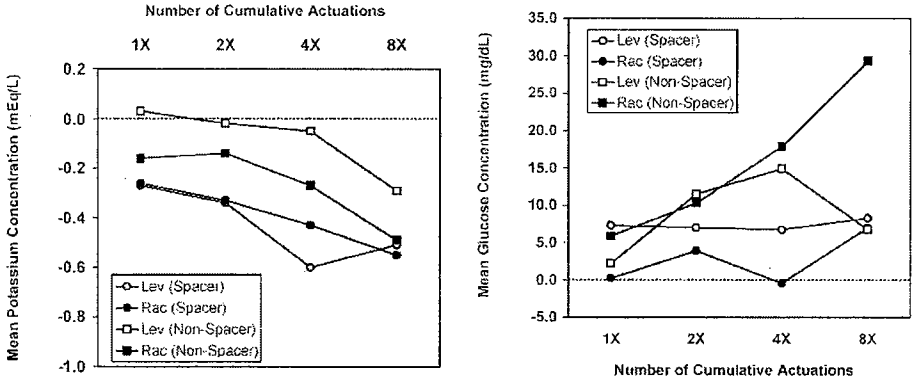
Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 118]

Reviewer's Comment: The change in potassium and glucose is expected with beta adrenergic agonists. The largest change in potassium and glucose appears to be with racemic albuterol in Study 051-310. Study 051-310 utilized spacers (unconditioned), which significantly increased the (R)-albuterol exposure of racemic albuterol HFA compared to levalbuterol HFA.

Pediatric Studies

In the pediatric cumulative dose studies, there appears to be some dose response for potassium and glucose. Figure 11 shows that after 2 actuations of both racemic albuterol HFA and levalbuterol HFA, additional dosing produces a decrease in potassium concentration as well as an increase in glucose level. However, the dose response relationship is not as clear as in the adult cumulative dose studies.

Figure 11 Mean change in serum potassium and glucose concentrations following cumulative dosing in Study 051-311



Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 190]

Reviewer's Comment: The change in potassium and glucose is expected with beta adrenergic agonists.

7.1.7.5 Special assessments

This section is not applicable as no laboratory assessments were deemed critical.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (heart rate, respiratory rate, systolic and diastolic blood pressure) were measured pre-dose and serially post dose at each clinic visit in the multidose studies. Temperature was measured once per clinic visit (pre-dose).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

As in other sections of the review, the adult and pediatric vital sign data will be discussed separately. The vital signs data from the multiple dose studies was pooled because the studies incorporated a placebo treatment group. In addition, the multiple dose studies were of longer duration than the dose ranging and cumulative dose studies. The dose ranging and cumulative dose studies were reviewed specifically for a dose response relationship.

7.1.8.3 Standard analyses and explorations of vital signs data

A review of the adult multiple dose studies demonstrated that there was no significant change from predose values in the mean heart rate, systolic blood pressure, and diastolic blood pressure

measurements in any of the treatment groups after a single dose or after 4-8 weeks of QID dosing [N21730\N_000\2004-05-11\clinstat\iss.pdf p 140-142].

A review of the pediatric multiple dose studies demonstrated that there was no clinically significant change from predose values in the mean heart rate, systolic blood pressure, and diastolic blood pressure measurements in any of the treatment groups [N21730\N_000\2004-05-11\clinstat\iss.pdf p 208-211].

7.1.8.4 Additional analyses and explorations

In the adult multiple dose studies, there were similar percentages of subjects in each treatment group with a heart rate increase > 20bpm, a SBP increase > 20mmHg, and DBP >10mmHg.

Table 37 Categorical Summary of Heart Rate and Blood Pressure Measures in the Adult Multiple Dose Studies (051-353, 051-355, 051-305)

n (%)	Levalbuterol HFA 90mcg n=445	Levalbuterol HFA 180mcg n=41	Racemic Albuterol HFA 180mcg n=218	Placebo HFA-134a n=206
Heart Rate ↑ >20 bpm	49 (11%)	5 (12%)	18 (8%)	19 (9%)
SBP ↑ > 20 mm Hg	61 (14%)	9 (22%)	33 (15%)	31 (15%)
DBP↑ > 10 mm Hg	180 (40%)	17 (42%)	91 (42%)	79 (38%)

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 143]

The adult dose ranging study was complicated by the exercise challenge. However, similar changes in heart rate, blood pressure, and respiratory rate were noted across the treatment groups [N21730\N_000\2004-05-11\clinstat\iss.pdf p 143]. The adult cumulative dose studies suggested a dose response relationship. After two actuations of both racemic albuterol HFA and levalbuterol HFA, additional dosing produced an dose-related increase in heart rate. No significant dose response was noted with systolic or diastolic blood pressure.

In the pediatric multiple dose studies, more subjects in the active treatment groups than the placebo group demonstrated a heart rate increase > 20 bpm. The percentage of subjects with a SBP increase >20mmHg and DBP increase >10mmHg was greater in the placebo group than in the levalbuterol HFA treatment groups [N21730\N_000\2004-05-11\clinstat\iss.pdf p 212].

Table 38 Categorical Summary of Heart Rate and Blood Pressure Measures in the Pediatric Multiple Dose Studies (051-354, 051-306)

n (%)	Levalbuterol HFA 90mcg n=445	Levalbuterol HFA 180mcg n=41	Racemic Albuterol HFA 180mcg n=218	Placebo HFA-134a n=206
Heart Rate ↑ >20 bpm	30 (29%)	12 (35%)	23 (33%)	15 (22%)
SBP ↑ > 20 mm Hg	21 (12%)	4 (12%)	11 (16%)	11 (16%)
DBP↑ > 10 mm Hg	42 (40%)	18 (53%)	30 (43%)	37 (54%)

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 143]

In the pediatric dose ranging study similar changes in heart rate, blood pressure, and respiratory rate were noted across the treatment groups [N21730\N_000\2004-05-11\clinstat\iss.pdf p 213].

The pediatric cumulative dose study did not demonstrate convincing dose response relationship for heart rate change or blood pressure change [N21730\N_000\2004-05-11\clinstat\iss.pdf p 214].

7.1.9 Electrocardiograms (ECGs)

The data from the clinical studies demonstrated no consistent mean change in ECG measures. In adults, the levalbuterol HFA treatment group had slightly higher percentage of subjects with QT_{C-F} values >450ms and subjects with a QT_{C-F} change from predose 30-60msec than the other treatment groups. The cumulative dose studies showed a dose related increase in QTc interval with doses greater than 4 actuations of both racemic albuterol HFA and levalbuterol HFA. Details regarding the ECG findings are discussed in the following section.

The current product label for racemic albuterol HFA contains the following language in the Warnings section "beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression." The Applicant has included similar language in the proposed Xopenex HFA product label, which is appropriate.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were collected at screening as well as pre-dose and 30 minutes post-dose for each of the clinic visits (Visits 2-6). The post-dose ECG were obtained closed to Cmax, which occurred at approximately 0.54 hr (Table 4). All ECGs were over-read by a central cardiologist. Standard ECG measurements were measured including: heart rate, QT interval, PR interval, QRS duration, RR interval, QT_{C-F} (Fridericia), and QT_{C-B} (Bazett). Changes from pre-dose in heart rate, QT_{C-F} and QT_{C-B} were calculated for each visit.

Preclinical studies were not conducted for this Application. As a 505(b)(2) Application, the Applicant relies upon the Agency's determination of the safety and efficacy of an approved product the approved Proventil HFA safety database, which includes preclinical studies conducted with racemic albuterol.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The adult and pediatric ECG will be discussed separately. The ECG data from the two Phase 3 adult multiple dose studies (Studies 051-353 and 051-355) were pooled because these studies were placebo-controlled and the ECG data were over-read by a central ECG facility. The ECGs in Study 051-305 were not centrally overread, thus, Study 051-305 will be discussed separately. The dose ranging and cumulative dose studies were reviewed specifically for a dose response relationship. For the pediatric population, Study 051-306 did not have centrally overread ECGs; therefore, Study 051-354 and Study 051-306 will be discussed separately.

Beta agonists have been reported to be associated with ECG changes, including QT interval prolongation. The QT interval will be a focus of this section. QT interval data will be presented corrected by both the Bazett's and Fridericia's formula. The Bazett formula tends to overcorrect at elevated heart rates, which are seen with beta agonist use. Therefore, this section will focus on the Fridericia corrected QT interval.

7.1.9.3 Standard analyses and explorations of ECG data

Adult Studies

Analyses of the pooled ECG data for Studies 051-353 and 051-355 showed no consistent mean changes in ECG measures. The largest mean increases in QT_{c-F} and QT_{c-B} were 2.6ms and 2.3ms, respectively, in the levalbuterol HFA 90mcg treatment group compared to -2.0, -4.4ms, in the placebo group and 1.4ms, 1.4ms, in the racemic albuterol HFA treatment group. The Applicant summarized the QT measures categorically, which is displayed in Table 39.

Table 39 Post-First Dose Measures of QT_{c-F} and QT_{C-B} in Studies 051-353 and 051-355

ECG Parameter	Levalbuterol HFA 90mcg n=403	Racemic Albuterol HFA 180mcg n=170	Placebo HFA-134a n=166
QT_{c-F} (ms)			
>450 ms	16 (4.0)	1 (0.6)	5 (3.0)
>500 ms	0	0	0
Change from predose 30-60ms	39 (9.7)	15 (8.4)	12 (7.2)
Change from predose >60ms	2 (0.5)	0	1 (0.6)
QT_{C-B} (ms)			
>450 ms	47 (11.7)	10 (5.6)	10 (6.0)
>500 ms	2 (0.5)	0	0
Change from predose 30-60ms	67 (16.6)	33 (18.4)	20 (12.0)
Change from predose >60ms	7 (1.7)	1 (0.6)	1 (0.6)

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 128]

As shown above, there were slightly higher percentages of subjects in the levalbuterol HFA 90mcg group than in the other treatment groups with the following:

- QT_{C-F} values >450ms
- QT_{C-F} change from predose 30-60msec

However, the percentage of subjects with QT_{C-F} values >450ms was similar between the levalbuterol HFA group and the placebo group. The percentage of subjects with a QT_{C-F} change from predose 30-60msec was similar between the levalbuterol HFA group and the racemic albuterol HFA group.

In Studies 051-353 and 051-355, similar rates of ECG abnormalities were noted before and after dosing in each treatment group. One episode of atrial fibrillation was noted in a 52-year-old male in the levalbuterol HFA 90mcg group [N21730\N_000\2004-05-11\clinstat\iss.pdf p 129-130].

The ECG results for Study 051-305 showed no significant differences in mean changes in ECG measures across the treatment groups. A 13 year old subject in the levalbuterol HFA 90mcg group had a QT_{C-F} >500ms [N21730\N_000\2004-05-11\clinstat\iss.pdf p 130].

The ECG results from the adult dose ranging study (Study 051-308) showed the levalbuterol HFA treated subjects had slightly longer mean QT intervals than racemic albuterol treated subjects. There was no change in incidence of abnormal ECGs with increased dosing. There was no clear dose-related QT_c effect with the active treatment groups except possibly a change from pre-dose QT_{C-F} of 30-60ms. One subject in the racemic albuterol HFA 360mcg treatment group had a QT_{C-F} >500ms [N21730\N_000\2004-05-11\clinstat\iss.pdf p 131-132].

Pediatric Studies
Analyses of the ECG data from Study 051-354 showed no consistent mean changes in ECG measures. The categorical summary of the data showed similar changes in the QTc interval in the two active treatment groups. ECG changes included prolonged PR interval, first degree AV block, prolonged QT, abnormal axis, minor IVCD, sinus arrhythmia, sinus and bradycardia [N21730\N_000\2004-05-11\clinstat\iss.pdf p 200-202].

Analyses of the ECG data from Study 051-306 showed no consistent mean changes in ECG measures. Rates of subjects in the levalbuterol HFA group with QT_{C-B} >450ms, QT_{C-B} and QT_{C-F} changes from pre-dose of 30-60ms and >60ms were similar to rates in the racemic albuterol group [N21730\N_000\2004-05-11\clinstat\iss.pdf p 202].

In the pediatric dose ranging study (051-312), mean ECG measures were similar across treatment groups [N21730\N_000\2004-05-11\clinstat\iss.pdf p 202].

7.1.9.4 Additional analyses and explorations

The ECG data from cumulative dose Study 051-309 (no spacers) showed a clear dose response increase in mean changes in QT_{C-B} and QT_{C-F} for both levalbuterol HFA and racemic albuterol HFA. At 8X and 16X, the mean change in QT_{C-F} with levalbuterol HFA was 7.3ms and 10ms compared to 8.1ms and 14.5ms for the racemic albuterol HFA group. Other ECG changes included T wave changes, abnormal U waves, first degree block, sinus bradycardia, and depressed ST segment
[N21730\N_000\2004-05-11\clinstat\iss.pdf p 133-139].

The ECG data from cumulative dose Study 051-310 (spacer study) showed a dose related increase in heart rate for both levalbuterol HFA and racemic albuterol HFA. In general, the increase in mean QT_{C-F} showed a dose response with both levalbuterol HFA and racemic albuterol HFA and the change in QT_{C-F} from predose 30-60ms showed a dose response [N21730\N_000\2004-05-11\clinstat\iss.pdf p 133-139].

The ECG data from the pediatric cumulative dose Study 051-311 demonstrated a dose related increase in heart rate in both the levalbuterol HFA and racemic albuterol HFA treatment groups; however, no dose related mean change in QT_{C-F} was observed. The percentage of subjects with

QT_{C-F} changes from pre-dose of 30-60ms appeared to be dose related [N21730\N_000\2004-05-11\clinstat\iss.pdf p 207].

7.1.10 Immunogenicity

This section is not applicable because levalbuterol is a small synthetic molecule and thus, is not suspected of eliciting an immune response.

7.1.11 Human Carcinogenicity

This section is not applicable as human carcinogenicity studies have not been performed with levalbuterol. However, carcinogenicity studies with racemic albuterol sulfate in rats showed an increased incidence of benign leiomyomas at approximately 15 times the maximum recommended daily inhalation dose of albuterol sulfate for adults on a mg/m^2 basis [Proventil HFA product label].

7.1.12 Special Safety Studies

The Applicant did not conduct any safety studies to evaluate a specific safety concern.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

This section is not applicable as beta adrenergic agonists do not have a history of abuse potential or withdrawal phenomena. In the Applicant's literature search no reports of levalbuterol abuse or dependence were noted [N21730\N_000\2004-05-11\clinstat\clinsum.pdf p 2641].

7.1.14 Human Reproduction and Pregnancy Data

No studies of levalbuterol HFA have been conducted in pregnant women, thus the safety in this population has not been established. Similar to racemic albuterol and levalbuterol hydrochloride, levalbuterol HFA is a Pregnancy Category C. The Applicant has appropriately included language in the proposed product label about the marketing experience with racemic albuterol in pregnant women, use during labor and delivery, use for tocolysis, and use in nursing mothers. The proposed language is consistent with the current Xopenex Inhalation Solution and Proventil HFA product labels.

The Applicant has included appropriate language in the proposed product label regarding the marketing experience of racemic albuterol, in which various congenital anomalies have been reported. No consistent pattern has been discerned and a relationship between racemic albuterol and congenital anomalies has not been established. The proposed product label also states levalbuterol HFA should be used during pregnancy only if the potential benefit outweighs the risk, which is appropriate.

Because beta adrenergic agonists may interfere with uterine contractility, the use of levalbuterol HFA during labor should be restricted to those patients in whom the benefits outweigh the risks.

The proposed product label appropriately addresses the use of levalbuterol HFA in labor and delivery. Levalbuterol HFA has not been studied for the management of preterm labor. The proposed product label states the benefit to risk ratio of levalbuterol HFA for tocolysis has not been established.

It is not known if (R)-albuterol is excreted in human milk and caution should be exercised when levalbuterol HFA is administered to nursing women. The Applicant included appropriate information in the proposed product label regarding nursing mothers.

There were two pregnancies in the adult multidose studies. One subject terminated the pregnancy and the other subject was found to be pregnant during the single-blind placebo period. She was discontinued from the study prior to receiving double-blind treatment [N21730\N_000\2004-05-11\clinstat\iss.pdf p 223]. Seven pregnancies have been documented in the ongoing Study 051-356. Two subjects have delivered normal babies, one terminated the pregnancy, one was documented prior to randomization, and the follow up for the other three is ongoing [N21730\N_000\2004-10-29\update\clinsum.pdf p 53-54].

7.1.15 Assessment of Effect on Growth

This section is not applicable as clinical studies to evaluate the effect on growth were not submitted with this application.

7.1.16 Overdose Experience

The symptoms expected with overdose of levalbuterol HFA are those of excessive beta-adrenergic receptor stimulation, such as tachycardia, nervousness, tremor, palpitations, hypokalemia, and arrhythmias. Subjects in cumulative dose studies with up to 16 actuations of levalbuterol HFA in two hours demonstrated an increase in heart rate (5-10 bpm), an increase in glucose (10-20 mg/dL), and a decrease in potassium (0.2-0.4 mEq/L). In addition to beta adrenergic effects, other adverse reactions associated with levalbuterol could be exaggerated with overdose, such as seizures, angina, hypertension or hypotension, headache, dry mouth, nausea, dizziness, fatigue, malaise, and insomnia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with the overdose of levalbuterol HFA MDI [N21730\N_000\2004-05-11\clinstat\clinsum.pdf, p 2574].
Reviewer's Comment: Similar information is contained in the Ventolin HFA, Proventil HFA, and Xopenex Inhalation Solution product labels.

The primary route of elimination of albuterol enantiomers is through renal excretion. Although the utility of charcoal administration in overdose has not been adequately studied, the available data suggests charcoal administration has little impact on plasma (R)-albuterol levels. There is insufficient evidence to determine if dialysis or forced diuresis is beneficial for overdose of levalbuterol. In the case of overdose, the judicious use of a cardioselective beta-blocker may be considered, although resultant bronchospasm is a risk in some patients. One study reported that 40 mg of IV propranolol was superior to 100 mg of atenolol in reversing the metabolic effects of albuterol in healthy volunteers, although both were equally effective in reversing the

cardiovascular effects. In the event of overdose, standard measures should be taken to remove any unabsorbed drug. Discontinuation of levalbuterol HFA, as well as symptomatic and supportive treatment, is recommended [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 2575].
Reviewer's Comment: The Sponsor has included language in the Overdosage section of the product label, which is the same language as in the Xopenex Inhalation Solution and Proventil HFA product labels.

7.1.17 Postmarketing Experience

The postmarketing experience with Xopenex (levalbuterol HCl) Inhalation Solution suggests the majority of reported AEs are not serious. Of the serious AEs, about half were expected based upon the product label. The Applicant submitted a summary of postmarketing experience with Xopenex Inhalation Solution (levalbuterol HCl). Seven hundred seventy-six post-marketing adverse experiences have been reported in patients receiving levalbuterol HCl. Commonly reported adverse events included: tachycardia, chest pain, dyspnea, lack of drug effect, increased cough, dizziness, tremor, rash, urticaria, parasthesias, and nervousness. The commonly reported AEs are consistent with what is listed in the Xopenex Inhalation Solution product label.

Of the reported AEs, 119 were deemed serious with 55 considered unexpected based upon labeling and 64 considered expected. According to the Applicant, the majority of reported serious events considered unexpected consisted of only one patient report. The unexpected events reported in more than one patient were mainly confined to the respiratory system. Unexpected serious events reported by more than one patient were dyspnea, apnea, hyperventilation, respiratory disorder, abnormal lab test, bronchitis, agitation, and hemorrhage. No safety related changes have been made to the Xopenex Inhalation Solution product label since approval [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 261-266].

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 40 and Table 41 display the enumeration of subjects for the adult and pediatric studies, respectively. More detailed descriptions of the studies are located in Table 2 and Table 3.

Table 40 Enumeration of Subjects for Adult Phase 2 & 3 Studies				
	Levalbuterol HFA 90mcg n(%)	Racemic Albuterol HFA 180mcg n(%)	Placebo HFA-134a n(%)	Total n (%)
Multiple Dose Studies				
051-305	83 (14.0)	39 (11.9)	40 (19.4)	162 (15.4)
051-353	219 (37.1)	119 (36.2)	107 (51.9)	445 (42.3)
051-355	184 (31.1)	60 (18.2)	59 (28.6)	303 (28.8)
Overall Study Counts	486 (82.2)	218 (66.3)	206 (100.0)	910 (86.4)
Dose Ranging Study				
051-308 (cross over)	27 (4.6)	35 (10.6)	-	62 (5.9)
Cumulative Dose Study				
051-310 (cross over)	31 (5.2)	31 (9.4)	-	32 (3.0)
051-309 (cross over)	47 (8.0)	45 (13.7)	-	49 (4.7)
Overall Study Counts	78 (13.2)	76 (23.1)	-	81 (7.7)

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 55]

Table 41 Enumeration of Subjects for Pediatric Phase 2 & 3 Studies				
	Levalbuterol HFA 90mcg n(%)	Racemic Albuterol HFA 180mcg n(%)	Placebo HFA-134a n(%)	Total n (%)
Multiple Dose Studies				
051-306	62 (33.0)	31 (27.0)	34 (49.3)	127 (37.2)
051-354	76 (40.4)	39 (33.9)	35 (50.7)	150 (44.0)
Overall Study Counts	138 (73.4)	70 (60.9)	69 (100.0)	277 (81.2)
Dose Ranging Study				
051-312 (cross over)	19 (10.1)	14 (12.2)	-	33 (9.7)
Cumulative Dose Study				
051-311 (cross over)	31 (16.5)	31 (27.0)	-	31 (9.1)

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 153]

7.2.1.2 Demographics

In general, the demographics and baseline characteristics were similar among the treatment groups in the adult multidose studies as shown in below in Table 42. The majority of the subjects were caucasian with a mean age of 31-36 years and an FEV1 percent predicted of 64-65%.

Table 42 Demographics and Baseline Characteristics for the Adult Multidose Studies Study 051-353, Study 051-355, and Study 051-305						
		Levalbuterol 90 mcg n = 445	Levalbuterol 180mcg n = 41	Racemic Albuterol n = 218	Placebo n = 206	Total n=910
Gender	Male	206 (46%)	27 (66%)	105 (48)%	95 (46%)	433 (48%)
	Female	239 (54%)	14 (34%)	113 (52%)	111 (54%)	477 (52%)
Age (yrs)	Mean (min,max)	35 (12, 80)	31 (12, 77)	35 (12, 81)	36 (12, 79)	35 (12,81)
Race	Caucasian	322 (72%)	36 (88%)	150 (69%)	147 (71%)	655 (72%)
	Black	75 (17%)	43 (20%)	33 (16%)	33 (16%)	153 (17%)
	Hispanic	29 (7%)	3 (7%)	17 (8%)	15 (7%)	64 (7%)
	Asian	12 (3%)	0	6 (3%)	6 (3%)	24 (3%)
	Other	7 (2%)	0	2 (1%)	5 (2%)	14 (2%)
FEV_1 Screening (L)	Mean	2.2	2.4	2.3	2.2	2.2
FEV_1 Percent Predicted	Mean	63.6	65.9	65.1	65.0	64.5

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 59]

The demographics for the adult dose ranging study and cumulative dose studies are described separately. The cumulative dose studies were crossover studies, so the demographics were the same between the treatment groups. In the cumulative dose studies (Study 051-309, Study 051-310) there was a predominance of males, with a mean age of 32, and FEV1% predicted of 69%. The dose ranging study had a younger population with a mean age of 22-23 years and a FEV1 percent predicted between 87-89%.

In the pediatric studies, the demographics and baseline characteristics were similar among the treatment groups as shown in below in Table 43. The majority of the subjects were male with a mean age of 8 years. Although caucasians were the most common racial group, approximately a third of the subjects were black. The mean FEV1 percent predicted was 70%.

Table 43 Demographics and Baseline Characteristics for the Pediatric Multidose Studies Study 051-354, Study 051-306						
		Levalbuterol 90 mcg n = 104	Levalbuterol 180mcg n = 34	Racemic Albuterol n = 70	Placebo n = 69	Total n=277
Gender	Male	62 (60%)	18 (53%)	42 (60%)	44 (64%)	166 (60%)
	Female	42 (40%)	16 (47%)	28 (40%)	25 (36%)	111 (40%)
Age	Mean (min,max)	8.4 (4,11)	8.1 (4,11)	8.5 (4,11)	8.6 (4,11)	8.4 (2.1)
Race	Caucasian	47 (45%)	20 (60%)	40 (57%)	34 (49%)	141 (51%)
	Black	38 (37%)	7 (21%)	18 (26%)	22 (32%)	85 (31%)
	Hispanic	17 (16%)	5 (15%)	9 (13%)	10 (15%)	41 (15%)
	Asian	1 (1%)	1 (3%)	2 (3%)	2 (3%)	6 (2%)
	Other	1 (1%)	1 (3%)	1 (1%)	1 (1%)	4 (1%)
FEV_1 Percent Predicted	Mean	70	71	70	70	70

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 158]

The cumulative dose study was a crossover study, so the demographics were the same between the treatment groups. In the cumulative dose study (Study 051-311) there was a predominance of females and the mean age was 9. In the dose ranging study (Study 051-312) there was one notable difference between the treatment groups. The levalbuterol group had no blacks while the racemic albuterol group had 30% blacks.

7.2.1.3 Extent of exposure (dose/duration)

Table 44 displays the extent of exposure in the adult multiple dose studies. Study 051-308 was four weeks duration, while Studies 051-353 and 051-355 were eight weeks duration. The compliance appears to have been high in all study groups.

Table 44 Extent of Exposure for Adult Multiple Dose Studies Study 051-305, Study 051-353, Study 051-355

	Levalbuterol HFA 90 mcg n = 445	Levalbuterol HFA 180mcg n = 41	Racemic Albuterol HFA 180mcg n = 218
Duration of DB Treatment , Mean Days	50.3	27.3	47.4
Duration: 051-305, Mean Days	28.3	27.3	26.6
Duration of 051-353 and 051-355, Mean Days	52.6	-	52.0
Mean daily DB dose level (mcg)	355.8	719.5	712.5
Mean # puffs per day	7.9	8.0	7.9

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 58]

As in the adult multidose studies, the compliance appears to have been high in all the treatment groups in the pediatric multiple dose studies as shown below in Table 45.

Table 45 Extent of Exposure for Pediatric Multiple Dose Studies Study 051-306 and Study 051-354

	Levalbuterol HFA 90 mcg n = 104	Levalbuterol HFA 180mcg n = 34	Racemic Albuterol HFA 180mcg n = 70
Duration of DB Treatment , Mean Days	25.6	20.7	24.8
Duration: 051-306, Mean Days	21.1	20.7	21.2
Duration of 051-354, Mean Days	27.3	-	27.6
Mean daily DB dose level (mcg)	349.9	711.3	698.8
Mean # puffs per day	7.8	7.9	7.8

Source: [N21730\N_000\2004-05-11\clinstat\iss.pdf p 155]

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The safety of levalbuterol HFA is also be supported by the previous finding of the safety of Xopenex Inhalation Solution (levalbuterol hydrochloride) and Proventil HFA. Xopenex Inhalation Solution is an approved drug product containing (R)-albuterol, while Proventil HFA is an approved drug product containing both (R) and (S)-albuterol.
Reviewer's Comment: As a 505(b)(2) application, the Applicant may rely upon the Agency's previous finding of safety of an approved drug. Since the exposure to (R)-albuterol is less with levalbuterol HFA than with racemic albuterol HFA and Xopenex Inhalation Solution, this application is supported by the agency's previous finding of the safety of racemic albuterol HFA and Xopenex Inhalation Solution.

The Applicant also submitted a literature review and the postmarketing experience with levalbuterol hydrochloride to support the safety of levalbuterol HFA. The literature review and postmarketing experience are discussed in the following sections.

7.2.2.2 Postmarketing experience

The postmarketing experience with Xopenex (levalbuterol HCl) Inhalation Solution suggests the majority of AEs are not serious. Of the serious AEs, about half were expected based upon the product label. The Applicant submitted a summary of postmarketing experience with Xopenex Inhalation Solution (levalbuterol HCl). Seven hundred seventy-six post-marketing adverse experiences have been reported in patients receiving levalbuterol HCl. Commonly reported adverse events included: tachycardia, chest pain, dyspnea, lack of drug effect, cough increased, dizziness, tremor, rash, urticaria, parasthesias, and nervousness. The commonly reported AEs are consistent with what is listed in the Xopenex Inhalation Solution product label.

Of the reported AEs, 119 were deemed serious with 55 considered unexpected based upon labeling and 64 considered expected. According to the Applicant, the majority of reported serious events considered unexpected consisted of only one patient report. The unexpected serious events reported in more than one patient were mainly confined to the respiratory system. Unexpected events reported by more than one patient were dyspnea, apnea, hyperventilation, respiratory disorder, abnormal lab test, bronchitis, agitation, and hemorrhage. No safety related changes have been made to the Xopenex Inhalation Solution product label since approval [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 261-266].

7.2.2.3 Literature

The Applicant performed a literature search to provide relevant safety information to support the safety of levalbuterol HFA. The literature search included beta adrenergic agonist literature with special reference to racemic albuterol and clinical literature pertaining to the levalbuterol nebulized formulation [N21730\N_000\2004-05-11\clinstat\clinsum.pdf, p 2601-2651].

The literature search provided evidence that the adverse events of levalbuterol and racemic albuterol are consistent with the systemic effects of beta adrenergic agonists. Beta-mediated effects include the following: tremor, nervousness, dizziness, insomnia, increased serum glucose, increased heart rate, QT_c effects, arrhythmias, torsade de pointes, chest pain, hypokalemia, nausea, dyspepsia, and leg cramps.

Specific safety findings in the literature search included the following cases:

- Torsades de pointes in a racemic albuterol subject later found to have congenital prolonged QT syndrome
- Death of a 59 year old male who was treated with nebulized racemic albuterol hospitalized for angina, developed chest pain with acute ECG changes, and subsequently underwent CABG surgery. He died of ventricular fibrillation following surgery.
- Angina and myocardial infarction in a 73 year old following nebulized racemic albuterol administration

- Two cases of overdose (one levalbuterol and one racemic albuterol) that were treated symptomatically and resolved.

Although the literature search did not note paradoxical bronchospasm associated with levalbuterol use, the search did identify paradoxical bronchospasm associated with racemic albuterol use. The Applicant appropriately states that the potential for occurrence of paradoxical bronchospasm with levalbuterol use cannot be ruled out.

According to the Applicant, the literature search did not identify any special populations that might be at increased risk with the use of beta agonists.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience submitted by the Applicant is adequate with the exception of limited device performance data in the pediatric population. The ICH guidelines for drugs intended for long term treatment of non-life threatening conditions estimates the total number of subjects necessary to assess the safety of a new drug is about 1500, with about 300-600 subjects treated for 6 months, and 100 subjects treated for one year. Because this is a 505(b)(2) application that relies upon the Agency's previous determination of the safety of albuterol and levalbuterol HCl, the number of subjects necessary for the safety assessment is less. The number of subjects with short term exposure to levalbuterol HFA in this application is 591 adults and 188 children. In addition, the Applicant submitted interim data from a long-term (12 month) safety study in 297 adult subjects treated with levalbuterol HFA.

The design, doses, and safety monitoring in the Phase 3 studies were acceptable. The placebo and active controlled design of the Phase 3 studies was appropriate to answer critical questions. The duration of the clinical studies was shorter than typically expected with a bronchodilator. However, the Division indicated in a meeting with the Applicant that shorter duration studies would be acceptable if device performance was adequately addressed in the overall clinical program. Refer to Section 6.1.3 for details. The doses chosen by the Applicant for the Phase 3 studies were acceptable; however, the dose ranging pediatric study suggests the 45 mcg levalbuterol HFA dose may also be effective. The Division indicated in a meeting with the Applicant on October 29, 2003, that the 90mcg levalbuterol HFA dose was acceptable. Finally, the Applicant adequately monitored for potential class effects (beta adrenergic mediated effects) of levalbuterol HFA in the clinical studies.

Device performance is an important part of the safety and efficacy assessment of a new metered dose inhaler. Device performance is summarized in Section 7.2.9.2 and discussed in detail in the Appendices. Usually device performance is incorporated into the Phase 3 clinical studies. However, in this clinical development program, device performance was incorporated into an ongoing long term safety study. The in-use data is adequate to assess the device performance in adults, but no in-use data was submitted to assess the device performance in children.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Preclinical studies were not performed for this application as racemic albuterol sulfate is an approved drug substance. As a 505(b)(2) application, the Applicant may rely upon the Agency's previous finding of safety, which includes preclinical testing conducted with albuterol sulfate.

7.2.5 Adequacy of Routine Clinical Testing

To support this application, the Applicant incorporated appropriate clinical monitoring into the clinical studies. Clinical monitoring included laboratory parameters, vital signs, ECGs, and adverse events. The Applicant particularly focused upon assessing for potential beta mediated adverse events, which was appropriate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This is a 505(b)(2) application that can rely on the Agency's previous finding of safety and efficacy of racemic albuterol and levalbuterol HCl and reference previous metabolism, clearance, and interaction studies conducted with albuterol sulfate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Because racemic albuterol and levalbuterol HCl are approved drugs, the side effect profile of levalbuterol HFA can be predicted. The Applicant's effort to detect potential adverse events included an assessment of beta adrenergic effects, such as ECG changes, hypokalemia, and hyperglycemia. The Applicant's evaluation for potential adverse events in the clinical studies is acceptable.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the quality and completeness of the data available to conduct the safety review is acceptable. However, the device performance database is somewhat limited in that in-use data was not assessed in the pediatric population. Ideally, the Applicant should have assessed device performance with levalbuterol HFA in all of the Phase 3 clinical studies.

7.2.9 Additional Submissions, Including Safety Update

The Applicant electronically submitted the 120-day safety update on October 29, 2004. The safety update included clinical information and device performance data from an ongoing 12-month safety study (Study 051-356) reviewed in this section. In addition, the safety update included an updated literature review, which was discussed in Section 7.2.2.3.

7.2.9.1 Safety Update

Study 051-356 is an ongoing multicenter, randomized, active-controlled, open-label, parallel-group safety study for 12 months in male and female subjects ≥ 12 years of age with stable asthma. Subjects were randomized to 90mcg levalbuterol HFA QID or 180mcg Proventil HFA QID. A review of the interim safety data from Study 051-356 does not suggest a new safety signal for levalbuterol HFA. In general, the reported AEs were similar between levalbuterol HFA and racemic albuterol HFA and are comparable to the AEs reported in the Phase 3 clinical studies. More asthma AEs were noted in the levalbuterol HFA group (11.4%) than in the racemic albuterol HFA group (7%). However the discontinuation rate due to asthma, asthma SAEs, and severe asthma AEs were similar between the two groups. A detailed review of the interim results of Study 051-356 is located in the Appendices.

7.2.9.2 Device Performance

Device performance had been an issue discussed with the Applicant in several meetings with the Division. The Applicant had been informed in the February 19, 2002, meeting to address device performance in actual clinical use. The Applicant did not request an EOP2 meeting and failed to incorporate device performance into the Phase 3 clinical studies. In a meeting with the Applicant on October 29, 2003, the Division questioned whether the Applicant had acceptable data on device performance. On November 25, 2003, the Applicant amended the ongoing safety study (051-356), which had been initiated in January 2003, to include collection of information regarding device performance. The safety update includes information on device performance as of July 1, 2004, from the ongoing safety study.

In general, in Study 051-356, the device complaint rate was low. The complaint rate for levalbuterol HFA was 0.024 (39 complaint/1626 canisters) compared to 0.017 (16 complaint/967 canisters) for racemic albuterol HFA. The most common complaints were related to clogging. In vitro testing of the complaint devices indicated DCU was occasionally outside specifications, but returned within specifications after proper washing. Thus, proper washing of the device appears to be important for reliable device performance. From the prospectively collected complaint devices, only two canisters were confirmed device failures by in vitro testing (no propellant). A sample of 180 non-complaint devices did not fail in vitro analyses. The device failure rate is 0.0118 with a 95% confidence interval for the failure rate of 0 and 0.0028. One limitation of Study 051-356 is that it does not provide device performance data for children age 4-11 years. The device complaints in the adult studies were generally clog-related, which leads this reviewer to believe device complaints in the pediatric population would also be clog related. Again, proper washing of the device appears to be important for reliable device performance. A. detailed review of the interim device performance data of Study 051-356 is located in the Appendices.
Reviewer's Comment: Of note, one device was found to be empty on in vitro testing after being stored in the cargo hold of an airplane in flight.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.3.1.1 Beta Adrenergic Mediated Adverse Events

Beta adrenergic agonists have been studied extensively and have the potential to produce certain beta-mediated adverse events, such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, dyspepsia, chest pain, arrhythmia, and worsening hypertension. Beta mediated adverse events were noted in the adult and pediatric clinical studies; however, the incidences were low. In the adult studies, dizziness was more common in the levalbuterol HFA group compared to the placebo group. Dizziness is included in the table of AEs recommended for the product label. In the pediatric studies, dyspepsia was more common in the levalbuterol HFA 90mcg group (1%) compared to the placebo group (0%); however, the incidence was only 1% and is not necessary to include in the product label.

7.3.1.1.1 Hypokalemia

Minimal changes in mean potassium concentration were noted in the clinical studies across the treatment groups. However there did appear to be a dose dependent decrease in potassium levels noted in the cumulative dose studies with 8X and 16X dosing as shown in Figure 10 in Section 7.1.7.4. The Applicant has appropriately included language in the proposed product label regarding the potential of levalbuterol to produce significant hypokalemia.

7.3.1.1.2 Hyperglycemia

Similarly, minimal changes in mean glucose concentration were noted in the clinical studies across the treatment groups. However there did appear to be a dose dependent increase in glucose levels noted in the cumulative dose studies with 8X and 16X dosing as shown in Figure 11 in Section 7.1.7.4. The Applicant has appropriately included language in the proposed product label regarding the potential of levalbuterol to aggravate diabetes mellitus and ketoacidosis.

7.3.1.1.3 Cardiovascular Effects

Beta adrenergic agonists can produce clinically significant cardiovascular effects including changes in heart rate, blood pressure, ECG changes, or cardiovascular symptoms. Each of the potential cardiovascular effects will be discussed briefly.

Significant changes in mean heart rate and blood pressure were not noted in the clinical studies with levalbuterol HFA. Cumulative dose studies showed some increase in heart rate following 8X cumulative dosing; however, blood pressure did not show any significant change. Additional details regarding changes in vital signs is located in Section 7.1.8.

Overall, there were no consistent changes in mean ECG parameters across treatment groups in the multiple dose studies. Because of the potential effect of beta agonists on the QT interval, the Applicant performed additional analyses of the QT interval. The levalbuterol HFA treatment group showed a slightly higher incidence of QT_{C-F} >450ms and change QT_{C-F} from predose of

30-60msec. One consistent finding in the cumulative dose studies is the dose related increase in mean QT_c interval with cumulative dosing of levalbuterol HFA and racemic albuterol HFA. Additional details regarding ECGs is located in Section 7.1.9.

Cardiovascular symptoms in the clinical studies were uncommon in any treatment group. Regardless, the Applicant's proposed product label appropriately contains information regarding the potential cardiovascular effects of levalbuterol, including QT_c prolongation, and recommends use with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

7.3.1.2 Asthma Adverse Events

When all three adult multiple dose studies are pooled, the incidence of asthma adverse events in adults was more common in the levalbuterol HFA 90 mcg treatment group (9.4%) compared to the placebo group (5.8%); however, the incidence was similar to the racemic albuterol HFA treatment group (8.7%) [Table 25]. When just the two Phase 3 multiple dose studies (051-353 and 051-355) are pooled, the incidence of asthma adverse events in the levalbuterol HFA treatment group was 9.4% versus 7.3% in the racemic albuterol group and 6.0% in the placebo group. The pediatric studies showed that the incidence of asthma adverse events was less in the levalbuterol HFA 90mcg treatment group (8.7%) than in the placebo group (14.5%) [Table 27]. The ongoing safety study also has shown an increase in asthma AEs in the levalbuterol HFA group (11.4%) compared to the racemic albuterol HFA group (7.0%).

The Applicant's subgroup analyses to investigate the increased incidence in asthma AEs in adults suggested that there were more subjects with severe asthma (FEV1 <60%) in the levalbuterol HFA group (31.5%) than in the placebo group (27.7%). In addition, the subgroup analyses suggested some of the asthma exacerbations may be related to respiratory infection. However, the subgroup analyses were interpreted with caution due to the post hoc nature and small number of subjects. It is unclear why an increase in asthma AEs was noted in the adult studies. The increased asthma AEs should not necessarily preclude approval as the finding is not consistent across age groups. However, the proposed product label should contain information regarding the increased asthma AEs noted in the adult studies.
Reviewer's Comment: The three Phase 3 clinical adult and pediatric studies (051-353, 051-354, 051-355) were combined to determine if there was a correlation between asthma AEs and race. The combined Phase 3 studies show that asthma AEs were more common in the active treatment groups. Levalbuterol HFA was associated with a slightly higher percentage of subjects with asthma AEs. The percentage of Caucasian and African American subjects with asthma AEs in the levalbuterol HFA treatment group was similar to the percentage of Caucasian and African American subjects with asthma AEs in the racemic albuterol HFA treatment group.

Table 46 Frequency of Asthma AEs by Racial Subgroups for Studies 051-353, 051-355, and 051-354				
	Levalbuterol HFA 90mcg	**Racemic Albuterol HFA 180mcg**	**Placebo HFA134a**	**Total**
Total Number of subjects	479	218	201	898
Subjects with asthma AE, n (%)	46 (9.6)	18 (8.3)	15 (7.5)	79 (8.8)
No of asthma events, n (%)	52 (10.9)	20 (9.2)	15 (7.5)	87 (9.7)
Caucasians	328	146	131	605
Subjects with asthma AE, n (%)	34 (10.3)	9 (6.2)	7 (5.3)	50 (8.3)
No of asthma events, n (%)	37 (11.3)	11 (7.5)	7 (5.3)	55 (9.1)
African American	97	45	39	181
Subjects with asthma AE, n (%)	10 (10.3)	3 (6.7)	4 (10.3)	17 (9.4)
No of asthma events, n (%)	12 (12.4)	3 (6.7)	4 (10.3)	19 (10.5)
Hispanic	39	18	20	77
Subjects with asthma AE, n (%)	2 (5.1)	5 (27.8)	3 (15.0)	10 (13.0)
No of asthma events, n (%)	3 (7.7)	5 (27.8)	3 (15.0)	11 (14.3)
Other	15	9	11	35
Subjects with asthma AE, n (%)	0	1 (11.1)	1 (9.1)	2 (5.8)
No of asthma events, n (%)	0	1 (11.1)	1 (9.1)	2 (5.8)

7.3.1.3 Paradoxical Bronchospasm

Overall, the incidence of paradoxical bronchospasm was highest in the placebo group (9.8%). For the purpose of this application, paradoxical bronchospasm was defined as a ≥15% decrease in FEV1 within one hour of in clinic dosing of study medication. The rate of paradoxical bronchospasm was similar between the levalbuterol HFA 90mcg treatment group (3.4%) and the racemic albuterol treatment group (2.8%). The Applicant has proposed appropriate language in the Warnings section of the proposed product label regarding paradoxical bronchospasm.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

In this safety review, the adult/adolescent data and the pediatric safety data are addressed separately. The safety data are presented as pooled data and individual study data. In general, the safety data from the multiple dose studies are pooled, while the safety data from the cumulative dose studies and dose-ranging studies are presented separately. For details on the pooled studies, refer to Section 7.1. The pooling of the multiple dose studies was performed because the multidose studies have more subjects, provide more exposure to the study medication, and are placebo-controlled. The dose-ranging studies and cumulative dose studies provide additional safety data, but this review emphasizes the multiple dose studies. Deviations from the pooling described above are appropriately indicated.

In addition, for the purposes of this review, safety data for levalbuterol, regardless of manufacturer or actuator design, are combined.

7.4.1.2 Combining data

When safety data was pooled for the purpose of this review, the number of events was combined as the numerator, while the combined number of subjects was the denominator.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

In general, the dose ranging studies did not provide convincing evidence of an increase in AEs with the higher doses of levalbuterol. However, the cumulative dose studies showed overall AEs increased with dose accumulation. Increased reports of dizziness and nervousness suggested potential dose response with cumulative dosing. The cumulative dose studies also suggested a dose response relationship with cumulative dosing and a decrease in potassium, an increase in glucose, and an increase in heart rate. Also, the cumulative dose studies demonstrated a dose related increase in QTc with cumulative dosing of levalbuterol HFA or racemic albuterol HFA.

7.4.2.2 Explorations for time dependency for adverse findings

The Applicant analyzed the time to onset for select AEs in the adult and pediatric studies and did not find any significant differences between treatment groups other than there was a shorter time to onset of dyspepsia with placebo than with levalbuterol HFA [N21730\N_000\2004-05-11\clinstat\iss.pdf, p 96 & 177].

7.4.2.3 Explorations for drug-demographic interactions

The Applicant analyzed the relationship between the reported AEs and age, race, and gender and found the AEs were consistent across the demographic subgroups [N21730\N_000\2004-05-11\clinstat\iss.pdf, p 225].

7.4.2.4 Explorations for drug-disease interactions

Analyses of the safety data suggested that subjects with a history of cardiac disease or endocrine disease did not have an increased medical risk with levalbuterol use [N21730\N_000\2004-05-11\clinstat\iss.pdf, p 225]. However, the Applicant's proposed product label appropriately includes information regarding the potential cardiovascular effects of levalbuterol and to use with caution in patients with cardiovascular disorders. In addition, the proposed product label appropriately states that levalbuterol HFA should also be used with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus.

7.4.2.5 Explorations for drug-drug interactions

The Applicant did not conduct formal drug-drug interaction studies as part of the levalbuterol HFA program because the Applicant could reference the known drug-drug interactions for racemic albuterol [N21730\N_000\2004-05-11\clinstat\iss.pdf, p 226].

The Applicant included appropriate labeling regarding racemic albuterol drug interactions with beta blockers, diuretics, digoxin, monoamine oxidase inhibitors, and tricyclic antidepressants.

7.4.3 Causality Determination

Beta adrenergic agonists have been studied extensively and are known to have the potential to produce certain beta-mediated adverse events, such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, dyspepsia, chest pain, arrhythmia, worsening hypertension, hypokalemia, increased glucose, and ECG changes. The finding of any of the above listed AEs were assumed to be a systemic effect of levalbuterol.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen for adults and children 4 years of age and older is 2 inhalations (90 mcg) repeated every 4 to 6 hours. The Applicant's clinical studies demonstrated the efficacy of 90mcg levalbuterol HFA as a bronchodilator in the proposed population. From a safety standpoint, 90mcg levalbuterol HFA was well-tolerated in both adults and children and provided less exposure to (R)-albuterol than the currently marketed 180mcg racemic albuterol HFA. The recommended dosing regimen is supported by the duration of effect.

The adult dose ranging study suggested that levalbuterol HFA 90mcg and 180mcg provided more bronchoprotection than 45mcg in adults. Thus, the dose selection of 90mcg in adults appears to be appropriate; however the study was complicated by the use of spacers. Although the Applicant also studied the 90mcg levalbuterol HFA dose in children, the pediatric dose ranging study suggested that 45mcg levalbuterol HFA may be effective in children. It should be noted that the dose ranging studies utilized an exercise induced bronchospasm model, which may not necessarily identify the optimal clinical dose. However, in this reviewer's opinion, the 45mcg dose of levalbuterol HFA warrants further investigation in children. A detailed discussion of the dose response relationship is located in Section 5.2.

In terms of dosing in special populations, dosing modification is not recommended for subjects with cardiac, endocrine, or respiratory disease. However, because of the potential beta mediated adverse effects, the proposed product label recommends cautious use in patients with cardiovascular disorders, convulsive disorder, hyperthyroidism, or diabetes mellitus. A detailed discussion of dosing in special populations is discussed in detail in Section 8.3.

8.2 Drug-Drug Interactions

The Applicant did not conduct formal drug-drug interaction studies as part of the levalbuterol HFA program, but referenced information regarding known drug-drug interactions with racemic albuterol. The Applicant included appropriate labeling regarding racemic albuterol drug interactions with beta blockers, diuretics, digoxin, monoamine oxidase inhibitors, and tricyclic antidepressants. The proposed label states that beta blockers can block the effect of beta adrenergic receptor agonists and can produce severe bronchospasm. For diuretics, the ECG changes and/or hypokalemia that may result from some diuretics could be worsened by beta agonists. Studies with racemic albuterol have shown that digoxin levels can decrease a mean 16-22% with racemic albuterol use. Finally, caution should be used when administering levalbuterol HFA with monoamine oxidase inhibitors or tricyclic antidepressants because the action of albuterol on the vascular system may be potentiated.
Reviewer's Comment: The proposed labeling is consistent with the language in other albuterol products.

8.3 Special Populations

Because this Application relies upon the Agency's previous determination of the safety of albuterol and levalbuterol HCl, studies to assess use in special populations were not conducted. For racemic albuterol, special dosing is not recommended based upon race, gender, age. In addition, analyses of data in the clinical studies conducted by the Applicant do not support special dosing based upon race, gender or age.

Dosing modification is not recommended for subjects with cardiac, endocrine, or respiratory disease. However, because of the potential beta mediated adverse effects, the proposed product label recommends cautious use in patients with cardiovascular disorders, convulsive disorder, hyperthyroidism, or diabetes mellitus.

As with racemic albuterol, there are no adequate and well-controlled studies in pregnant women; therefore, levalbuterol HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Similarly, it is not known if (R)-albuterol is excreted in human milk and, therefore, a decision should be made whether to discontinue nursing or to discontinue the drug. A more detailed discussion of the use in pregnancy, labor and delivery, and in nursing mothers is in Section 7.1.14.

8.4 Pediatrics

The Applicant's pediatric development plan consists of the four clinical studies conducted in children ages 4 to 11 and a request for a partial waiver of studies in pediatric subjects less than 4 years of age. In support of the partial waiver of studies in subjects under 4 years of age, the Applicant states it does not expect levalbuterol HFA MDI use in children under 4 years of age nor does it expect that studies of an MDI product in this age range can be reasonably accomplished. The Applicant plans to focus the clinical development in the pediatric population

on Xopenex Inhalation Solution via nebulization, which is the preferred and typical method of administration in children under 4 years of age [September 27, 2004 submission].
Reviewer's Comment: The use of MDIs with a spacer and facemask in very young children is common practice. In addition, other Applicants have designed studies to investigate the use of MDIs in children under 4 years of age. Thus, the Applicant's request for partial waiver should be denied. One potential issue to address in the pediatric development plan is investigating the 45mcg dose of levalbuterol in the pediatric population.

8.5 Advisory Committee Meeting

This section is not applicable as no advisory committee meeting was held to discuss this application.

8.6 Literature Review

The Applicant performed a literature search to support the safety of levalbuterol HFA. As discussed in Section 7.2.2.3, the literature provides evidence that adverse events noted with levalbuterol and racemic albuterol are consistent with the systemic effects of beta adrenergic agonists. Beta-mediated effects include the following: tremor, nervousness, dizziness, insomnia, increased serum glucose, increased heart rate, QT_c effects, arrhythmia, torsade de pointes, chest pain, hypokalemia, nausea, dyspepsia, and leg cramps.

8.7 Postmarketing Risk Management Plan

Because the long-term safety of racemic albuterol is well-established, a post-marketing risk management plan is not recommended.

8.8 Other Relevant Materials

8.8.1 Spacer Use

The Applicant used spacers in Study 051-308, 051-310, and 051-311. However, the Phase 3 clinical studies demonstrated the efficacy of levalbuterol HFA without spacer use. Because the Division knows patients use spacers, we looked more carefully at the use of levalbuterol HFA with a spacer to determine if the proposed product label should include specific language regarding use with a spacer. The Division determined specific language in the product label regarding spacer use was not necessary.

Because the results of Phase 2 studies suggested racemic albuterol HFA was more potent than levalbuterol HFA, the Applicant conducted in vitro testing to determine the impact of spacers and conditioning of spacers. As discussed in Section 3.1 and shown in Table 1, the conditioning of a spacer can affect the Fine Particle Dose (FPD) of (R)-albuterol with levalbuterol HFA. The Applicant considers conditioning a spacer to be the initial cleaning of the spacer according to manufacturer's instructions. The use of a conditioned spacer increases the FPD of levalbuterol

HFA from 23mcg (R)-albuterol without a spacer to 28 mcg (R)-albuterol with a conditioned spacer. If the spacer is not conditioned, the FPD is lower at 20mcg (R)-albuterol. Interestingly, the FPD of (R)-albuterol with racemic albuterol HFA increases from 23mcg to 30mcg with an unconditioned spacer and 32mcg with a conditioned spacer.
Reviewer's comment: The directions for the ~ spacer recommend soaking the spacer in warm water with detergent for 15 minutes then rinsing well prior to first use, then repeating weekly. Compliance with the recommendation for weekly cleaning may be low in clinical practice.

The effect of spacer use on exposure of (R)-albuterol was compared in Study 051-311, which was a cumulative dose crossover study in children with and without spacers. The PK parameters from Study 051-311 showed that the administration of levalbuterol HFA with a conditioned spacer increases the exposure to (R)-albuterol. Similarly, the administration of racemic albuterol HFA with a spacer increases the exposure to (R)-albuterol. It is important to note, however, that the exposure to (R)-albuterol from levalbuterol HFA administered with a spacer remains less than the exposure to (R)-albuterol with racemic albuterol HFA administered with or without a spacer. The results for plasma concentrations for (R)-albuterol are detailed below in Table 47.

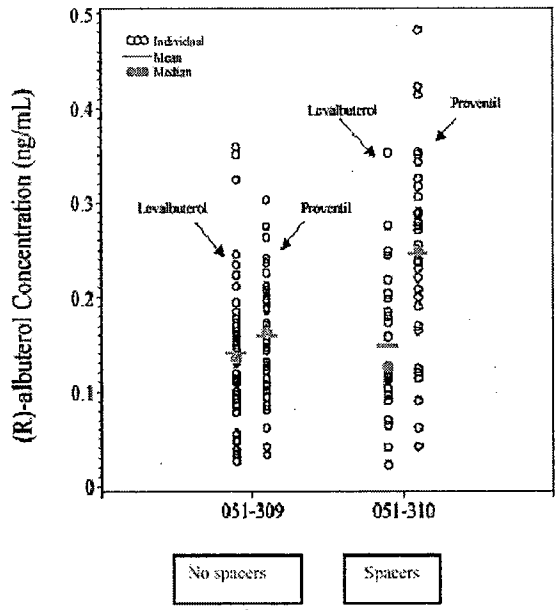
Table 47 (R)-Albuterol Concentration in Cumulative Dose Study 051-311 (ITT Population)

	Levalbuterol		Racemic Albuterol	
median (ng/mL)	Non-spacer N=19	Spacer N=10	Non-spacer N=19	Spacer N=10
Pre-1X Dose (0 hr)	BLQ	0.029	0.016	0.010
Post 1X Dose (0.5 hr)	0.044	0.065	0.082	0.097
Post 2X Dose (1.0 hr)	0.106	0.130	0.145	0.159
Post 4X Dose (1.5 hr)	0.170	0.205	0.291	0.292
Post 8X Dose (2.0 hr)	0.386	0.413	0.461	0.548

Source: N21730\N_000\2004-05-11\hpbio\hupharm\051-311.pdf, p 92
Reviewer's Comment: Study 051-311 was conducted with spacers that were appropriately conditioned. Earlier studies (051-308 and 051-310) were conducted with spacers, which the Applicant asserts were not necessarily appropriately conditioned.

The Applicant performed a cross study comparison of the PK data between the cumulative dose studies to determine the effect of spacers on (R)-albuterol exposure. The Applicant compared Study 051-309 (without spacers) and Study 051-310 (with presumably unconditioned spacers). The Applicant concluded that with levalbuterol HFA use, the exposure to (R)-albuterol was similar with and without a spacer; however, with racemic albuterol HFA use, the exposure to (R)-albuterol was greater with the use of a spacer. The cross study comparison is shown below in Figure 12.

Figure 12 Cross Study Comparison of (R)-Albuterol Exposure with and without Spacers Study 051-309 & Study 051-310



Source: N21730\N_000\2004-05-11\hpbio\hpsum.pdf p 31

Reviewer's Comment: Conditioning of the spacer was not specified in Study 051-310. With use of an unconditioned spacer, levalbuterol HFA provides less exposure to (R)-albuterol than racemic albuterol HFA. In vitro studies (Table 1) and Study 051-311 (Table 47) suggest that with a properly conditioned spacer, the exposure to (R)-albuterol is less with levalbuterol HFA than with racemic albuterol HFA.

To summarize, the conditioning of the spacer appears to affect the exposure to (R)-albuterol with levalbuterol HFA. Use of a properly conditioned spacer increases exposure to (R)-albuterol for both levalbuterol HFA and racemic albuterol HFA. However, spacer use with racemic albuterol increased (R)-albuterol exposure to a greater extent than with levalbuterol HFA. Use of an unconditioned spacer with levalbuterol HFA does not significantly change the exposure to (R)-albuterol compared to without a spacer.

9 OVERALL ASSESSMENT

9.1 Conclusions

The data submitted in this Application are adequate, from a clinical perspective, to support approval. The three Phase 3, placebo and active-controlled studies establish the efficacy of 90mcg levalbuterol HFA for the treatment/prevention of bronchospasm in adults, adolescents and children ages 4 to 11 years with asthma. Efficacy was established by the demonstration of a

clinically meaningful improvement in the peak percent change in FEV1 averaged over the double blind period following administration of levalbuterol HFA as compared to placebo. Secondary endpoints, including percent change in FEV1, percent predicted FEV1, and peak percent change FVC further support the efficacy of levalbuterol HFA. The studies did not establish a significant improvement in physician or subject global assessment, asthma symptom scores, quality of life scores, or rescue medication use.

The dose finding for this application was less than adequate because the Applicant started the Phase 3 studies prior to completing the dose ranging studies. The Applicant chose 90mcg levalbuterol HFA to study in both adult and pediatric subjects. The adult dose ranging study did indicate that 90mcg levalbuterol HFA was the appropriate dose to further study in adults. The adult study was complicated by the use of spacers. However, the pediatric dose ranging study suggested that 45mcg levalbuterol HFA may be effective in children. It should be noted that the dose ranging studies utilized an exercise induced bronchospasm model, which may not identify the optimal dose for clinical use. However, the exercise induced bronchospasm model provides a comparison with the approved racemic albuterol HFA. The results of the pediatric study do suggest, however, that 45mcg levalbuterol HFA may be effective in children and thus, warrants further study in pediatric subjects.

Although the Phase 3 studies were designed to compare the levalbuterol HFA group to placebo group, the Applicant included an active control group treated with racemic albuterol HFA. As expected, racemic albuterol HFA was also superior to placebo for key spirometry endpoints. In general, levalbuterol HFA produced results similar to racemic albuterol HFA. However, differences in efficacy variables were noted between levalbuterol HFA and racemic albuterol HFA in the individual studies. Occasionally the differences were statistically significant, but were not consistent across different studies. In addition, it is unclear if any differences noted would be clinically significant. Thus, the conclusion is that levalbuterol HFA produced results similar to racemic albuterol HFA.

Levalbuterol 90mcg HFA provides lower exposure to (R)-albuterol than 180mcg racemic albuterol HFA. The extent of patient exposure to levalbuterol HFA during the development program is adequate. In the clinical studies, adverse events attributable to levalbuterol HFA were related to the systemic beta adrenergic agonist effect. Although an increased incidence of asthma adverse events was noted in the adult multidose studies, the increase was not noted in the pediatric study. In addition, the incidence of asthma AEs with levalbuterol HFA was similar to the incidence of asthma in the group receiving racemic albuterol HFA, which is an approved medication. Device performance as assessed in the ongoing long term safety study is adequate. Thus, the safety profile of levalbuterol HFA is acceptable.

9.2 Recommendation on Regulatory Action

From a clinical perspective, the data submitted in this NDA provide adequate support for Approval. The clinical studies demonstrate that 90mcg levalbuterol HFA is superior to placebo and provides clinically meaningful bronchodilation in patients with asthma. Efficacy was established by the demonstration of a clinically meaningful improvement in the peak percent

change in FEV1 averaged over the double blind period following administration of levalbuterol HFA as compared to placebo. Secondary endpoints, including percent change in FEV1, percent predicted FEV1, and peak percent change FVC further support the bronchodilator efficacy of levalbuterol HFA.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Because the long term safety of racemic albuterol is well-established, postmarketing risk management activities are not recommended for levalbuterol HFA.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments for this application.

9.3.3 Other Phase 4 Requests

There are no required Phase 4 requests for this application.

9.4 Labeling Review

The proposed product label was reviewed in detail. The following are general comments regarding the proposed product label. At the time of the finalization of this review, labeling negotiations are ongoing.

In the Clinical Trials section:

- All
  should be deleted.
- The text should be revised to provide a general introduction regarding the combined efficacy and safety database.
- The proposed label contains too many graphs. The mean percent change in FEV1 versus time in Study 051-353 is recommended for the product label.
- The median time to onset of a 15% increase in FEV1 reflects data for Visit 2 only and should be clarified.
- The median duration of a 15% increase in FEV1 of 3 to 4 hours reflects data for responders only and should be clarified.
- In the Pediatrics section, should be removed

The Geriatrics section should be revised to be consistent with 21CFR 201.57(f)(10).

In the Adverse Reactions section of the proposed product label:

- All r —
  — should be deleted.
- The number of subjects in the adult studies should be 748, not —
- Table 2 in the proposed product label has an incorrect number of subjects in the placebo group listed. The number of subjects should be 166, not —
- Table 3 should be revised to only include the AEs reported in >2% of patients in the levalbuterol HFA group and more common than in the placebo group.
- The —
  —
  — , should also be deleted.

DMETS reviewed the container labels, carton, and package insert of Xopenex HFA and had the following comments [Linda Wisniewski, DMETS Review, November 17, 2004].

- Increase font of established name so it is at least ½ the size of the proprietary name.
- Use a color combination that provides sufficient contrast and greater readability
- Change the graphics —

DDMAC reviewed the proposed draft labeling and provided comments [Jialynn Wang, DDMAC Review, February 14, 2005]. The Division reviewed the comments and incorporated many of the suggestions into the revised product label.

At the time of the finalization of this review, a revised product label has been conveyed to the Applicant. Labeling negotiations are ongoing.

9.5 Comments to Applicant

There are no comments to convey to the Applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study 051-353

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

Reviewer's Comment: Study 051-353 was conducted with levalbuterol HFA-B, which was manufactured by — 3M is the to-be-marketed manufacturer. However, according to the

CMC reviewer, the pertinent CMC attributes of the 3M and — levalbuterol products are similar.

10.1.1.2 Objectives

The primary objective of Study 051-353 was to investigate the efficacy of levalbuterol HFA90 mcg versus placebo in the treatment and prevention of bronchoconstriction in adolescent and adult subjects with asthma. Secondary objectives included: 1) investigation of the efficacy of levalbuterol HFA90 mcg versus racemic albuterol 180 mcg; 2) characterization of the PK of (R)-albuterol and (S)-albuterol in subjects 12 years of age and older with asthma; 3) determination of the safety and tolerability of levalbuterol HFA [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1113].

10.1.1.3 Study Design

Study 51-353 was a double-blind, randomized, placebo- and active-controlled, double-dummy, multicenter, parallel-group trial divided into two periods. Period 1 was a one week, single-blind, placebo run-in with racemic albuterol CFC MDI (90 mcg per actuation) used as rescue medication. Period 2 was an 8 week, double-blind, active-treatment period with the following 3 treatment groups [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1114]:

- Levalbuterol HFAHFA MDI 90 mcg (2 actuations, 45 mcg each) QID
- Racemic albuterol HFA MDI 180 mcg (2 actuations, 90 mcg each) QID
- Placebo HFA MDI (2 actuations) QID.

10.1.1.3.1 Study Duration

The total duration of the study was nine weeks, which included a 1 week run-in period and 8 weeks of active treatment. The study was performed during the period between May 29, 2002, and January 10, 2003. The final study report is dated March 1, 2004 [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 4].

10.1.1.3.2 Study Population

A total of 500 subjects, 12 years of age and older, with at least a 6 month history of asthma and a FEV1 of $\geq$ 45% to $\leq$ 75% of predicted were enrolled into the study [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 4].

10.1.1.3.3 Inclusion Criteria

The following is a list of the inclusion criteria for Study 051-353 [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1128-1129].

- Male or females 12 years of age and older
    - For subjects 12-17 years of age, informed consent must be signed by the subject's parent or legal guardian
- Asthma diagnosis documented for 6 months prior to Visit 1, as defined by ATS
- Reversibility of airflow obstruction $\geq$ 12% within 15-30 minutes following 180 mcg racemic albuterol MDI

- $FEV_1 \geq 45\%$ and $\leq 75\%$ of predicted at Visit 1
- Stable asthma in the opinion of the investigator and using a β-adrenergic agonist, and/or anti-asthma anti-inflammatory medication, and/or OTC asthma medication for at least 6 months prior to Visit 1
- Good health and not suffering from any chronic condition that might affect their respiratory function
- CXR within 12 months prior to randomization which is essentially normal
- Negative serum pregnancy at Visit 1 for female subjects
- Acceptable birth control method for women of child bearing potential
- Ability to complete diary cards, understand instructions, and perform PEF measurements

10.1.1.3.4 Exclusion Criteria

The following is a list of the pertinent exclusion criteria for study 051-353 [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1129-1131].

- Lactating or pregnant females
- History of hospitalization for asthma within 45 days prior to screening or life-threatening asthma (intubation, hypercapnea, respiratory arrest, or hypoxic seizures) within 12 months prior to screening
- Known sensitivity to levalbuterol HFA or racemic albuterol or any of the excipients contained in the formulations
- Significant disease other than asthma
- History of bronchopulmonary aspergillosis or allergic alveolitis
- History of drug abuse within 12 months prior to screening
- History of >10 pack years of cigarette smoking or use of any tobacco products within 6 months prior to screening
- History of upper or lower respiratory tract infection 2 weeks prior to screening
- Clinically significant abnormal laboratory values or abnormal ECG

10.1.1.3.5 Study Centers

A total of 56 investigators in the United States participated in Study 051-353. Subjects were randomized at 54 of the study sites [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 25].

10.1.1.3.6 Materials

The following were the treatments for Study 051-353 [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 34]:

- Levalbuterol HFA MDI 45 mcg (Lot #2A260, —., exp. date 1/04)
- Proventil HFA MDI 6.7g (Lot # GCD011A, Schering, exp. date 4/04)
- Placebo HFA MDI - to match levalbuterol HFA (Lot #2A221, —, exp. date 1/04)
    - Vehicle only HFA MDI - HFA-134a propellant containing ethanol and oleic acid
- Placebo MDI -to match racemic albuterol (Lot#CM020023, 3M, exp. date 4/07)
- Placebo MDI –to match racemic albuterol (Lot #CM020024, 3M, exp. date 4/07)
- Racemic albuterol CFC 17g (Lot# 2741, —, exp. date 4/03).

Reviewer's Comment: — is not the proposed commercial manufacturer of the drug product. The proposed commercial manufacturer is 3M.

Rescue medication was supplied as racemic albuterol CFC MDI (90 mcg per actuation) during the run-in period and for subjects randomized to placebo or racemic albuterol treatment. Subjects randomized to levalbuterol HFA were supplied levalbuterol HFA (45 mcg per actuation) as rescue medication.

10.1.1.3.7 Concomitant Therapy

The protocol included the following restrictions regarding medications during the course of the study [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1131-1134]:

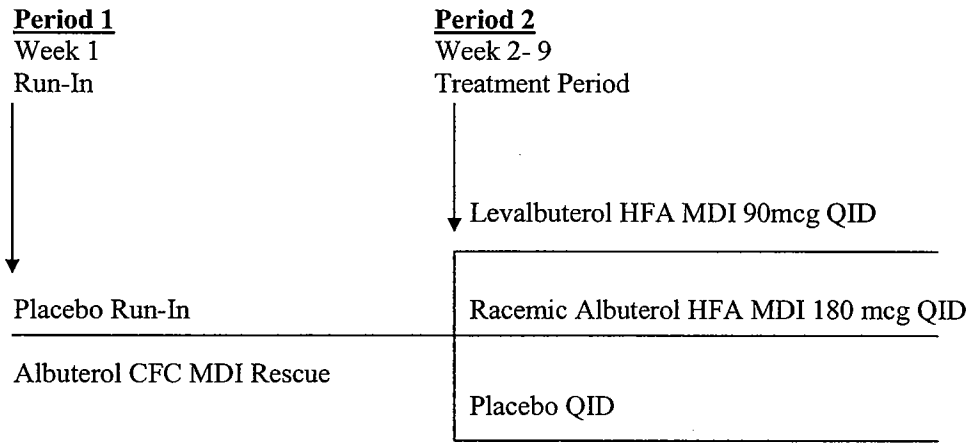
- Adrenergic Bronchodilators were not allowed during the study. Subjects had to discontinue all adrenergic bronchodilators with the following washout periods:
  - Inhaled, short acting $\geq$ 7 hours
  - Nebulized, short acting $\geq$ 10 hours
  - Inhaled, long acting $\geq$ 24 hours
  - Oral QID or TID preparations $\geq$ 24 hours
  - Oral BID preparations $\geq$ 36 hours
- Corticosteroids (parenteral) were not allowed during the study and must have been discontinued at least 30 days prior to screening.
  - One 5 day course of oral corticosteroids or treatment was allowed during the study. Continuation in the study was at the discretion of the investigator. If a subject required more than 5 days or required a second course of oral steroids, the subject was discontinued from the study.
- Corticosteroids (inhaled) were allowed if subjects were maintained on low to moderate doses ($\leq$ 660 mcg fluticasone/day or $\leq$ 800mcg beclomethasone/day) for at least 4 weeks prior to screening.
- Non-prescription asthma medications were not allowed during the study.
- Ipratropium bromide was not allowed during the study and must have been discontinued at least 48 hours prior to screening.
- Theophylline was allowed if the subject had been on a stable dose for 30 days prior to screening.
- Nedocromil sodium and cromolyn sodium were allowed if subjects were on a stable dose at least 10 days prior to screening.
- Leukotriene inhibitors were allowed provided the subject had been on a stable dose for 4 weeks prior to screening
- Immunotherapy was allowed for subjects who had been on maintenance therapy for at least 60 days prior to screening.
- Antibiotics were allowed for treatment of acute respiratory infections.
- Mucolytics, expectorants, decongestants, and antihistamines were allowed at the discretion of the investigator.
- Other medications used to treat chronic conditions were allowed if the subject had been on a stable dose prior to screening. Any changes in dosage were recorded in the CRF.

10.1.1.3.8 Conduct

Investigators agreed to conduct the study in accordance with the principles of Good Clinical Practice (GCP). Informed consent was obtained prior to any screening or treatment study procedures being performed [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1138]. Following an initial screening visit, for the run-in period subjects were provided 2 MDI placebos (placebo HFA MDI and placebo CFC MDI) and single-blind racemic albuterol CFC MDI (90mcg per actuation) to be used as needed. Peak flows and daily diaries were collected during the run-in period. PEF were to be measured immediately upon rising and before the first daily dose of study drug. A PEF Stability Limit (PEFSL) for each subject was calculated for each subject at Visit 2. PEFSL was defined as 80% of the mean morning PEF value during the run-in period [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1120].

Following the run-in period, subjects were randomized to 8 weeks of active treatment in a 2:1:1 fashion into the treatment groups as shown in Figure 13. Figure 13 is a schematic diagram of Study 051-353.

Figure 13 Study Design for Study 051-353



Depending on the randomized treatment group, each subject received one of the following three treatments [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1135]:

- Levalbuterol HFA treatment group
  -2 actuations (45 mcg per actuation) levalbuterol tartrate HFA MDI QID
  -2 actuations placebo matching racemic albuterol HFA MDI QID
  -Rescue therapy with levalbuterol tartrate HFA MDI (45mcg per actuation)
- Racemic albuterol HFA treatment group (active comparator)
  -2 actuations (90mcg per actuation) racemic albuterol HFA MDI QID
  -2 actuations placebo matching levalbuterol HFA MDI QID
  -Rescue therapy with racemic albuterol CFC MDI (90mcg per actuation)
- Placebo treatment group
  -2 actuations from placebo matching levalbuterol HFA MDI QID

-2 actuations from placebo matching racemic albuterol HFA MDI QID
-Rescue therapy with racemic albuterol CFC MDI (90mcg per actuation)

At each visit, subjects were supplied with three MDIs. Two of the MDIs were dispensed as study medication (one active and one dummy; one with a blue actuator and one with a yellow actuator). The third MDI was marked for rescue use only. All the rescue devices were enclosed in a blue polypropylene masking device [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1135-1136].

After the start of the double-blind treatment period at Visit 2, subjects returned approximately every two weeks for additional visits and study assessments as shown in Table 48. Office visits were scheduled between the hours of 6am and 9am.

Table 48 Study 051-353 Study Assessments

	Period 1 Run-In		Period 2 – Active Treatment				Optional F/U	Telephone
Clinic Visit	1 Screening	2	3	4	5	6	F/U	Telephone
Week	-1	0	2	4	6	8	8.5	9
Days	-7	0	14	28	42	56	59	63
Informed Consent	X							
Inclusion/Exclusion	X	X						
Medical History & CXR[1]	X							
Physical Exam	X					X	X	
Dispense Study/Rescue Meds	X	X	X	X	X			
Return Study/Rescue Meds		X	X	X	X	X		
ECGs	X (pre-dose)	X[2]	X[2]	X[2]	X[2]	X[2]	X	
Adverse Events	X	X	X	X	X	X	X	X
Vital Signs	X	X[3]	X	X[3]	X	X[3]	X	
Spirometry (pre-dose)	X		X		X		X	
Serial Spirometry		X[4]		X[5]		X[4]		
Peak Expiratory Flow	X	X	X	X	X	X		
Laboratories	X		X			X	X	
Serum K+, Glucose	X	X	X			X		
Pharmacokinetics (R) and (S)-albuterol		X[6]	X[7]			X[8]		
Serum Pregnancy	X					X		
Urine Pregnancy		X		X				
Theophylline levels (if applicable)	X					X		
Health Status/ QOL		X[9]				X[9]		
Global Assessment						X[9]		
Review of Diary Card/Completion		X	X	X	X	X		
Assess Compliance		X	X	X	X	X		
Concomitant Meds	X	X	X	X	X	X	X	X

1 CXR within last 12 months
2 ECG: pre-dose and 30 minutes post-dose
3 Vital signs: pre-dose, post dose at 20 minute intervals for the first hour, at 2 hours, and at discharge
4 Serial spirometry: pre-dose, immediately post-dose, at 15-minute intervals for the first 2 hours, then hourly until 8 hours post-dose
5 Serial spirometry: pre-dose, immediately post-dose, at 15-minute intervals for the first 2 hours, then hourly until 4 hours post-dose
6 PK samples: pre-dose, 1-2 hours and 4-6 hours post-dose
7 Single PK sample
8 PK samples: pre-dose, 0.25, 0.5, 1,2,4, and 8 hours post-dose
9 Health Status/QOL/Global Assessment: Performed fist at Visits 2 and 6. Subject global evaluations completed at beginning of Visit 6 and physician global evaluation completed at end of Visit 6

Source: N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1117

Throughout the treatment period, subjects completed diary cards (including medication compliance and symptoms) and recorded rescue medication use. PEF were collected using the MiniWright™ PEF meter. PEF were measured in the morning upon rising before the first dose of study drug, in the evening before the last dose of study drug, and at 15 minutes post evening dose. Subjects performed 3 maneuvers on each occasion and recorded the highest effort. [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1121& 1126].

Reviewer's Comment: The original protocol specified collection of AM PEF pre and post dose; however, the final version of the diary cards did not collect AM post dose PEF.

Pulmonary function testing was performed at baseline and every two weeks during the treatment period. Serial spirometry was performed only at Week 0 (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 6). Serial spirometry measurements included: pre-dose, immediately post-dose, 15-minute intervals for 2 hours post-dose, then hourly until 4 (Visit 4) or 8 hours post dose (Visit 2 & 6). Spirometry measurements were collected and standardized according to ATS guidelines. Subjects were to have: 1) abstained from Xanthine or caffeine-containing food or beverages 5 hours prior to testing; 2) withheld study rescue medication at least 7 hours prior to testing; 3) withheld inhaled corticosteroids for at least 10 hours prior to testing; and 4) withheld leukotriene inhibitors for at least 12 hours prior to testing [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1121 & 1123].

Asthma symptoms were monitored by the subject completing a diary and medical event calendar, which were reviewed at each clinic visit. In addition, an Asthma Quality of Life Questionnaire and SF-36 Health Survey were completed at Visit 2 and Visit 6.

Pharmacokinetic parameters were assessed at Visits 2, 3, and 6. Serial blood samples were obtained according to Table 48. At Visit 2 (Week 0), samples were obtained pre-dose, 1-2 hours post-dose, and 4-6 hours post-dose. At Visit 3 (Week 2), a single blood sample was obtained pre-dose. Finally at Visit 6 (Week 8), samples were obtained pre-dose, 0.25, 0.5, 1, 2, 4, and 8 hours post-dose [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1117].

Safety parameters included: AEs, vital signs, ECGs, clinical laboratories, physical examinations, asthma attacks, and rescue medication usage, which were assessed throughout the study according to Table 48.

The final symptom and safety evaluation was performed on Visit 6. An optional follow-up clinic visit was scheduled as necessary for any clinically significant laboratory finding or new AE at Visit 6. All subjects who entered the treatment period were contacted by telephone approximately a week after Visit 6 to inquire about AEs and concomitant medications [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1152].

10.1.1.3.9 Data Analysis

Per the protocol, the primary efficacy endpoint was the FEV1 (peak percent change from predose averaged over the double-blind period). An analysis of covariance was specified to assess the treatment difference. Many secondary endpoints were specified and are discussed in detail in the efficacy results section. Comparisons were to be made among treatment groups but the primary comparison was between levalbuterol HFA and placebo [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1116].

10.1.1.3.10 Amendments

One amendment was made to the original protocol on April 5, 2002. The amendment provided the following pertinent revisions [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 75-76]:

- Medication description revised to describe the "double-dummy" approach
- Ipratropium removed from list of allowed concomitant medication

- Maximum allowed fluticasone increased from 440 mcg to 660 mcg
- All protocol references to changes in FEV_1, FVC, and $FEF_{25-75\%}$ efficacy parameter calculations following treatment were revised to state that these would be calculated from visit predose. In addition all FEV_1 change and percent change parameters were calculated with study baseline (predose at Visit 2).
- For Visit 3 and Visit 5, the 12-lead ECG was performed at 30 minutes post-dose.

Changes to the analyses plan prior to unblinding of the data were described in an administrative letter dated May 22, 2002. The following is a list of pertinent changes [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 76-77]:

- Clarification of the morning peak flow analysis. The final version of the subject diary cards did not collect AM PEF pre-dose and post-dose. Therefore calculations utilizing AM post-dose PEF or morning percent change in PEF were not performed. All inferential analyses for all peak flow parameters were removed.

Reviewer's Comment: The Applicant did report the AM PEF and PEF data; however, only performed analyses on the in-clinic PEF. The at-home AM PEF was used to calculate the PEF stability limit during the run-in period, which was incorporated into the asthma action plan for the treatment period.

- Removal of selected secondary efficacy and safety endpoints.

The following is a list of the pertinent changes to the analyses plan after data availability [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 77-81]:

- A summary of subjects with paradoxical bronchoconstriction at each visit was added
  - FEV1 decrease $\geq$ 15% within one hour of clinic dosing
- Non-compartment PK parameters of (R)-albuterol, including C_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}4)}$, t_{max}, $R_{AUC(S/R)}$, and $R_{Cmax(S/R)}$ were added at Visit 6
- Subgroup analyses for Steroid Users and Non-Steroid Users
- Asthma AEs over time were summarized by subgroups
- Summaries using Kaplan Meier estimates of the survival curve for the time to first use of rescue medication during spirometry were added.

10.1.1.4 Results

10.1.1.4.1 Subject Disposition

The disposition of the subjects enrolled in Study 051-353 is summarized in Table 49. Of the 500 subjects who enrolled at Visit 1, 445 subjects successfully completed the run-in period and were randomized at Visit 2. The majority of the subjects who were discontinued from the run-in period failed to meet entry criteria for randomization. Ten subjects were discontinued from the run-in period due to adverse events [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 83].
Reviewer's Comment: The protocol did not clearly specify what the criteria were to be eligible for randomization into the treatment period. From the subject disposition results, subjects were not eligible for randomization for the following reasons: 1) failure to meet FEV_1 criteria; 2)

abnormal ECG, CXR, or laboratory values; 3) experience of an AE during run-in period; and 4) noncompliance with diary cards and medical events calendar.

Of the 445 subjects randomized to one of the three double-blind treatment groups, 389 (87.4%) completed the study, while 56 (12.6%) terminated early. The percentage of subjects who discontinued study treatment was slightly higher in the levalbuterol treatment group. A higher percentage of subjects discontinued from the levalbuterol treatment group due to an AE than in the racemic albuterol or placebo group (6.8% vs. 3.4% and 4.7%, respectively). The most common reason for discontinuation due to an AE was asthma exacerbation, which occurred in 12 (5.5%), 3 (2.5%), and 2 (1.9%) of the subjects in the levalbuterol, racemic albuterol, and placebo group, respectively [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 82-83]. The AEs for each of the treatment group will be addressed further in the safety results section.
Reviewer's Comment: A higher percentage of subjects discontinued study treatment in the levalbuterol group. The most common reason for discontinuation due to an AE was asthma.

Table 49 Subject Disposition for Study 051-353

	Run In Period	Levalbuterol HFA 90mcg	Racemic Albuterol HFA 180mcg	Placebo HFA-134a
Enrolled (N=500)				
Discontinued	55			
Did not meet criteria for randomization	34 (61.8%)			
AE	10 (18.2%)			
Voluntary withdrawal	5 (9.1%)			
Lost to follow-up	5 (9.1%)			
Noncompliant	1 (1.8%)			
Randomized (N=445)*		219	119	107
Completed (N=389)		188 (85.8%)	106 (89.1%)	95 (88.8%)
Discontinued (N=56)		31 (14.2%)	13 (10.9%)	12 (11.2%)
AE (N=24)		15 (6.8%)	4 (3.4%)	5 (4.7%)
Protocol Violation (N=4)		2 (0.9%)	1 (0.8%)	1 (0.9%)
Voluntary withdrawal (N=19)		9 (4.1%)	7 (5.9%)	3 (2.8%)
Lost to follow-up (N=4)		2 (0.9%)	1 (0.8%)	1 (0.9%)
Other (N=5)		3 (1.4%)	0 (0%)	2 (1.8%)

* Randomized in 2 :1 :1 ratio
Source: N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 82-83.

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The Applicant summarized the protocol violations for each treatment group in Study 051-353. Approximately 75% of the subjects in each treatment group had a least one protocol violation. The most common protocol violation was the use of a disallowed medication, which occurred in approximately 75% of the subjects in each treatment group. The most common disallowed medications were short-acting beta agonists, antihistamines, and corticosteroids. The Applicant reported that of the subjects who had a protocol violation due to use of short-acting beta agonists, most resulted from either the restart of the rescue medication at Visit 6 or insufficient wash-out prior to Visit 1. The Applicant reports that most of these subjects did not report using these agents during the study period [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 84-85].

The use of antihistamines during the study period was attributed mostly to subjects who used antihistamines both prior to and during the study on a regular basis. The use of corticosteroids during the study was attributed mostly to the dose not being stable for 4 weeks prior to study entry. The Applicant states this was in part due to a change from a corticosteroid/beta agonist combination to a corticosteroid only prior to Visit 1 [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 85].

Since a large percentage of subjects used disallowed medications, Table 50 summarizes some of the protocol deviations due to pertinent disallowed medications.

Table 50 Summary of Disallowed Medications in Study 051-353

	Levalbuterol HFA 90mcg n=219	Racemic Albuterol HFA 180mcg n=110	Placebo HFA-134a n=107
Use of disallowed medication	167 (76.3%)	90 (75.6%)	79 (73.8%)
Corticosteroid (oral, nasal, intravenous)	132(60.3%)	70 (58.8%)	70 (65.4%)
Prednisone	17 (7.8%)	3 (2.5%)	5 (4.7%)
Fluticasone	104 (47.5%)	50 (42.0%)	51 (47.7%)
Salbutamol	79 (36.1%)	45 (37.8%)	44 (41.1%)
Salmeterol	11 (5.0 %)	3 (2.5%)	5 (4.7%)

Source: N21730\N_000\2004-05-11\clinstat\051-353.pdf, Table 14.3.1.10

Reviewer's Comment: A large proportion of study subjects were documented to have used a disallowed medication. Use of a short-acting beta agonist was a common protocol violation and this could potentially influence the results of the study. The Applicant provided the number of subjects with protocol deviations for beta agonists, but did not provide a further breakdown. The Applicant did state, however, that the majority of protocol deviations for short acting beta agonists were for the restart of beta agonists at Visit 6 or insufficient washout period prior to Visit 1. In addition, the Applicant stated that most subjects did not report using short acting beta agonists during the study period.

In a Response to Information Request dated January 17, 2005, the Applicant provided additional information regarding the protocol violation due to beta agonist use. As shown below in Table 51, the primary reason for protocol violation due to beta agonist use was due to restart of beta agonist at Visit 6. The Applicant stated that it was unlikely beta agonists were used at Visit 6 because PFTs and end of study procedures were to be performed after at least a 7 hour washout period. At Visit 6, subjects were instructed to resume beta agonists as part of the asthma management, which accounted for the large number of subjects in this category, according to the Applicant.

Table 51 Protocol Violations for Beta Agonist Use in Study 051-353

	Levalbuterol HFA 90mcg n=219	Racemic Albuterol HFA 180mcg n=110	Placebo HFA-134a n=107
Use of disallowed medication	167 (76.3%)	90 (75.6%)	79 (73.8%)
Insufficient beta agonist washout at Visit 1	6 (2.7)	9 (7.6)	4 (3.7)
Possible beta agonist use during study period	14 (6.4)	6 (5.0)	4 (3.7)
Restart beta agonist at Visit 6	91 (41.6)	50 (42.0)	48 (44.9)

Source: N21730\N_000\2005-01-17\clinstat\clinsum.pdf

Reviewer's Comment: It remains unclear to this reviewer why the Applicant would consider resumption of beta agonist treatment at the end of the study a protocol violation. That being said, the resumption of beta agonist therapy at Visit 6 was similar across treatment groups and thus, should not affect the results of the study.

Protocol violations also included: failure to meet all entry criteria, noncompliance, and failure to withhold study medication for ≥ 7 hours prior to PFTs [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 84]. However, the number of subjects with other protocol violations was small in comparison to the disallowed medication and unlikely to influence the conclusion of the study. *Reviewer's Comment: Two subjects received the wrong study medication, one in the levalbuterol group and one in the racemic albuterol group. Two subjects should not influence the results of the study.*

10.1.1.4.2 Demographics and Baseline Characteristics

Table 52 below summarizes the demographics and baseline characteristics of the subjects who were randomized into one of the treatment groups for Study 051-353.

Table 52 Demographics and Baseline Characteristics in Study 051-353

	Levalbuterol HFA 90mcg n = 219	Racemic Albuterol HFA 180mcg n = 119	Placebo HFA-134a n = 107
Gender			
Male	102 (46.6%)	53 (44.5%)	42 (39.3%)
Female	117 (53.4%)	66 (55.5%)	65 (60.7%)
Age			
Mean	35.2	34.4	36.2
Range	12-80	12-76	12-76
Race			
Caucasian	151 (68.9%)	87 (73.1%)	75 (70.1%)
Black	42 (19.2%)	22 (18.5%)	15 (14.0%)
Hispanic	17 (7.8%)	7 (5.9%)	10 (9.3%)
Asian	5 (2.3%)	1 (0.8%)	4 (3.7%)
Other	4 (1.8%)	2 (1.7%)	3 (2.8%)
FEV_1 Screening (L)			
Mean	2.18	2.23	2.15
Range	1.09-3.66	1.02-3.74	1.14-3.59
FEV_1 Percent Predicted			
Mean	63.9	65.1	65.2
Range	43-85	47-75	41-75

Source [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 87.

Demographic and baseline characteristics for the randomized population (ITT population) were similar among the treatment groups. The mean age of subjects ranged from 34.4 years to 36.2 years. More than half of the subjects in each treatment group were females, and approximately 70% of subjects in each treatment group were Caucasian. The FEV_1 percent of predicted at baseline was similar among the treatment groups with the mean ranging from 63.9% to 65.2%. The screening FEV1 was slightly higher in the racemic albuterol treatment group as compared with either the levalbuterol or placebo treatment groups (2.23 L vs. 2.18 L and 2.15 L, respectively); however, the difference is not likely to influence the conclusion of the study [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 87].

10.1.1.4.3 Efficacy

10.1.1.4.3.1 Primary

The primary efficacy parameter was the peak percent change FEV_1 from visit predose averaged over the double-blind period. Pulmonary function testing was performed at baseline and every two weeks during the treatment period. Serial spirometry was performed only at Week 0 (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 6). Serial spirometry measurements included: pre-dose, immediately post-dose, 15-minute intervals for 2 hours post-dose, then hourly until 4 or 8 hours post dose. At clinic visits when serial spirometry was not conducted, predose spirometry was measured. Spirometry measurements were collected and standardized according to ATS guidelines.

All efficacy and safety analyses were performed using the ITT population, which was the population of randomized subjects who received at least one dose of study medication. The Applicant performed the analysis using an ANCOVA model with effects for treatment, investigator, and baseline FEV_1 (study baseline or visit predose). Table 53 is a summary of the peak percent change in FEV_1 averaged over the double-blind period (primary endpoint) and the peak percent change in FEV_1 at Visit 2, Visit 4, and Visit 6 (secondary endpoints) for each treatment group in Study 051-353 [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 89].

Table 53 Peak Percent Change FEV_1 from Visit Pre-dose for Study 051-353
ITT Population

Peak Percent Change in FEV_1 from Visit Pre-dose	Levalbuterol HFA 90mcg n=219	Racemic Albuterol HFA 180mcg n=119	Placebo HFA-134a n=107
Averaged over Double-Blind Period[1] (Primary EP)			
LS Mean (SE)	25.63 (0.87)	28.98 (1.15)	13.94 (1.21)
Pairwise p-value vs. Placebo[2]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[2]	0.018		
Visit 2[3]			
LS Mean (SE)	30.94 (1.19)	34.75 (1.59)	19.67 (1.67)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[4]	0.052		
Visit 4[3]			
LS Mean (SE)	22.59 (1.05)	25.11 (1.38)	10.69 (1.46)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[4]	0.144		
Visit 6[3]			
LS Mean (SE)	22.25 (1.19)	25.66 (1.54)	10.70 (1.61)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[4]	0.077		

1 Peak percent change in FEV1 from visit predose averaged over the double-blind period was calculated by first taking the difference in peak FEV1 recorded during the serial spirometry day (Visits 2, 4, and 6) and the visit predose FEV1. This result was then divided by visit predose FEV1 and multiplied by 100. The three peak percent change values were then averaged.
2 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.
3 Peak percent change in FEV1 from visit predose refers to the maximum FEV1 recorded during the visit minus the FEV1 observed at visit predose, divided by the visit predose FEV1 and multiplied by 100.
4 Pairwise tests of treatment effect were conducted using ANCOVA with treatment, investigator effects and visit predose FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.
Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 90, 121]

Levalbuterol HFA and racemic albuterol HFA were both statistically superior to placebo based upon the primary endpoint. The mean peak percent increase in FEV_1 in the levalbuterol HFA treatment group was 25.6%; however, racemic albuterol HFA produced a larger increase in peak percent change FEV_1 than levalbuterol HFA. This difference was statistically significant ($p<0.05$). Levalbuterol HFA and racemic albuterol HFA were both statistically superior to placebo for the peak percent change in FEV_1 at Visits 2, 4, and 6. At each of these visits, the effect size was numerically greater in the racemic albuterol HFA group.

The peak percent change in FEV1 was greatest for all three treatment groups at Visit 2 and declined with each subsequent visit. However, levalbuterol HFA and racemic albuterol HFA

both demonstrated a statistically significant increase in peak percent change in FEV1 over placebo throughout the study. The reason for the decrease in response as the study progressed appears to be partly explained by an increase in test day pre-dose FEV1, based upon the following rationale. A review of the peak percent change in FEV1 from study baseline at Visit 2, 4, and 6 showed that the levalbuterol and racemic albuterol groups were superior to placebo throughout the study. Although the peak percent change in FEV1 from study baseline decreased from Visit 2 to Visit 6 in the levalbuterol and racemic albuterol groups, the decrease was approximately 3-4% as opposed to the 8-9% decrease noted from Visit 2 to Visit 6 when using the predose visit FEV1. Thus, when comparing the peak percent change FEV1 from visit predose and study baseline, the smaller decrease in peak percent change FEV1 from study baseline noted as the study progressed suggests that the visit predose FEV1 increased as the study progressed.
Reviewer's Comment: Levalbuterol HFA was superior to placebo for the pre-specified primary endpoint, but racemic albuterol HFA was numerically superior to levalbuterol HFA.

The Applicant also analyzed the primary endpoint for steroid users and non-steroid users, which was a post-hoc analysis. Both levalbuterol and racemic albuterol produced a significantly greater LS mean peak percent change in FEV1 from visit predose as compared with placebo averaged over the double-blind treatment period in both steroid users and non-steroid users.

10.1.1.4.3.2 Secondary

Secondary efficacy parameters included the following [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 1121-1122]:

- AUC for FEV1 at each week and double-blind average
- Peak change in FEV_1 from visit predose FEV1 at each week
- Peak percent of predicted FEV_1 at each week and double-blind average
- Peak change and peak percent change in FVC and $FEF_{25-75\%}$ from visit predose at each week and double-blind average
- Time to peak change at each week
- Peak percent change FEV1 from visit predose at each week
- Number and percent of responders
- Time to onset of response and duration of response
- Asthma signs and symptoms based upon diary cards
- Use of rescue medication based upon diary cards
- Asthma Attack (defined by protocol) and recorded as AE
- Peak expiratory flow
- Quality of Life as measured by the Asthma Quality of Life Questionnaire and SF-36 Health Survey
- Global Evaluation as measured by the subject and physician at Visit 6

In addition, all percent change and change in FEV1 from visit predose were repeated using Study Baseline (predose Visit 2) also.

10.1.1.4.3.2.1 Spirometry

Table 54 summarizes additional spirometry secondary efficacy endpoints for Study 051-353.

Table 54 Additional Spirometry Endpoints for Study 051-353
ITT Population

	Levalbuterol HFA 90mcg n=219	Racemic Albuterol HFA 180mcg n=119	Placebo HFA-134a n=107
AUC_{0-8} for FEV_1 Percent Change from Visit Predose[1] (DBAvg)			
LS Mean (SE) %-hr	109.57 (6.20)	130.17 (8.25)	59.86 (8.68)
Pairwise p-value vs. Placebo[2]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[2]	0.043		
AUC_{0-8} for FEV_1 Percent Change from Visit Predose[1] (Visit 2)			
LS Mean (SE) %-hr	144.02 (8.54)	163.39 (11.36)	89.84 (11.96
Pairwise p-value vs. Placebo[2]	< 0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[2]	0.166		
AUC_{0-8} for FEV_1 Percent Change from Visit Predose[1] (Visit 6)			
LS Mean (SE) %-hr	74.14 (7.12)	90.42 (9.24)	24.54 (9.67)
Pairwise p-value vs. Placebo[2]	< 0.001	< 0.001	
Pairwise p-value vs. Racemic Albuterol[2]	0.158		
Peak % Change FVC from Visit Predose (DBAvg)[3]			
LS Mean (SE)	18.45 (0.75)	19.73 (0.99)	12.40 (1.05)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[4]	0.295		
Peak % Change FEF 25-75% from Visit Predose (DBAvg)[5]			
LS Mean (SE)	54.98 (1.92)	62.38 (2.56)	29.94 (2.69)
Pairwise p-value vs. Placebo[6]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[6]	0.019		
Peak % Predicted FEV_1 (DBAvg)[7]			
LS Mean (SE)	82.34 (0.69)	85.03 (0.91)	76.66 (0.96)
Pairwise p-value vs. Placebo	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol	0.017		
Peak % Predicted FEV_1 (Visit 2)[7]			
LS Mean (SE)	83.89 (0.70)	86.35 (0.93)	77.40 (0.98)
Pairwise p-value vs. Placebo	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol	0.028		
Peak % Predicted FEV1 (Visit 6)[7]			
LS Mean (SE)	82.19 (0.91)	83.80 (1.18)	75.84 (1.24)
Pairwise p-value vs. Placebo	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol	0.275		

1 Area under the FEV1 percent change curve averaged over the double-blind period was calculated by first applying the linear trapezoidal method to the FEV1 percent change from baseline (visit predose or study baseline) obtained during Visits 2 and 6. These two AUC values were then averaged.

2 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.

3 Peak percent change in FVC from visit pre-dose averaged over the double-blind period was calculated by first taking the difference between the peak FVC recorded during the serial spirometry day (Visits 2, 4, and 6) and the visit pre-dose FVC. This result was then divided by visit pre-dose FVC and multiplied by 100. The three peak percent change from visit pre-dose values were then averaged.

4 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FVC as the covariate. The tests were performed using a one degree of freedom contrast.

5 Peak percent change in FEF 25-75% from visit pre-dose averaged over the double-blind period was calculated by first taking the difference between the peak FEF 25-75% recorded during the serial spirometry day (Visits, 2, 4 and 6) and the visit pre-dose FEF 25-75%. This result was then divided by visit pre-dose FEF25-75% and multiplied by 100. The three peak percent changes from visit pre-dose values were then averaged.

6 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEF 25-75% as the covariate. The tests were performed using a one degree of freedom contrast.

7 Peak percent of predicted FEV1 was calculated by dividing the peak FEV1 recorded during a serial spirometry day (Visits 2, 4, and 6) by the predicted FEV1 determined at Screening (Visit 1), and then multiplying by 100. For the double-blind average, the three resulting peak percent of predicted values were averaged.
Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 91, 99, 418, 464]

As shown in Table 54, the peak percent change in FVC and FEF 25-75% and FEV_1 percent change AUC, averaged over the double-blind period were significantly greater for levalbuterol HFA and racemic albuterol HFA compared to the placebo HFA. The AUC FEV1 percent change for levalbuterol HFA was significantly less than racemic albuterol HFA. As noted with the peak FEV1 percent change, the FEV1 percent change AUC declined from Visit 2 to Visit 6 for both levalbuterol HFA and racemic albuterol HFA. The peak percent of predicted FEV1 was significantly greater for levalbuterol HFA and racemic albuterol HFA compared to placebo. At Visit 2 and averaged over the double blind period, the racemic albuterol HFA group achieved a statistically higher peak percent predicted FEV1 compared to the levalbuterol HFA group. However, by Visit 6, there was no statistical significance between the levalbuterol HFA and racemic albuterol HFA treatment groups.

The Applicant determined the number of responders, which were defined as subjects experiencing ≥ 15% improvement in FEV1 from visit predose. As shown in Table 55, the number of responders was greater in the levalbuterol HFA and racemic albuterol HFA treatment groups when compared to the placebo group at each visit. The racemic albuterol HFA group had a larger percentage of responders than the levalbuterol HFA group at each visit. The percent of responders decreased as the study progressed, which the Applicant attributed to the increase in predose FEV1 over time [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 353].

Table 55 Responders in Study 051-353 (ITT Population)

n (%)	Levalbuterol HFA 90mcg n=219	Racemic Albuterol HFA 180mcg n=119	Placebo HFA-134a n=107
Visit 2	186 (84.9)	103 (86.6)	58 (54.2)
Visit 4	126 (62.7)	76 (68.5)	20 (20)
Visit 6	112 (59.9)	69 (65.7)	23 (24.2)

Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 353]

Time to peak change in FEV_1 from visit predose was analyzed for Visits 2, 4, and 6 and was similar between levalbuterol HFA and racemic albuterol HFA. The mean time to peak change for levalbuterol HFA was 95, 89, and 95 minutes for Visit 2, 4, and 6, respectively while the mean time to peak change for racemic albuterol HFA was 102, 80, and 90 minutes for Visit 2, 4, and 6, respectively [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 290]. The median times to 15% increase FEV1 were 6.3 and 4.0 minutes, respectively for levalbuterol HFA and racemic albuterol HFA at Visit 2 and 50.7 and 29.8, respectively at Visit 6. The Applicant attributed the increase in median time at Visit 6 to an increase in predose FEV1, which resulted in fewer subjects achieving a 15% response [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 103, 373].
Reviewer's Comment: The median times or 15% response appear to represent interpolation, as FEV1 was measured at 15 minute intervals. There is a notable difference in median times at Visit 6 between levalbuterol HFA and racemic albuterol HFA. The increase in median time from Visit 2 to Visit 6 may be secondary to fewer responders at Visit 6.

The duration of response was defined as the amount of time during which there was a ≥ 15% increase in FEV1 relative to the visit predose value. The median duration of 15% response was 184 minutes with levalbuterol HFA , 260 minutes with racemic albuterol HFA, and 2 minutes with placebo at Visit 2 and 33, 64, and 0 minutes, respectively at Visit 6 [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 374-375].

Reviewer's Comment: In this study, levalbuterol HFA and racemic albuterol HFA had a similar time to onset at Visit 2, but racemic albuterol HFA had a much shorter time to onset at Visit 6. In addition, the duration of effect of racemic albuterol HFA was longer than levalbuterol HFA at both Visit 2 and Visit 6.

10.1.1.4.3.2.2 Peak Expiratory Flow (PEF)

PEF was measured with the MiniWright PEF meter at home. Because the finalized patient diaries did not include an AM pre-dose and post-dose PEF measurement, calculations using the AM PEF were not performed. The Applicant did report the average morning PEF using the home measurements. PEF was measured at each clinic visit pre-dose and 15 minutes post-dose. The highest of 3 maneuvers at each time period was recorded. The in clinic peak flow change was calculated at each clinic visit and is summarized in Table 56, which shows that levalbuterol and racemic albuterol improved peak flow more than placebo at each clinic visit throughout the study.

Table 56 In Clinic PEF (L/min) – Percent Change from Visit Pre-dose* for Study 051-353
ITT Population

	Levalbuterol HFA 90mcg n=219	Racemic Albuterol HFA 180mcg n=119	Placebo HFA-134a n=107
Visit 1 Mean (SD)	20.92 (15.34)	24.08 (23.84)	19.17 (12.35)
Visit 2 Mean (SD)	18.46 (14.83)	22.83 (20.73)	5.03 (8.57)
Visit 3 Mean (SD)	14.54 (14.31)	20.05 (24.03)	2.47 (8.19)
Visit 4 Mean (SD)	15.62 (14.63)	16.49 (14.81)	1.50 (6.73)
Visit 5 Mean (SD)	15.41 (14.55)	17.17 (16.42)	1.31 (6.97)
Visit 6 Mean (SD)	15.73 (19.05)	17.80 (18.96)	1.22 (6.16)

* Percent change in peak flow from visit pre-dose was calculated by subtracting the in-clinic pre-dose peak flow from the in-clinic 15 minute post-dose peak flow, multiplying by 100, and dividing by the in-clinic pre-dose peak flow.
Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 471-472]

Reviewer's Comment: Usually a comparison is made between AM and PM PEF measurements for each treatment group. It is unclear why the pre-specified PEF measurements were not included in the patient diaries. The am PEF and pm pre-dose and post-dose PEF measurements were submitted with the application, but no analysis was performed on these measurements. However, the Applicant provided clinic measurements of PEF pre and post medication dose and determined the percent change as shown above. The home PEF measurements were used for the asthma action plan. If subjects dropped below 80% of their run-in mean PEF, they were instructed to call the investigator.

Reviewer's Comment: It is unclear why the placebo group would have had such a large increase in PEF at Visit 1.

10.1.1.4.3.2.3 Asthma Symptoms

Asthma symptom scores were recorded by the subjects throughout the study. Subjects answered 8 questions in the following areas daily:

- Difficulty breathing
- Cough
- Wheeze
- Activity Limitation
- Level of Activity Limitation
- Overall Symptom Score
- Nighttime Asthma (1&2) – Number of awakenings and time to fall back to sleep

Subjects recorded the nighttime symptoms each morning and recorded the other six symptoms each evening. The symptoms were scored by the subject on a scale of 0 to 4, in which '0' means none of the time and '4' means all of the time. The Applicant compared the scores between the treatment groups and determined there were no appreciable differences between the treatment groups [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 106]. In this reviewer's opinion, there was no significant difference in the improvement in asthma symptom scores from Visit 2 to Visit 6 in any of the treatment groups.

Reviewer's Comment: Asthma symptoms were not measured by a validated patient reported outcomes instrument.

10.1.1.4.3.2.4 Asthma Quality of Life Questionnaire & SF-36

The adult or pediatric Asthma Quality of Life Questionnaire (AQLQ) and the SF-36 Health Survey were administered at Visit 2 (Week 0) and Visit 6 (Week 8). For the AQLQ, four areas (Activity Limitations, Symptoms, Emotional Function, Exposure to Environmental Stimuli) were assessed using a seven point scale to rate each item from a score of 7 (no impairment) to a score of 1 (severe impairment). The SF-36 is a quality of life instrument that is not disease specific. It consists of 36 items grouped into 8 domains (Physical Functioning, Role Physical, Bodily Pain, General Physical Health, Vitality, Social Function, Role Emotional, and General Mental Health). Two domains were assessed in this study – Physical Functioning and General Health. Raw scores were transformed to a 0-100 scale. Table 57 displays a summary of the results for the quality of life questionnaires in Study 051-353.

Table 57 AQLQ and SF-36 for Study 051-353 (ITT Population)			
	Levalbuterol HFA 90mcg	Racemic Albuterol HFA 180mcg	Placebo HFA-134a
AQLQ* Overall Score Age ≥ 18			
Visit 2 Mean (SD)	4.70 (1.04)	4.57 (1.03)	4.61 (1.09)
Visit 6 Mean (SD)	5.02 (0.99)	4.96 (1.00)	4.92 (1.16)
AQLQ* Overall Score Age < 18			
Visit 2 Mean (SD)	5.36 (1.08)	5.00 (0.98)	5.54 (0.90)
Visit 6 Mean (SD)	5.83 (0.97)	5.17 (0.91)	5.84 (0.76)
SF-36 Physical Functioning Score**			
Visit 2 Mean (SD)	69.63 (19.88)	72.93 (18.60)	72.42 (19.90)
Visit 6 Mean (SD)	74.35 (18.57)	75.94 (17.61)	74.95 (19.27)
SF-36 General Health Score**			
Visit 2 Mean (SD)	62.36 (18.56)	63.93 (18.28)	63.39 (19.32)
Visit 6 Mean (SD)	64.99 (18.14)	62.87 (19.43)	64.45 (18.74)

* Scores range from 1 to 7. Higher scores indicate a higher quality of life.
** Scores range from 0 to 100. Higher scores indicate a higher quality of life.
Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 493, 502, 506, 507]

The Applicant compared the change in the individual domains of the AQLQ for each treatment group in adults between Visit 2 and Visit 6. Although each treatment group experienced a modest increase in score, there was no statistical significance between the treatment groups. The Applicant did not perform a statistical comparison between the treatment groups in subjects < 18 years of age [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 106, 498-501].
Reviewer's Comment: This is acceptable because there were only 20-40 subjects per treatment group less than 18 years of age.

For the SF-36, the baseline (Visit 2) domain scores were similar among the treatment groups. At Visit 6, the domain scores increased for the levalbuterol treatment group. There were no significant differences among the treatment groups for the change in Physical Functioning Score and the change in General Health Score [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 508-509].

10.1.1.4.3.2.5 Global Evaluation

At Visit 6 (Week 8), the physician and subject completed a global assessment of asthma symptoms based upon the treatment period. Subjects answered questions based upon a numerical scale, while physicians answered questions and circled responses on more of a subjective scale (much better, moderately better, the same, slightly worse, etc.). Overall from the beginning of the study, more subjects rated their symptoms improved to some degree in the levalbuterol HFA and racemic albuterol HFA group than in the placebo group. A statistical comparison was not performed [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 510].
Reviewer's Comment: The global evaluations were not measured by a validated patient or physician reported outcomes instrument.

10.1.1.4.4 Pharmacokinetic Endpoint Outcomes

The pharmacokinetic (PK) data from this study will be reviewed in depth, along with the PK data from the remainder of the clinical program in a separate document by the OCPB Reviewer. The following is a brief discussion of the PK data from this study.

PK samples for (R)- and (S)-albuterol were collected at Visit 2 (pre-dose, 1-2 hours post-dose, and 4-6 hours post-dose), Visit 3 (pre-dose), and Visit 6 (pre-dose, 0.25, 0.5, 1, 2, 4, and 8 hours post-dose).

The plasma concentration of (R)-albuterol for both levalbuterol and racemic albuterol was highly variable. Some subjects in the levalbuterol treatment group had measurable levels of (S)-albuterol during the study. The highest detectable levels of (S)-albuterol in the levalbuterol group were on Visit 2, which was the first day of treatment. It is possible that some of the subjects may have still had some (S)-albuterol in their system from the rescue medication during the run-in period. After Visit 2, the mean concentration of (S)-albuterol in the levalbuterol group ranged from 0.07 ng/mL to 0.107 ng/mL, which is much lower than the (S)-albuterol concentration in the racemic albuterol HFA group [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 110].

Reviewer's Comment: The increase in (S)-albuterol compared to (R)-albuterol concentration noted with the racemic albuterol HFA may be that (R)-albuterol interferes with the metabolism of (S)-albuterol. Although levalbuterol HFA is only the (R)-albuterol, some subjects still had (S)-albuterol detected. Potential explanations for the presence of (S)-albuterol with levalbuterol HFA use include the use of racemic albuterol or inadequate washout, conversion of (R)-albuterol to (S)-albuterol in vitro, or conversion of (R)-albuterol to (S)-albuterol in vivo.

PK parameters were calculated from plasma concentrations obtained on Visit 6. Table 58 displays the summary statistics for the PK parameters for (R) –albuterol in the levalbuterol group and (R) and (S) –albuterol in the racemic albuterol dosing group.

Table 58 PK Parameters for (R)-albuterol and (S)-albuterol for Study 051-353
ITT Population

	Levalbuterol HFA 90mcg			Racemic Albuterol HFA 180mcg					
	(R) -albuterol			(R) -albuterol			(S) -albuterol		
	n	Mean (SD)	Median (min-max)	n	Mean (SD)	Median (min-max)	n	Mean (SD)	Median (min-max)
C_{max} (ng/mL)	182	0.31 (0.75)	0.20 (0.05-9.90*)	102	0.29 (0.23)	0.23 (0.04-1.48)	107	0.76 (0.44)	0.65 (0.12-2.58)
t_{max} (hr)	182	0.85 (1.07)	0.52 (0-8.0)	102	0.72 (0.80)	0.50 (0-4.0)	107	1.26 (0.93)	1.02 (0-4.1)
$AUC_{(0\text{-}last)}$ (ng·hr/mL)	182	1.12 (2.32)	0.737 (0.16-30.12)	102	0.99 (0.77)	0.82 (0.06-5.31)	107	3.68 (2.38)	3.32 (0.44-15.5)
$AUC_{(0\text{-}4)}$ (ng·hr/mL)	168	0.70 (0.91)	0.528 (0.15-10.32)	97	0.69 (0.46)	0.57 (0.12-2.72)	96	2.34 (1.27)	2.11 (0.29-5.96)

* The Applicant states the 9.90 value is aberrant.
Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 114]

Reviewer's Comment: The Applicant excluded many more time points from the PK analysis for the levalbuterol group (11) than the racemic albuterol group (1) due to abnormally high

concentrations of (R)-albuterol [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 113]. This is acceptable. When the Applicant performed the population PK analyses on the combined PK data, subjects were not excluded.

The mean C_{max} and mean $AUC_{(0-4)}$ of (R)-albuterol were similar between the levalbuterol HFA and racemic albuterol HFA treatment groups. The Applicant performed a relative exposure analysis at the presumed steady-state to compare levalbuterol HFA to racemic albuterol HFA. According to the analysis, the 90% confidence interval for the ratio of the geometric mean for the C_{max} and $AUC_{(0-4)}$ of levalbuterol HFA and racemic albuterol HFA is 95%, indicating a comparable relative exposure [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 119].

The mean t_{max} for the levalbuterol HFA group was 0.85 hr (approximately 50 minutes), compared to the mean tmax of 0.72 (approximately 42 minutes) hr for racemic albuterol HFA.

The Applicant performed a comparison of the (R) and (S)-albuterol PK parameters for the racemic albuterol treatment group. In the racemic albuterol group, the C_{max} and AUC for (S)-albuterol were much higher than the mean PK parameters for (R)-albuterol.

10.1.1.4.5 Safety

The safety findings from this study, along with the safety data from the other clinical studies, will be reviewed in depth in the Integrated Review of Safety section of this review. A summary of the safety findings from this study follows.

Table 59 is a summary of the extent of exposure for the levalbuterol HFA and racemic albuterol HFA treatment groups for Study 051-353 [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 128].

Table 59 Summary of Extent of Exposure for Study 051-353 (ITT Population)

Daily Dose Level for Double Blind Treatment Period (mcg)	Levalbuterol HFA 90mcg n=217	Racemic Albuterol HFA 180mcg n=119
Mean (SD)	356.50 (15.82)	708.84 (43.40)

Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 128]

Reviewer's Comment : Because the levalbuterol group was dosed 90mcg QID (360mcg daily) and the racemic albuterol groups was dosed 180mcg QID (720mcg daily), the above table demonstrates that the daily dose level for both the levalbuterol and racemic albuterol group was close to the dose described in the protocol.

10.1.1.4.5.1 Adverse Events

Adverse events were reported in approximately 50% of the subjects in each treatment group. There were 483 adverse events reported by 225 subjects in the ITT population. In general, a larger percentage of subjects reported AEs in the placebo and racemic albuterol groups than in the levalbuterol group. However, a higher percentage of subjects discontinued secondary to AEs in the levalbuterol group. In addition, there was a higher incidence of asthma adverse events in the levalbuterol group. There were 8 SAEs during the treatment period. The percent

of subjects with serious adverse events was similar among the treatment groups. There were no deaths. Table 60 displays a summary of adverse events reported in ≥ 2% of subjects in each of the treatment groups, as reported by the Applicant.

Table 60 Summary of Adverse Events (AEs) Reported in ≥ 2% Subjects in Study 051-353
ITT Population During the Double-Blind Period

	Levalbuterol HFA 90mcg (n=219)	Racemic Albuterol HFA 180mcg (n=119)	Placebo HFA-134a (n=107)
	n (%)	n (%)	n (%)
Any adverse event	104 (47.5)	61 (51.3)	60 (56.1)
Discontinued due to AE	15 (6.8)	4 (3.4)	5 (4.7)
Serious adverse event	3 (1.4)	2 (1.7)	1 (0.9)
Asthma adverse events	**23 (10.5)**	**8 (6.7)**	**6 (5.6)**
Headache	26 (11.9)	8 (6.7)	13 (12.1)
Asthma	**23 (10.5)**	**8 (6.7)**	**6 (5.6)**
Asthma Attack*	**22 (10.0)**	**6 (5.0)**	**5 (4.7)**
Viral infection	23 (10.5)	9 (7.6)	10 (9.3)
Pharyngitis	12 (5.5)	3 (2.5)	4 (3.7)
Rhinitis	10 (4.6)	4 (3.4)	4 (3.7)
Pain	9 (4.1)	4 (3.4)	5 (4.7)
Accidental Injury	8 (3.7)	7 (5.9)	6 (5.6)
Urinary tract infection	6 (2.7)	1 (0.8)	4 (3.7)
Dizziness	4 (1.8)	1 (0.8)	3 (2.8)
Sinusitis	4 (1.8)	3 (2.5)	6 (5.6)
Dyspepsia	3 (1.4)	1 (0.8)	5 (4.7)
Nausea	3 (1.4)	3 (2.5)	3 (2.8)
Abdominal Pain	2 (0.9)	1 (0.8)	4 (3.7)
Diarrhea	2 (0.9)	0	4 (3.7)
Back Pain	2 (0.9)	2 (1.7)	3 (2.8)
Rash	1 (0.5)	1 (0.8)	3 (2.8)
Fever	0	0	3 (2.8)

* An asthma attack was a subcategory of asthma AES that required one of the following four criteria: 1)hospitalization; 2) an ER visit; 3) intervention with an oral burst or parenteral corticosteroids; or 4) an unscheduled clinic visit to treat acute asthma symptoms.
Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 130]

Headaches, asthma, and viral infection were the most common AEs. AEs more common in the levalbuterol group included respiratory system complaints, such as asthma symptoms, asthma attacks, rhinitis, and pharyngitis. An asthma attack was a subcategory of asthma AEs that required one of the following: 1)hospitalization; 2) an ER visit; 3) intervention with an oral burst or parenteral corticosteroids; or 4) an unscheduled clinic visit to treat acute asthma symptoms. Asthma attacks were more common in the levalbuterol HFA treatment group. The Applicant noted that a respiratory infection may have been the trigger for some of the asthma attacks and explain the increased rate of asthma adverse events in the levalbuterol HFA group.
Reviewer's Comment: There is a similar incidence of viral infections in the levalbuterol and placebo groups, yet the proportion of asthma attacks is higher in the levalbuterol group.

The Applicant included a table of potential beta adrenergic mediated side effects, such as chest pain, tachycardia, dyspepsia, nausea, leg cramps, dizziness, hypertension, insomnia, and nervousness. Overall potential beta adrenergic mediated side effects were infrequent and no significant differences among the treatment groups were noted [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 134].

During the double blind treatment period, 6 subjects reported 8 SAEs. The following is a breakdown of the SAEs.

- Levalbuterol HFA group (3 subjects, 1.4%)
  - Ovarian cyst
  - Accidental injury (2)
  - Asthma & Hypertension (Discontinued due to SAE)
- Racemic albuterol HFA (2 subjects, 1.7%)
  - Breast carcinoma
  - Herniated cervical discs (Discontinued due to SAE)
- Placebo (1 subject, 0.9%)
  - Prostate disorder (Discontinued due to SAE)

In addition, 24 subjects had AEs that led to discontinuation of treatment: 15 (6.8%), 4 (2.4%), and 5 (4.7%) in the levalbuterol, racemic albuterol, and placebo groups, respectively. The most common AE leading to discontinuation was asthma exacerbation, which accounted for 11 subjects discontinuing in the levalbuterol treatment group [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 139].

10.1.1.4.5.2 Laboratory Evaluations

Serum potassium and glucose levels were measured predose and post-dose (1-2 hours) at Visit 2 and Visit 6. As shown in Table 61, no significant changes in potassium or glucose were noted among the treatment groups. The Applicant analyzed the change in potassium and glucose by shift tables. Approximately 8% of subjects in each group shifted from a normal to an elevated glucose by the end of the treatment. Approximately 3%, 0.8%, and 0% of subjects shifted from a normal potassium to a low potassium level during the treatment period in the levalbuterol, racemic albuterol, and placebo groups, respectively and 3.7%, 1.7%, and 0% shifted from normal potassium to a high potassium in the levalbuterol, racemic albuterol, and placebo groups, respectively [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 183].

Table 61 Summary of Potassium and Glucose Changes from Visit Predose in Study 051-353
ITT Population During the Double-Blind Period

	Levalbuterol (n=219)	Racemic Albuterol (n=119)	Placebo (n=107)
Potassium (mEq/L)			
Visit 2 (n)	213	116	103
Mean (SD)	0.03 (0.32)	0.03 (0.36)	0.05 (0.34)
Visit 6 (n)	176	97	83
Mean (SD)	0.03 (0.36)	-0.3 (0.39)	-0.5 (0.34)
Glucose (mg/dL)			
Visit 2 (n)	213	116	103
Mean (SD)	2.61 (18.15)	5.52 (19.97)	-0.34 (14.75)
Visit 6 (n)	180	102	84
Mean (SD)	1.00 (17.19)	3.88 (17.30)	-1.82 (18.46)

Source: [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 182]

10.1.1.4.5.3 Vital Signs and Physical Examinations

No significant change in heart rate, blood pressure or physical examination was noted among the treatment groups during the double blind period [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 186-190, 194].

10.1.1.4.5.4 Electrocardiograms

No consistent significant change in QT_{c-F} was noted among the treatment groups. The largest mean increase in the QT_{c-F} was in the racemic albuterol HFA group at Visit 6 with an increase of 1.6ms. Prolongation of the QT_{c-F} interval >450 ms occurred in 1.8%, 0%, and 0.9% of subjects in the levalbuterol HFA, racemic albuterol HFA, and placebo treatment groups, respectively. The percentage of subjects with a change in the QT_{c-F} of 30-60ms was comparable among treatment groups. No subjects experienced a change in the QT_{c-F} of >60ms from visit predose to post-dose and no subjects demonstrated a QT_{c-F} >500ms [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 190-194].

10.1.1.4.5.5 Rescue Medication, Paradoxical Bronchoconstriction

Subjects in the active treatment groups demonstrated a greater decrease in rescue medication use (when compared to the single-blind run-in period) compared to the placebo group. Initially, the racemic albuterol group demonstrated a greater decrease in rescue medication use than the levalbuterol group, but by the end of the study, the decrease in rescue medication was similar between the levalbuterol HFA (-0.54 days) and racemic albuterol HFA (-0.56 days) treatment groups. Both active treatment groups showed more of a decrease in rescue medication use than the placebo group (-0.04 days) [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 195-197].

Paradoxical bronchospasm was defined as a ≥ 15% decrease in FEV1 within one hour of clinic dosing. During the serial spirometry the percent of subjects with paradoxical bronchoconstriction was 4.1%, 2.5%, and 7.5% for the levalbuterol HFA, racemic albuterol HFA, and placebo treatment groups, respectively [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 198].
Reviewer's Comment: Paradoxical bronchospasm was a post hoc analysis.

10.1.1.5 Discussion and Conclusions

10.1.1.5.1 Efficacy

Study 051-353 demonstrated that 90 mcg levalbuterol HFA was superior to placebo on the pre-specified primary efficacy endpoint: the peak percent change in FEV1 from visit predose averaged over the double-blind period. The mean peak percent change in FEV1 from visit predose average over the double-blind period was 25.63% in the levalbuterol HFA group versus 13.94% in the placebo group. The difference is statistically significant. The American Thoracic Society defines a bronchodilator response as an increase in FEV1 of $\geq$ 12% and 200mL. The increase in peak percent change in FEV1 in the levalbuterol HFA group over the placebo group 11.69%, which is likely clinically significant.

Efficacy was supported by statistically significant improvements in the levalbuterol HFA group as compared to the placebo group in the following secondary endpoints:

- AUC for FEV1 percent change from visit predose averaged over the double-blind period
- Peak percent change in FVC and $FEF_{25-75\%}$ from visit predose.

In general none of the non-spirometric outcome variables demonstrated a statistically significant benefit in the levalbuterol HFA group. Significant treatment group differences were not observed for the adult AQLQ or the SF-36 Health Survey assessments. There were no appreciable differences between treatment groups in any asthma symptom score.

This study did not demonstrate that levalbuterol HFA was superior to racemic albuterol HFA on the pre-specified primary endpoint, secondary spirometry endpoints, or quality of life scores. In fact, for many of the endpoints, including the primary endpoint, peak % predicted FEV1 averaged over the double-blind period, peak % change $FEF_{25-75\%}$ averaged over the double-blind period, and AUC_{0-8} for FEV1 % change from visit predose, racemic albuterol HFA was statistically superior to levalbuterol HFA,

10.1.1.5.2 Safety

In Study 051-353, common AEs in the levalbuterol HFA treatment group were headache, asthma, and viral infection. There appears to be a safety signal of asthma in the levalbuterol HFA treatment group. Although the incidence of adverse events was slightly less in the levalbuterol HFA group, the incidence of asthma and asthma attacks (10.5%, 10.0%) in the levalbuterol HFA group was approximately twice the incidence in the racemic albuterol HFA (6.7%, 5.0%) and placebo groups (5.6%, 4.7%). A larger proportion of subjects in the levalbuterol HFA group discontinued treatment due to an adverse event. In addition, the most commonly reported adverse event in the levalbuterol HFA treatment group leading to discontinuation was asthma.

Levalbuterol HFA was not associated with significant changes in vital signs, laboratories, physical examination, or changes in ECG.

10.1.1.5.3 Pharmacokinetics

Some subjects in the levalbuterol treatment group had measurable levels of (S)-albuterol during the study. However, subjects in the racemic albuterol group were exposed to much higher concentrations of (S)-albuterol compared to (R)-albuterol. Based upon (R)-albuterol, the exposure of 90mcg levalbuterol (mean C_{max} 0.198 ng/mL, mean AUC_{0-4} 0.528 ng·hr/mL) was comparable to 180mcg racemic albuterol (mean C_{max} 0.227 ng/mL, mean AUC_{0-4} 0.574 ng·hr/mL). In addition, the mean tmax was comparable between levalbuterol (0.85 hr) and racemic albuterol (0.72 hr).

10.1.2 Study 051-355

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

Reviewer's Comment: Study 051-355 was conducted with levalbuterol HFA manufactured by two different manufacturers, 3M (to-be-marketed manufacturer) and —

10.1.2.1 Protocol

Study 051-355 was very similar in design to Study 051-353; therefore, only the differences in the protocols will be discussed briefly. Study 051-355 is the only pivotal study to compare the two different manufacturers of levalbuterol HFA used in the pivotal studies: levalbuterol HFA-A (3M) and levalbuterol HFA-B —. The proposed commercial manufacturer is 3M (levalbuterol HFA-A) Thus, one of the secondary objectives of this study was to demonstrate comparability between levalbuterol HFA-A 90 mcg and levalbuterol HFA-B 90 mcg [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 1072].

Study 051-355 had the same design as Study 051-353, except in Period 2 subjects were randomized in a 2:1:1:1 fashion into the following 4 treatment groups for the 8 week active treatment period [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 36, 1073]:

1) Levalbuterol HFA-A MDI 90 mcg (2 actuations, 45 mcg each) QID
   - Lot No. 020539, 3M, exp. date 6/03
2) Levalbuterol HFA-B MDI 90 mcg (2 actuations, 45 mcg each) QID
   - Lot No. 2A260, —, exp. date 1/04
3) Racemic albuterol HFA MDI 180 mcg (2 actuations, 90 mcg each) QID
   -Lot No. GCI025A, Schering, exp. date 9/03
4) Placebo HFA MDI (2 actuations) QID
   - Vehicle only HFA MDI – HFA-134a propellant containing ethanol and oleic acid
   -Lot No. 2A221. —, exp. date 1/04

Unlike Study 051-353, the rescue medication for all subjects in Study 051-355 was open-label Pirbuterol (0.2mg per actuation, Maxair Autohaler, Lot No. 020578, 3M, exp. date 1/04). Racemic albuterol CFC (Lot No. 2-BBS-538) was used for reversibility testing. Instead of the double dummy design, all the MDI study medication canisters were covered in a polypropylene masking device [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 1096].

Reviewer's Comment: It is unclear how well the polyproylene masking device served to maintain the blind.

The study was performed during the period between December 23, 2002, and June 25, 2003. The final study report is dated January 30, 2004 [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 1]. Approximately 564 subjects were screened and 314 were randomized in Period 2.

A total of 49 investigators in the United States randomized subjects in Study 051-355.The Sponsor audited 8 of the 49 participating sites and found all sites to be in compliance except one – Study Center 0118 (Dr. —). At Study Center 0118, a study coordinator split a subject's PK blood specimen into two vials for two time points. The study coordinator was dismissed and follow up audits did not reveal further deficiencies [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 64].
Reviewer's Comment: The falsified data of one subject is not likely to affect the outcome of the study.

An amendment was made to the original protocol on November 13, 2002, which included standardizing pulmonary function testing using — spirometer and software. PFT results were electronically recorded [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 77].

The following changes to the analyses plan were made prior to unblinding the data; [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 78]:

- Subgroup analyses by steroid use, asthma controller medication use, and age
- Summary of relative frequency of peak % change in FEV1 averaged over the double-blind period was added
- A frequency of subjects with paradoxical bronchoconstriction was added
- A summary of time to first use of rescue medication during spirometry was added
- The proportion of asthma attacks summary was removed
- Summaries by subgroup for asthma events and asthma attacks and a summary of the duration of asthma adverse events and asthma attacks were added
- Relative exposure analyses were added.

The following is a list of the pertinent changes to the analyses plan after data availability [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 78-79]:

- Reviews of concomitant medication listing occurred after data unblinding
- Tabular summaries of peak % predicted FEV1 were added for steroid and non-steroid users
- AUC_{0-4} was added as a primary PK parameter
- Unequal variances were used when performing relative exposure analyses.

10.1.2.2 Results

10.1.2.2.1 Subject Disposition

Subject disposition for Study 051-355 is shown in Table 62. Of the 303 subjects randomized to one of the four double-blind treatment groups, 264 (87.1%) completed the study, while 39 (12.9%) terminated early. The percentage of subjects who discontinued from each treatment group was similar among the treatment groups; however, the percentage of subjects who discontinued due to an AE was less in the two levalbuterol groups [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 79].

Table 62 Subject Disposition for Study 051-355 (ITT population)

	Levalbuterol – A HFA 90mcg	Levalbuterol – B HFA 90mcg	Racemic Albuterol HFA 180mcg	Placebo HFA-134a
Enrolled (N==387)				
Randomized (N==303)*	122	62	60	59
Completed (N=264)	108 (88.5)	54 (87.1)	51 (85.0)	51 (86.4)
Discontinued (N=39)	14 (11.5)	8 (12.9)	9 (15.0)	8 (13.6)
AE (N=20)	7 (5.7)	3 (4.8)	6 (10.0)	4 (6.8)
Protocol Violation (N=2)	0	2 (3.2)	0	0
Voluntary withdrawal (N=6)	3 (2.5)	1 (1.6)	0	2 (3.4)
Lost to follow-up (N=2)	0	0	2 (3.3)	0
Did not meet entry criteria (N=4)	1 (0.8)	2 (3.2)	1 (1.7)	0
Other (N=5)	3 (2.5)	0	0	2 (3.4)

* Randomized in 2:1:1:1 ratio
Source: N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 79.

The Applicant summarized the protocol violations for each treatment group in Study 051-355. As in Study 051-353, approximately 74% of the subjects in each treatment group had a least one protocol violation, the most common being the use of a disallowed medication. The most common disallowed medications were short-acting beta agonists, antihistamines, and corticosteroids. The Applicant reported that of the subjects who had a protocol violation due to use of short-acting beta agonists, most resulted from either the restart of the rescue medication at Visit 6 or insufficient wash-out prior to Visit 1. The Applicant reports that most of these subjects did not report using these agents during the study period [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 80].

The use of antihistamines during the study period was attributed mostly to subjects who used antihistamines both prior to and during the study on a regular basis. The use of corticosteroids during the study was attributed mostly to the dose not being stable for 4 weeks prior to study entry. The Applicant states this was in part due to a change from a corticosteroid/beta agonist combination to a corticosteroid only prior to Visit 1 [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 80].

Reviewer's Comment: A large proportion of study subjects were documented to have used a disallowed medication. Use of a short-acting beta agonist was a common protocol violation and this could potentially influence the results of the study. The Applicant provided the number of subjects with protocol deviations for beta agonists, but did not provide a further breakdown. The Applicant did state, however, that the majority of protocol deviations for short acting beta agonists were for the restart of beta agonists at Visit 6 or insufficient washout period prior to Visit 1. In addition, the Applicant stated that most subjects did not report using short acting beta agonists during the study period.

In a Response to Information Request dated January 17, 2005, the Applicant provided additional information regarding the protocol violation due to beta adrenergic agonist use. As shown below, the primary reason for protocol violation due to beta agonist use was due to restart of beta agonist at Visit 6. The Applicant stated that is was unlikely that beta agonists were used at Visit 6 because PFTs and end of study procedures were to be performed after at least a 7 hour washout period. At Visit 6, subjects were instructed to resume beta agonists as part of their asthma management, which accounted for the large number of subjects in this category, according to the Applicant.

Table 63 Protocol Violations for Beta Agonist Use in Study 051-355 (ITT Population)

	Levalbuterol HFA-A 90mcg n=122	Levalbuterol HFA-B 90mcg n=62	Racemic Albuterol HFA 180mcg n=60	Placebo HFA-134a n=59
Use of disallowed medication	81 (66.4%)	42 (67.7%)	37 (61.7%)	30 (50.8%)
Insufficient beta agonist washout at Visit 1	13 (10.7%)	3 (4.8%)	10 (16.7%)	2 (3.4%)
Possible beta agonist use during study period	3 (2.5%)	8 (12.9%)	9 (15.0%)	4 (6.8%)
Restart beta agonist at Visit 6	32 (26.2%)	13 (21.0%)	15 (25.0%)	13 (22.0%)

Source: N21730\N_000\2005-01-17\clinstat\clinsum.pdf

Reviewer's Comment: It remains unclear to this reviewer why the Applicant would consider resumption of beta agonist treatment at the end of the study a protocol violation. That being said, the resumption of beta agonist therapy at Visit 6 was similar across treatment groups and thus, should not affect the results of the study. However, two of the active treatment groups had 12-15% of the subjects with possible beta agonist use during the study. This could complicate interpretation of the results of the study.

10.1.2.2.2 Demographics and Baseline Characteristics

Table 64 below summarizes the demographics and baseline characteristics of the subjects who were randomized into one of the treatment groups for Study 051-355.

Table 64 Demographics and Baseline Characteristics in Study 051-355
(ITT Population)

n (%)	Levalbuterol HFA-A 90mcg n-122	Levalbuterol HFA-B 90mcg n = 62	Racemic Albuterol HFA 180mcg n = 60	Placebo HFA-1341 n = 59
Gender				
Male	59 (48.4)	24 (38.7)	31 (51.7)	32 (54.2)
Female	63 (51.6)	38 (61.3)	29 (48.3)	27 (45.8)
Age				
Mean	36.5 (16.3)	36.1 (16.0)	38.2 (16.3)	35.1 (15.0)
Range	12-77	12-72	13-81	12-72
Race				
Caucasian	93 (76.2)	48 (77.4)	35 (58.3)	39 (66.1)
Black	20 (16.4)	7 (11.3)	14 (23.3)	13 (22.0)
Hispanic	6 (4.9)	5 (8.1)	6 (10.0)	4 (6.8)
Asian	1 (0.8)	2 (3.2)	5 (8.3)	2 (3.4)
Other	2 (1.6)	0	0	1 (1.7)
FEV_1 Screening (L)				
Mean	2.20	2.15	2.16	2.25
Range	1.26-3.74	1.17-3.58	1.26-3.52	1.19-3.63
FEV_1 % Predicted				
Mean	64.7	64.2	62.6	63.8
Range	45-87	45-82	45-82	44-83

Source [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 82.

Demographic and baseline characteristics for the randomized population were similar among the treatment groups with the following exceptions: more females (61%) in the levalbuterol HFA-B treatment group and more non-Caucasians in the levalbuterol HFA-B, racemic albuterol HFA, and placebo treatment groups. The mean age of subjects ranged from 35.1 years to 38.2 years. The FEV_1 percent of predicted at baseline and FEV1 at screening were similar among the treatment groups.

10.1.2.2.3 Efficacy

10.1.2.2.3.1 Primary

The primary efficacy parameter was same as in Study 051-353, the peak percent change FEV_1 from visit predose averaged over the double-blind period. Serial spirometry was performed at Week 0 (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 6). Serial spirometry measurements included: pre-dose, immediately post-dose, 15-minute intervals for 2 hours post-dose, then hourly until 4 (Visit 4) or 8 (Visit 2 & 6) hours post dose.

All efficacy and safety analyses were performed using the "ITT" population, which was defined as the population of randomized subjects who received at least one dose of study medication. The Applicant performed the analysis using an ANCOVA model with effects for treatment, investigator, and baseline FEV_1 (study baseline or visit predose). Table 65 is a summary of the peak percent change in FEV_1 averaged over the double-blind period (primary endpoint) and the peak percent change in FEV_1 at Visit 2, Visit 4, and Visit 6 (secondary endpoints) for each treatment group in Study 051-355 [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 84].

Table 65 Peak Percent Change FEV_1 for Study 051-355
ITT Population

Peak Percent Change in FEV_1	Levalbuterol HFA-A 90mcg n=122	Levalbuterol HFA-B 90mcg n=62	Racemic Albuterol HFA 180mcg n=60	Placebo HFA-134a n=59
Averaged over Double-Blind Period[1] (Primary EP)				
LS Mean (SE)	25.33 (1.05)	23.09 (1.05)	26.514 (1.49)	12.45 (1.49)
Pairwise p-value vs. Placebo[2]	<0.001	<0.001	<0.001	
Pairwise p-value vs. Levalbuterol B[2]	0.194			
Pairwise p-value vs. Racemic Albuterol[2]	0.654	0.132		
Visit 2[3]				
LS Mean (SE)	24.86 (1.32)	26.24 (1.83)	28.55 (1.88)	13.87 (1.88)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	<0.001	
Pairwise p-value vs. Levalbuterol B[4]	0.538			
Pairwise p-value vs. Racemic Albuterol[4]	0.105	0.375		
Visit 4[3]				
LS Mean (SE)	24.48 (15.05)	22.40 (1.81)	25.51 (1.83)	12.68 (1.84)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	<0.001	
Pairwise p-value vs. Levalbuterol B[4]	0.347			
Pairwise p-value vs. Racemic Albuterol[4]	0.644	0.226		
Visit 6[3]				
LS Mean (SE)	24.99 (1.43)	19.90 (2.00)	24.32 (2.06)	12.43 (2.05)
Pairwise p-value vs. Placebo[4]	<0.001	0.010	<0.001	
Pairwise p-value vs. Levalbuterol B[4]	0.038			
Pairwise p-value vs. Racemic Albuterol[4]	0.788	0.122		

1 Peak percent change in FEV1 from visit predose averaged over the double-blind period was calculated by first taking the difference in peak FEV1 recorded during the serial spirometry day (Visits 2, 4, and 6) and the visit predose FEV1. This result was then divided by visit predose FEV1 and multiplied by 100. The three peak percent change values were then averaged.
2 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.
3 Peak percent change in FEV1 from visit predose refers to the maximum FEV1 recorded during the visit minus the FEV1 observed at visit predose, divided by the visit predose FEV1 and multiplied by 100.
4 Pairwise tests of treatment effect were conducted using ANCOVA with treatment, investigator effects and visit predose FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.
Source: [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 84,235-237]

Levalbuterol HFA-A, levalbuterol HFA-B, and racemic albuterol HFA were statistically superior to placebo based upon the primary endpoint. Based upon the primary endpoint, there was no statistical difference between levalbuterol HFA-A and levalbuterol HFA-B nor was there a statistical difference between either of the levalbuterol HFA products and racemic albuterol HFA. A decrease in response in all the treatment groups was noted in Study 051-353 from Visit 2 to Visit 6. In this study, a decline in the peak percent change FEV1 was predominantly noted in the levalbuterol HFA-B group and racemic albuterol HFA group. The peak percent change FEV1 was essentially unchanged in the levalbuterol HFA-A treatment group from Visit 2 to Visit 6. Due to the decrease in response in the levalbuterol HFA-B treatment group from Visit 2 to Visit 6, levalbuterol HFA-A was statistically superior to levalbuterol HFA-B at Visit 6.
Reviewer's Comment: The Visit 2 and Visit 6 predose FEV1 values were not significantly different in the levalbuterol HFA-A treatment group, which is different from Study 051-353, in which the visit predose FEV1 increased from Visit 2 to Visit 6. Thus, the response to levalbuterol A was more consistent throughout the treatment period than in Study 051-353. The

decrease in response in the levalbuterol HFA-B, racemic albuterol HFA and placebo groups is likely due to an increase in visit predose FEV1 from Visit 2 to Visit 6.

10.1.2.2.3.2 Secondary

Pre-specified secondary efficacy parameters were similar to Study 051-353. The following sections review the findings from the pertinent secondary endpoints.

10.1.2.2.3.2.1 Spirometry

Table 66 summarizes additional spirometry secondary efficacy endpoints for Study 051-355.

Table 66 Additional Spirometry Endpoints for Study 051-355

	Levalbuterol HFA-A 90mcg n=122	Levalbuterol HFA-B 90mcg n=62	Racemic Albuterol HFA 180mcg n=60	Placebo HFA-134a n=59
AUC_{0-8} for FEV_1 % Change[1] from Visit Predose (DB Avg)				
LS Mean (SE) %-hr	105.28 (7.29)	80.18 (10.13)	95.08 (10.39)	29.14 (10.39)
Pairwise p-value vs. Placebo[2]	<0.001	<0.001	<0.001	
Pairwise p-value vs. Levalbuterol B[2]	0.044			
Pairwise p-value vs. Racemic Albuterol[2]	0.416	0.301		
AUC_{0-8} for FEV_1 Percent Change[1] from visit predose (Visit 2)				
LS Mean (SE) %-hr	107.2 (9.39)	106.4 (13.05)	115.37 (13.38)	35.81 (13.38)
Pairwise p-value vs. Placebo[8]	< 0.001	< 0.001	<0.001	
Pairwise p-value vs. Levalbuterol B[8]	0.963			
Pairwise p-value vs. Racemic Albuterol[8]	0.612	0.629		
AUC_{0-8} for FEV_1 Percent Change[1] from Visit Predose (Visit 6)				
LS Mean (SE) %-hr	97.37 (8.94)	50.50 (12.45)	72.83 (12.83)	27.75 (12.80)
Pairwise p-value vs. Placebo[8]	< 0.001	0.204	0.013	
Pairwise p-value vs. Levalbuterol B[8]	0.002			
Pairwise p-value vs. Racemic Albuterol[8]	0.115	0.210		
Peak % Change FVC from Visit Predose (DBAvg)[3]				
LS Mean (SE)	15.06 (0.69)	13.45 (0.96)	16.53 (0.98)	9.00 (0.98)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	<0.001	
Pairwise p-value vs. Levalbuterol B[4]	0.171			
Pairwise p-value vs. Racemic Albuterol[4]	0.217	0.025		
Peak % Change $FEF_{25-75\%}$ from Visit Predose (DBAvg)[5]				
LS Mean (SE)	58.54 (2.42)	52.32 (3.36)	55.13 (3.45)	28.22 (3.44)
Pairwise p-value vs. Placebo[6]	<0.001	<0.001	<0.001	
Pairwise p-value vs. Levalbuterol B[6]	0.131			
Pairwise p-value vs. Racemic Albuterol[6]	0.413	0.557		
Peak % Predicted FEV_1 (DBAvg)[7]				
LS Mean (SE)	79.61 (0.78)	80.07 (1.09)	80.14 (1.12)	73.15 (1.11)
Pairwise p-value vs. Placebo[9]	<0.001	<0.001	<0.001	
Pairwise p-value vs. Levalbuterol B[9]	0.729			
Pairwise p-value vs. Racemic Albuterol[9]	0.695	0.964		
Visit 2 Peak % Predicted FEV_1[7]				
LS Mean (SE)	80.26 (0.74)	80.67 (1.03)	81.48 (1.06)	72.76 (1.05)
Pairwise p-value vs. Placebo[9]	<0.001	<0.001	<0.001	
Pairwise p-value vs. Levalbuterol B[9]	0.744			
Pairwise p-value vs. Racemic Albuterol[9]	0.342	0.584		
Visit 6 Peak % Predicted FEV_1[7]				
LS Mean (SE)	79.47 (1.03)	79.78 (1.42)	78.98 (1.48)	74.43 (1.46)
Pairwise p-value vs. Placebo[9]	0.005	0.009	0.029	
Pairwise p-value vs. Levalbuterol B[9]	0.859			
Pairwise p-value vs. Racemic Albuterol[9]	0.789	0.698		

1 Area under the FEV1 percent change curve averaged over the double-blind period was calculated by first applying the linear trapezoidal method to the FEV1 percent change from baseline (visit predose or study baseline) obtained during Visits 2 and 6. These two AUC values were then averaged.

2 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and predose visit FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.

3 Peak percent change in FVC from visit pre-dose averaged over the double-blind period was calculated by first taking the difference between the peak FVC recorded during the serial spirometry day (Visits 2, 4, and 6) and the visit pre-dose FVC. This result was then divided by visit pre-dose FVC and multiplied by 100. The three peak percent change from visit pre-dose values were then averaged.

4 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FVC as the covariate. The tests were performed using a one degree of freedom contrast.

5 Peak percent change in FEF 25-75% from visit pre-dose averaged over the double-blind period was calculated by first taking the difference between the peak FEF 25-75% recorded during the serial spirometry day (Visits, 2, 4 and 6) and the visit pre-dose FEF 25-75%. This result was then divided by visit pre-dose FEF25-75% and multiplied by 100. The three peak percent changes from visit pre-dose values were then averaged.
6 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEF 25-75% as the covariate. The tests were performed using a one degree of freedom contrast.
7 Peak percent of predicted FEV1 was calculated by dividing the peak FEV1 recorded during a serial spirometry day (Visits 2, 4, and 6) by the predicted FEV1 determined at Screening (Visit 1), and then multiplying by 100. For the double-blind average, the three resulting peak percent of predicted values were averaged.
8 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.
9 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline percent predicted FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.

Source: [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 85, 267-268, 284, 287, 289, 100, 102]

As shown in Table 66, the area under the FEV1 percent change curve was significantly larger in all the active treatment groups relative to the placebo group. For the double blind treatment period, there was a larger AUC FEV1 percent change with levalbuterol HFA-A relative to levalbuterol HFA-B and no statistically significant difference between either of the levalbuterol HFA treatment groups versus the racemic albuterol HFA treatment group. Of note levalbuterol HFA-A had a numerically higher AUC FEV1 percent change than levalbuterol HFA-B or racemic albuterol HFA. At Visit 6, levalbuterol HFA-A was statistically superior to levalbuterol HFA-B. Although not shown in the table above, the AUC percent change FEV1 from study baseline, averaged over the double blind period was also determined. All three active treatment groups were superior to placebo. There was no statistical difference among the three active treatment groups [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 86].

The peak percent change in FVC and FEF 25-75% averaged over the double-blind period was significantly greater for all three active treatment groups compared to placebo. Racemic albuterol HFA produced a larger peak percent change in FVC than levalbuterol HFA-A and levalbuterol HFA-B.

The peak percent of predicted FEV1 was significantly greater for all active treatment groups compared to placebo. However, there was no statistical difference among the two levalbuterol HFA groups and racemic albuterol HFA or between the two levalbuterol HFA treatment groups.

Time to peak change in FEV_1 from visit predose was analyzed for Visits 2, 4, and 6 and was similar among the levalbuterol HFA treatment groups and racemic albuterol HFA. The following are the mean times to peak change for Visit 2, 4, and 6, respectively:

- Levalbuterol HFA-A - 101, 75, and 104 minutes
- Levalbuterol HFA-B – 106, 87, and 69 minutes
- Racemic albuterol HFA– 117, 82, and 94 minutes
- Placebo – 212, 136, and 200 minutes [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 283].

The Applicant determined the number of responders, which were defined as subjects experiencing ≥ 15% improvement in FEV1 from visit predose. The number of responders was greater in all three active treatment groups when compared to the placebo group [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 350]. The median times to a 15% increase

in FEV1 were 10.2, 5.5, and 6.7 minutes, respectively for levalbuterol HFA-A, levalbuterol HFA-B, and racemic albuterol HFA at Visit 2 and 16.3, 41.5, and 37.9 minutes, respectively, at Visit 6. All active treatment groups had a significantly shorter time to 15% response than placebo [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 371].

Table 67 Number of Responders in Study 051-355 (ITT Population)

	Levalbuterol HFA-A 90mcg n=122	Levalbuterol HFA-B 90mcg n=62	Racemic Albuterol HFA 180mcg n=60	Placebo HFA-134a n=59
Visit 2	94 (77%)	45 (73%)	50 (83%)	21 (36%)
Visit 4	84 (75%)	39 (71%)	36 (67%)	15 (28%)
Visit 6	82 (76%)	31 (57%)	32 (63%)	13 (26%)

Source: [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 350]

The Applicant provided the following mean percent changes in pre-dose FEV1 at Visit 6 relative to study baseline (pre-dose at Visit 2) [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 96]:

- Levalbuterol A -1.02%
- Levalbuterol B +5.32%
- Racemic albuterol +2.59%
- Placebo +5.65%.

Reviewer's Comment: It is unclear why the levalbuterol A treatment group would have a decline in pre-dose FEV1, while the other groups, including placebo, actually had an increase in pre-dose FEV1.

10.1.2.2.3.2.2 Peak Expiratory Flow (PEF)

Although PEF was to be measured at home and in the clinic, the Applicant only analyzed the results of the PEF measured at the clinic visits. PEF was measured at each clinic visit pre-dose and 15 minutes post-dose. All three active treatment groups demonstrated an increase in post-dose mean PEF from mean pre-dose PEF. In general the percent change in PEF was slightly higher in the racemic albuterol treatment HFA group. Of note, the morning PEF was slightly lower in each of the active treatment groups as compared to the placebo group [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 469-470].

Reviewer's Comment: The final version of the subject diaries did not collect both pre and post dose am PEF. Therefore, the Applicant did not perform analyses on the home PEF data. The home PEF data was reported in the Application. The home PEF were used for the asthma action plan during the study.

10.1.2.2.3.2.3 Asthma Symptoms

Asthma symptom scores were recorded by the subjects each morning and night. The individual symptom scores were slightly better in the levalbuterol HFA groups than in the placebo or racemic albuterol HFA groups. However, asthma symptoms were not measured by a validated patient reported outcomes instrument [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 473-490].

10.1.2.2.3.2.4 Quality of Life & SF-36

As in Study 051-353, the Applicant measured the quality of life with the Asthma Quality of Life Questionnaire and general health with the SF-36. There were no significant treatment differences for any of the domains in the AQLQ from Visit 2 to Visit 6. In addition, here were no statistically significant treatment differences in the two domains measured in the SF-36 (physical functioning and general health scores) from Visit 2 to Visit 6 [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 491-503].

10.1.2.2.3.2.5 Global Evaluation

As in Study 051-353, at Visit 6 (Week 8), the physician and subject completed a global assessment of asthma symptoms based on the treatment period. Overall from the beginning of the study, more subjects rated their symptoms improved to some degree in the active treatment groups than in the placebo group [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 103].

10.1.2.2.4 Pharmacokinetic Endpoint Outcomes

PK samples for (R)- and (S)-albuterol were collected at Visit 2 (pre-dose, 1-2 hours post-dose, and 4-6 hours post-dose), Visit 3 (pre-dose), and Visit 6 (pre-dose, 0.25, 0.5, 1, 2, 4, and 8 hours post-dose). The pharmacokinetic (PK) data from this study will be reviewed in depth, along with the PK data from the remainder of the clinical program in a separate document by the OCPB Reviewer. The following is a brief discussion of the PK data from this study.

As in Study 051-353, the plasma concentrations of (R)-albuterol were highly variable. Some subjects in the levalbuterol HFA treatment groups had measurable levels of (S)-albuterol during the study. PK parameters were calculated from plasma concentrations obtained on Visit 6. Table 68 displays the summary statistics for the PK parameters for (R) –albuterol in the levalbuterol treatment groups and (R) and (S) –albuterol in the racemic albuterol dosing group.

Table 68 PK Parameters for (R)-albuterol and (S)-albuterol for Study 051-355

	Levalbuterol HFA-A			Levalbuterol HFA-B			Racemic Albuterol HFA					
	(R) -albuterol			(R) -albuterol			(R) -albuterol			(S) -albuterol		
	n	Mean (SD)	Median (min-max)	n	Mean (SD)	Median (min-max)	n	Mean (SD)	Median (min-max)	n	Mean (SD)	Median (min-max)
C_{max} (ng/mL)	104	0.27 (0.24)	0.18 (0.02-1.23)	52	0.25 (0.22)	0.19 (0.03-1.19)	50	0.34 (0.50)	0.20 (0.04-3.46)	50	0.79 (0.62)	0.60 (0.06-3.93)
t_{max} (hr)	104	1.02 (1.50)	0.53 (0-8.0)	52	0.77 (0.82)	0.51 (0.2-8.0)	50	0.90 (1.35)	0.49 (0-8.0)	50	1.73 (1.72)	1.04 (0-8.0)
AUC $_{(0\text{-last})}$ (ng·hr/mL)	104	0.89 (0.41)	0.70 (0.08-3.40)	52	0.82 (0.61)	0.65 (0.22-3.39)	50	1.05 (1.30)	0.81 (0.09-9.34)	50	3.54 (1.99)	3.00 (0.29-9.05)
AUC $_{(0\text{-}4)}$ (ng·hr/mL)	97	0.57 (0.41)	0.50 (0.06-2.78)	51	0.54 (0.35)	0.46 (0.12-1.82)	48	0.69 (0.65)	0.54 (0.06-4.36)	48	2.28 (1.31)	2.00 (0.14-7.86)

Source: [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 110]

The C_{max} and $AUC_{(0\text{-}4)}$ of (R)-albuterol were similar among the three treatment groups. The two levalbuterol HFA products provided a similar exposure to (R)-albuterol. The Applicant performed a relative exposure analysis at the presumed steady-state to compare the two levalbuterol HFA products. According to the analysis, the two levalbuterol HFA products provide similar exposure. Levalbuterol HFA provided lower (R)-albuterol exposure than

racemic albuterol HFA, by approximately 11-14% [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 116].

The mean t_{max} for (R)-albuterol in the levalbuterol HFA-A group and the racemic albuterol HFA group were similar. The t_{max} for (S)-albuterol was much later than for (R)-albuterol. In the racemic albuterol HFA group, the C_{max} and AUC for (S)-albuterol were much higher than the mean PK parameters for (R)-albuterol.

10.1.2.2.5 Safety

The safety findings from this study, along with the safety data from the other clinical studies, will be reviewed in depth in the Integrated Review of Safety section of this review. A summary of the safety findings from this study follows.

Table 69 is a summary of the extent of exposure for the levalbuterol HFA and racemic albuterol HFA treatment groups for Study 051-355. All subjects were ≥80% compliant except one subject in the placebo group.

Table 69 Summary of Extent of Exposure for Study 051-355

Daily Dose Level for Double Blind Treatment Period (mcg)	Levalbuterol A n=122	Levalbuterol B n=62	Racemic Albuterol n=60
Mean	353.9	355.4	715.6

Source: [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 124]

Reviewer's Comment: Because the levalbuterol groups were dosed 90mcg QID (360mcg daily) and the racemic albuterol groups was dosed 180mcg QID (720mcg daily), the above table demonstrates that the daily dose level for both the levalbuterol and racemic albuterol group was close to the dose described in the protocol.

10.1.2.2.5.1 Adverse Events

Adverse events were reported in approximately 50% of the subjects in each treatment group. There was a higher incidence of SAEs in the placebo group. A higher incidence of asthma adverse events was noted in the levalbuterol HFA-A group compared to the placebo group; however, the incidence of asthma AEs was consistent with the racemic albuterol HFA group. There were no deaths. Table 70 displays a summary of adverse events reported in ≥ 2% of subjects in any of the treatment groups, as reported by the Applicant.

Table 70 Summary of Adverse Events (AEs) Reported in ≥ 2% Subjects in Study 051-355
ITT Population During the Double-Blind Period

	Levalbuterol HFA-A n=122	Levalbuterol HFA-B n=62	Racemic Albuterol HFA n=60	Placebo n=59
	n (%)	n (%)	n (%)	n (%)
Any adverse event	63 (51.6)	35 (56.5)	30 (50.0)	33 (55.9)
Discontinued due to AE	7 (5.7)	3 (4.8)	6 (10.0)	4 (6.8)
Serious adverse event	1 (0.8)	0 (0)	1 (1.7)	3 (5.1)
Asthma adverse events	**11 (9.0)**	**4 (6.5)**	**5 (8.3)**	**4 (6.8)**
Headache	12 (9.8)	8 (12.9)	6 (10.0)	6 (10.2)
Viral infection	12 (9.8)	3 (4.8)	10 (16.7)	8 (13.6)
Asthma	**11 (9.0)**	**4 (6.5)**	**5 (8.3)**	**4 (6.8)**
Asthma Attack*	**10 (8.2)**	**4 (6.5)**	**5 (8.3)**	**3 (5.1)**
Accidental Injury	9 (7.4)	1 (1.6)	3 (5.0)	4 (6.8)
Rhinitis	8 (6.6)	12 (19.4)	0	1 (1.7)
Pharyngitis	6 (4.9)	14 (22.6)	1 (1.7)	0
Pain	5 (4.1)	2 (3.2)	2 (3.3)	1 (1.7)
Cough Increased	4 (3.3)	4 (6.5)	0	3 (5.1)
Nausea	4 (3.3)	2 (3.2)	0	1 (1.7)
Back Pain	4 (3.3)	1 (1.6)	1 (1.7)	4 (6.8)
Fever	3 (2.5)	3 (4.8)	1 (1.7)	0
Neck Pain	3 (2.5)	0	0	0
Gastroenteritis	3 (2.5)	1 (1.6)	0	0
Myalgias	3 (2.5)	1 (1.6)	1 (1.7)	1 (1.7)
Dizziness	3 (2.5)	4 (6.5)	0	0
Conjunctivitis	2 (1.6)	2 (3.2)	0	0
Dyspepsia	2 (1.6)	2 (3.2)	0	4 (6.8)
Diarrhea	2 (1.6)	3 (4.8)	0	0
Sinusitis	1 (0.8)	4 (6.5)	2 (3.3)	2 (3.4)
Abdominal Pain	1 (0.8)	2 (3.2)	1 (1.7)	2 (3.4)
Chest Pain	1 (0.8)	0	4 (6.7)	1 (1.7)
Insomnia	1 (0.8)	0	0	2 (3.4)
Nervousness	0	0	1 (1.7)	2 (3.4)

* An asthma attack was a subcategory of asthma AES that required one of the following four criteria: 1)hospitalization; 2) an ER visit; 3) intervention with an oral burst or parenteral corticosteroids; or 4) an unscheduled clinic visit to treat acute asthma symptoms.
Source: [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 124-131]

Headaches, asthma, rhinitis, pharyngitis, and viral infection were the most common AEs. Rhinitis and pharyngitis were more common in the levalbuterol B treatment group than any other treatment group. An asthma attack was a subcategory of asthma AEs that required one of the following four criteria: 1)hospitalization; 2) an ER visit; 3) intervention with an oral burst or parenteral corticosteroids; or 4) an unscheduled clinic visit to treat acute asthma symptoms. The incidence of asthma attacks was similar between the levalbuterol HFA-A and racemic albuterol HFA treatment group, but both were higher than in the placebo group.

During the double blind treatment period, 5 subjects reported 6 SAEs. The following is a breakdown of the SAEs [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 134].

- Levalbuterol HFA-A (1 subject, 0.8%)

  - Accidental injury (2)
- Racemic albuterol HFA (1 subject, 1.7%)
  - Chest pain
- Placebo (3 subjects, 5.1%)
  - Appendicitis
  - Asthma (hospitalized)
  - Pneumonia

In addition, 20 subjects had AEs that led to discontinuation of treatment during the double blind treatment period. A higher incidence of discontinuation due to AEs was noted in the racemic albuterol HFA group. Asthma and chest pain were the most common AEs leading to discontinuation. The following is a breakdown of the discontinuations secondary to AEs [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 135-136]:

- Levalbuterol A (7)
  - Asthma (3)
  - Accidental injury (2)
  - Pneumonia
  - Chest pain
- Levalbuterol B (3)
  - URI
  - Asthma (2)
- Racemic Albuterol (6)
  - Asthma (3)
  - Chest pain (2)
  - Bronchitis
- Placebo (4)
  - Chest pain
  - Nervousness
  - Asthma (2).

10.1.2.2.5.2 Laboratory Evaluations

Serum potassium and glucose levels were measured predose and post-dose (1-2 hours) at Visit 2 and Visit 6. No significant changes in the mean potassium or glucose levels were noted among the treatment groups. Although the largest individual decrease in potassium was -1.3mEq/L in the levalbuterol HFA-A group, the mean post dose decrease in potassium for the levalbuterol HFA-A group was 0.02-0.03mEq/L. The active treatment groups in general demonstrated a larger change in glucose. The mean post dose increase in glucose among the treatment groups ranged from 0.13mg/dL (levalbuterol HFA-A) to 6.63mg/dL (racemic albuterol HFA) [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 160].

There were no clinically significant differences in the mean laboratory chemistry or hematology parameters measured at the end of the treatment period among the treatment groups [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 703-712].

10.1.2.2.5.3 Vital Signs and Physical Examinations

No significant change in heart rate was noted among the treatment groups. The percentage of subjects with a heart rate increase greater than 20 bpm was similar in the levalbuterol HFA groups and the placebo group. For blood pressure, the percentage of subjects with an increase in systolic blood pressure >20mmHg was higher in the racemic albuterol treatment group. The most frequent physical examination findings involved the ENT, respiratory or skin, extremities [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 165-167, 172].

Table 71 Summary of Heart Rate and Blood Pressure for Study 051-355

	Levalbuterol HFA-A n=122	Levalbuterol HFA-B n=62	Racemic Albuterol HFA n=60	Placebo HFA-134a n=59
Subjects with ↑HR>20bpm	20 (16%)	6 (10%)	5 (8%)	9 (15%)
Subjects with ↑ SBP >20mm Hg	17 (14%)	7 (11%)	12 (20%)	9 (15%)
Subjects with ↑ DBP >10mm Hg	51 (42%)	26 (42%)	24 (40%)	29 (49%)

Source: [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 165-167]

10.1.2.2.5.4 Electrocardiograms

ECGs were conducted pre-dose and 30 minutes post-dose at Visits 2-6. At each visit, the mean pre and post-dose values for heart rate, PR interval, QRS duration, QT interval, QT_{C-F}, QT_{C-B}, and RR interval were similar among the treatment groups. The largest mean increase in the QT_{c-F} was in the levalbuterol HFA-A group at Visit 2 with a mean increase of 4.4ms, which was significantly longer than in the placebo group at 0.2ms. However, the increase in QT_{c-F} was similar in all three active treatment groups. Prolongation of the QT_{c-F} interval >450 ms occurred in 6.6%, 4.8%, 1.7%, and 6.8% of subjects in the levalbuterol HFA-A, levalbuterol HFA-B, racemic albuterol HFA, and placebo treatment groups, respectively. The percentage of subjects with a change in the QT_{c-F} of 30-60ms was comparable among the active treatment groups. Two subjects in the levalbuterol HFA-A treatment group and 1 subject in the placebo group experienced a change in the QT_{c-F} of >60ms from visit predose to post-dose. Also one subject in the levalbuterol HFA-A treatment group developed atrial fibrillation during the treatment period [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 167-172].

10.1.2.2.5.5 Rescue Medication, Paradoxical Bronchoconstriction

Subjects reported slightly more asthma control days in the active treatment groups versus placebo. The mean number of days per week that rescue medication was used was lower in the active treatment groups compared to the placebo group. Subjects in the levalbuterol HFA A (12.3%) treatment group reported the lowest rate of rescue medication use during the study compared to 19%, 20% and 22% in the levalbuterol HFA-B, racemic albuterol HFA, and placebo groups, respectively [N21730\N_000\2004-05-11\clinstat\051-353.pdf, p 174-175].

Paradoxical bronchospasm was defined as a ≥ 15% decrease in FEV1 within one hour of clinic dosing. During the serial spirometry the number of subjects with paradoxical bronchoconstriction was 4, 0, 2, and 8 in the levalbuterol A, levalbuterol B, racemic albuterol, and placebo treatment groups, respectively [N21730\N_000\2004-05-11\clinstat\051-355.pdf, p 173].

10.1.2.3 Discussion and Conclusions

10.1.2.3.1 Efficacy

Study 051-355 demonstrated that 90 mcg levalbuterol HFA-A was superior to placebo on the pre-specified primary efficacy endpoint: the peak percent change in FEV1 from visit predose averaged over the double-blind period. The peak percent change in FEV1 from visit predose, averaged over the double-blind period was 25.33% in the levalbuterol A group versus 12.45% in the placebo group. The difference is statistically and clinically significant. The American Thoracic Society defines a bronchodilator response as an increase in FEV1 of $\geq$ 12% and 200mL. The mean increase in peak percent change in FEV1 in the levalbuterol HFA-A group over the placebo group was 12.88%, which is clinically significant.

Efficacy was supported by statistically significant improvements in the levalbuterol HFA-A group as compared to the placebo group in the following secondary endpoints:

- AUC for FEV1 percent change from visit predose averaged over the double-blind period
- Peak percent change in FVC and $FEF_{25-75\%}$ from visit predose.

In general, none of the non-spirometric outcome variables demonstrated a statistically significant benefit in the levalbuterol HFA-A treatment group. Significant treatment group differences were not observed for the adult AQLQ or the SF-36 Health Survey assessments.

A pertinent secondary objective was the comparison between levalbuterol HFA-A and levalbuterol HFA-B. Based upon the pre-specified primary endpoint, both were superior to placebo; however, there was no statistical difference between levalbuterol HFA-A and levalbuterol HFA-B. Levalbuterol HFA-A did demonstrate a slightly higher peak percent change in FEV1 (averaged over the double blind period), 25.33% versus 23.09% in the levalbuterol HFA-B treatment group. The difference is likely not clinically significant. Levalbuterol HFA-A maintained the peak percent change in FEV1 from Visit 2 (24.86%) to Visit 6 (24.99%); however, the levalbuterol HFA-B treatment group had a decline in the response from Visit 2 (26.24%) to Visit 6 (19.90%). The difference was primarily due to an increase in the baseline FEV1 of 5.5% in the levalbuterol HFA-B treatment group, while the levalbuterol HFA-A treatment group actually demonstrated a slight decline in the pre-dose FEV1 (-1%) from Visit 2 to Visit 6. The levalbuterol HFA-A treatment group demonstrated a higher mean AUC_{0-8} FEV percent change, higher mean peak percent change in FVC, and higher mean peak percent change in $FEF_{25-75\%}$ than the levalbuterol HFA-B treatment group. However, the differences were not statistically significant. Study 051-355 demonstrated that levalbuterol HFA-A 90mcg was similar to levalbuterol HFA-B 90mcg; however, levalbuterol HFA-A had numerically greater response on several endpoints.

Study 051-355 did not demonstrate that levalbuterol was superior to racemic albuterol on the pre-specified primary endpoint, secondary spirometry endpoints, or quality of life scores. Levalbuterol HFA-A and racemic albuterol HFA demonstrated similar outcomes.

10.1.2.3.2 Safety

Overall, the rates of adverse events were similar among the treatment groups. As in Study 051-353, there appears to be a safety signal of asthma adverse events in the levalbuterol A treatment group. However, in Study 051-355 the signal is not as marked as in Study 051-353. The incidence of asthma adverse events and asthma attacks in the levalbuterol HFA-A treatment group (9.0%, 8.2%) was similar to the incidence in the racemic albuterol HFA treatment group (8.3%, 8.3%); however, both were higher than the incidence in the placebo group (6.8%, 5.1%). A larger proportion of subjects in the racemic albuterol HFA group discontinued treatment due to an adverse event. Common AEs in the levalbuterol HFA treatment groups included: rhinitis and pharyngitis. Levalbuterol HFA was not associated with significant changes in vital signs, laboratories, physical examination, or changes in ECG.

10.1.2.3.3 Pharmacokinetics

Some subjects in the levalbuterol HFA treatment groups had measurable levels of (S)-albuterol during the study. Subjects in the racemic albuterol group were exposed to a much higher concentration of (S)-albuterol compared to (R)-albuterol. Based upon (R)-albuterol, the exposure of 90mcg levalbuterol HFA-A (mean C_{max} 0.27 ng/mL, mean AUC_{0-4} 0.57 ng·hr/mL) was comparable to 90mcg levalbuterol HFA-B (mean C_{max} 0.25 ng/mL, mean AUC_{0-4} 0.54 ng·hr/mL). However, both levalbuterol HFA-A and levalbuterol HFA-B have less (R)-albuterol exposure than 180mcg racemic albuterol (mean C_{max} 0.34 ng/mL, AUC_{0-4} 0.69 ng·hr/mL). The tmax for levalbuterol HFA-A, levalbuterol HFA-B, and racemic albuterol HFA was 1.02, 0.77, and 0.90 hr, respectively.

10.1.3 Study 051-354

An Efficacy, Safety, and Tolerability Study of Daily Dosing with Levalbuterol, Racemic Albuterol, and Placebo in Pediatric Subjects with Asthma

10.1.3.1 Protocol

Study 051-354 was similar in design to the adult studies (051-353 and 051-355); therefore, only the pertinent differences will be discussed. Study 051-354 is the only pivotal study in the pediatric population. The primary objective of Study 051-354 was to investigate the efficacy of levalbuterol 90 mcg versus placebo in the reversal of bronchoconstriction in pediatric subjects with asthma. Secondary objectives included: 1) investigation of the efficacy of levalbuterol 90 mcg versus racemic albuterol 180 mcg; 2) characterization of the PK of (R)-albuterol and (S)-albuterol in pediatric subjects with asthma; 3) determination of the safety and tolerability of levalbuterol [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 846].

Study 051-354 was a double-blind, randomized, placebo- and active-controlled, multicenter, parallel-group trial of levalbuterol in subjects 4 to 11 years of age with asthma. Subjects had to have at least a 6 month history of asthma and an FEV1 $\geq$ 45% to $\leq$ 80% of predicted, with $\geq$ 12% reversibility to racemic albuterol. As in Studies 051-353 and 051-355, there was a one week, single-blind placebo run-in period with racemic albuterol as rescue medication followed by an

active treatment period, Period 2. In Study 051-354, Period 2 was only 4 weeks [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 847].

Approximately 173 subjects were screened and 150 subjects were randomized in Period 2 in a 2:1:1 fashion into the following 3 treatment groups for the 4 week active treatment period:

- Levalbuterol HFA MDI 90 mcg (2 actuations, 45 mcg each) QID
  - Lot #HFA020539 — exp. date 1/03
- Racemic albuterol HFA MDI 180 mcg (2 actuations, 90 mcg each) QID
  - Lot #011081, exp. date 11/03
- Placebo HFA MDI (2 actuations) QID
  - Lot # 2A221, exp. date 1/04.

Rescue medication was double-blind levalbuterol inhalation solution 1.25mg/3mL (Lot #04801A, exp. date 8/03) for the levalbuterol arm, double-blind racemic albuterol inhalation solution 2.5mg/3mL (Lot # 06201C, exp. date 1/04) for the racemic albuterol arm, placebo arm, and the single-blind run-in period. All MDI canisters were covered in a polypropylene masking device. All subjects were supplied a PARI LC PLUS nebulizer and a DURA-Neb 3000 compressor for rescue medication use. Racemic albuterol CFC (Lot # 01802, exp. date 1/04) was used for reversibility testing [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 5].
Reviewer's Comment: Subjects were allowed to use spacers. Spacer users were defined as all subjects who used a spacer when administering double-blind study medication during at least half of the in-clinic dosing visits of interest (Visits 2,4, and 6).

The total duration of the study was five weeks, which included a 1 week run-in period and 4 weeks of active treatment. The study was performed during the period between December 11, 2002, and June 4, 2003. The final study report is dated January 9, 2004 [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 1].

Unlike the adult studies in which subjects were seen at the clinic every 2 weeks, in Study 051-354, subjects had weekly clinic visits during the 4 week active treatment period. At least 60 subjects were specified to have blood collected for PK analysis; however, the frequency of collection in the pediatric population was less than in the adult population. Serial spirometry was performed at Visit 2 (Week 0), Visit 4 (Week 2), and Visit 6 (Week 4). Assessments were otherwise similar to Study 051-353 and Study 051-355; however, the parent/guardian recorded asthma signs and symptoms, recorded rescue medication use, assisted and recorded PEF, and completed the Child Health Status Questionnaire. The primary endpoint was the same – peak percent change FEV1 from visit predose averaged over the double-blind period [N21730\N_000\2004-05-11\clinstat\051-354.pdf, p 848-850].

A total of 40 investigators in the United States participated in Study 051-354. Subjects were randomized at 38 of the study sites. The Sponsor audited 13 of the 38 participating sites for GCP compliance. The following deficiencies were noted at 4 sites [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 66, 83]:

- Angelique Barreto (Site 1000)

- Data collection and reporting for primary endpoint did not meet minimum standards; subject visit schedule and ECG data collection did not follow protocol

Reviewer's Comment: Dr. Barreto enrolled 10 subjects in Study 051-354. Site 1000 was chosen for a DSI audit.

- (Site 0902)
  - Lack of sufficient oversight; data collection and reporting for primary endpoint did not meet minimum standards; dates of investigator signature for ECG were not accurate or were false

Reviewer's Comment: Dr. enrolled 8 subjects in Study 051-354.'

- (Site 0685)
  - Data collection and reporting for primary endpoint did not meet minimum standards

Reviewer's Comment: Dr. enrolled 8 subjects in Study 051-354.

- (0953)
  - Data collection and reporting methods for primary endpoint did not meet minimum standards; one staff member not qualified and misrepresented her qualifications to the investigator; source documents for X-rays and medical history were not provided for verification.
  - Two subjects (09530165 and 09530166) were excluded from main analysis because they had their clinical procedures performed by the non-qualified staff member.

Reviewer's Comment: Dr. enrolled 7 subjects in Study 051-354.

Reviewer's Comment: A total of 33 subjects (19% study population) were enrolled in sites where data collection and reporting methods for the primary endpoint did not meet minimum standards. This could potentially affect the outcome of the study.

One amendment was made to the original protocol on December 9, 2002. The amendment provided for many clarifications of the protocol. One notable change was the addition of the Pediatric asthma quality of life questionnaire was added to the quality of life assessments at Visit 2 and Visit 6 [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 79-80].

Pertinent changes to the analyses plan prior to unblinding of the data included [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 81-82]:

- Calculations of FEV1 AUC, time to response, and duration of response were revised to reference 360 minutes rather than 480 minutes
- If no 15% response occurred, the duration was defined as zero
- Subgroup analyses by age, steroid use, asthma controlled medication use group were added
- Summary of paradoxical bronchoconstriction added
- Summary of time to first use of rescue medication during spirometry added
- Summaries by subgroup for asthma events and asthma attacks and summary of duration of asthma AEs and asthma attacks added

- Two new subgroups, spacer users and spacer nonusers were analyzed for demographics, baseline FEV1 data, selected efficacy endpoints, and selected safety measures.
    - Spacer users – all subjects who used a spacer when administering double-blind medication during at least half of the in-clinic dosing visits of interest (Visits 2, 4, and 6).
    - Spacer nonusers – all subjects who did not use a spacer when administering double-blind medication during at least half of the in-clinic dosing visits of interest (Visits 2, 4, and 6).

The following is a list of the pertinent changes to the analyses plan after data availability [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 82-83]:

- One subject excluded from spacer/spacer nonuser analyses (unknown use)
- Subgroup summaries of steroid use and asthma controller medication use were added
- "Modified ITT" population defined due to QA audit of study sites
    - Two subjects excluded from analysis due to data being obtained by non-qualified personnel
    - Subjects excluded if one FEV1 value >200% predicted
- Analyses of primary and key secondary endpoints performed on ITT population and Modified ITT population
- Additional analyses performed on a "compliant site population," which excluded the 4 noncompliant sites discovered during the QA audit (1000, 0902, 0953, 0685) for the primary endpoint and key secondary endpoints.

10.1.3.2 Results

10.1.3.2.1 Subject Disposition

The disposition of the subjects enrolled in Study 051-354 is summarized in Table 72. Of the 173 subjects who enrolled at Visit 1, 150 subjects were randomized at Visit 2. Of the 150 subjects randomized to one of the three double-blind treatment groups, 134 (89.3%) completed the study, while 16 (10.7%) terminated early. The percentage of subjects who discontinued was similar in the levalbuterol HFA and placebo group, while the percentage of subjects who discontinued was slightly lower in the racemic albuterol group. The primary reasons for discontinuation were AEs or protocol violations. The percentage of subjects who discontinued due to AEs was less in the levalbuterol HFA treatment group than in the placebo group. Asthma exacerbation was the AE leading to discontinuation in every treatment group.

Table 72 Subject Disposition for Study 051-354

	Levalbuterol HFA 90 mcg	Racemic Albuterol HFA 180mcg	Placebo HFA-134a
Enrolled (N=173)			
Randomized (N=150)*	76	39	35
Completed (N=134)	67 (88.2%)	36 (92.3%)	31 (88.6%)
Discontinued (N=16)	9 (11.8%)	3 (7.7%)	4 (11.4%)
AE (N=5)	1 (1.3%)	1 (2.6%)	3 (8.6%)
Protocol Violation (N=6)	4 (5.3%)	1 (2.6%)	1 (2.9%)
Voluntary withdrawal (N=1)	1 (1.3%)	0	0
Lost to follow-up (N=1)	1 (1.3%)	0	0
Did not meet entry criteria (N=1)	0	1 (2.6%)	0
Other (N=2)	2 (2.6%)	0	0

* Randomized in 2:1:1 ratio
Source: N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 85.

The Applicant summarized the protocol violations for each treatment group in Study 051-354. Sixty to 77% of the subjects in each treatment group had a least one protocol violation. The most common protocol violation was the use of a disallowed medication, which occurred in approximately 43-59% of the subjects in each treatment group. The most common disallowed medications were short-acting beta agonists, antihistamines, and corticosteroids. The Applicant reported that of the subjects who had a protocol violation due to use of short-acting beta agonists, most resulted from either the restart of the medication at Visit 6 or insufficient wash-out prior to Visit 1. The Applicant reports that most of these subjects did not report using these agents during the study period [N21730\N_000\2004-05-11\clinstat\pediatric asthma\051-354.pdf,p 88].

The use of antihistamines during the study period was attributed mostly to subjects who used antihistamines within 48 hours of study visit. According to the Applicant, most of the subjects had used antihistamines on a chronic basis. The use of corticosteroids during the study was attributed mostly to the dose not being stable for 4 weeks prior to study entry or total daily dosage too high. The Applicant states this was in part due to a change from a corticosteroid/beta agonist combination to a corticosteroid only prior to Visit 1 [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 88].

Reviewer's Comment: As in Studies 051-353 and 051-355, a large proportion of study subjects were documented to have used a disallowed medication. Unlike Study 051-353 and 051-355, the percentage of subjects with a protocol violation due to beta adrenergic agonist use was less in Study 051-354 (13%, 23%, and 17% in the levalbuterol HFA, racemic albuterol HFA and placebo group, respectively).

1.1.1.1.1 Demographics and Baseline Characteristics

Table 73 below summarizes the demographics and baseline characteristics of the subjects who were randomized into one of the treatment groups for Study 051-354.

Table 73 Demographics and Baseline Characteristics in Study 051-354 (ITT population)

	Levalbuterol HFA 90mcg n = 76	Racemic Albuterol HFA 180mcg n = 39	Placebo HFA-134a n = 35
Gender			
Male	49 (64.5%)	23 (59.0%)	22 (62.9%)
Female	27 (35.5%)	16 (41.0%)	13 (37.1%)
Age			
Mean	8.3	8.6	8.1
Range	4-11	4-11	4-11
Race			
Caucasian	36 (47.4%)	24 (61.5%)	17 (48.6%)
Black	28 (36.8%)	9 (23.1%)	11 (31.4%)
Hispanic	11 (14.5%)	5 (12.8%)	6 (17.1%)
Asian	1 (1.3%)	1 (2.6%)	1 (2.9%)
FEV_1 Screening (L)			
Mean	1.32	1.41	1.30
Range	0.32-2.53	0.71-2.41	0.78-2.16
FEV_1 Percent Predicted			
Mean	68.9	70.9	69.7
Range	42-84	53-81	52-80

Source [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 91.

Demographic and baseline characteristics for the randomized population (ITT population) were similar among the treatment groups. The mean age of subjects was approximately 8 years. More than half the subjects in each treatment group were male. There was a higher percentage of blacks in the levalbuterol HFA treatment group compared to the racemic albuterol HFA and placebo groups. Although not shown in the above table, there were slightly more steroid users in the levalbuterol HFA treatment group, 55% versus 49% and 37% in the racemic albuterol HFA and placebo treatment groups, respectively. Less than 15% of the subjects used a spacer [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 92].

10.1.3.2.2 Efficacy

As mentioned above, the ITT population consisted of all randomized subjects who received at least one dose of double-blind study medication. Because the Applicant's QA audit determined that an unqualified staff member performed PFTs on two subjects, the Applicant created the "Modified ITT" population. The Modified ITT population was the ITT population minus the two subjects who had PFTs collected by an unqualified staff member and minus three subjects who had clinically implausible spirometry values (FEV1 value >200%). The Modified ITT population became the primary analyses population; however, the Applicant did perform analyses on the ITT population for the primary and key secondary endpoints. Safety analyses were performed using the ITT population [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 89-90].

Reviewer's Comment: The use of a Modified ITT population was not pre-specified. However, the Applicant also performed analyses using the ITT population for the primary endpoint and key secondary endpoints.

10.1.3.2.2.1 Primary

The primary efficacy parameter was the peak percent change FEV_1 from visit predose averaged over the double-blind period. Pulmonary function testing was performed at baseline and every 2 weeks during the treatment period. Serial spirometry was performed at Week 0 (Visit 2), Week 2 (Visit 4), and Week 4 (Visit 6). Serial spirometry measurements included: pre-dose, immediately post-dose, 15-minute intervals for 2 hours post-dose, then hourly until 4 or 6 hours post dose.

As stated above, the Applicant performed analyses on the primary efficacy parameter using both the ITT and Modified ITT population. The Applicant performed the analysis using an ANCOVA model with effects for treatment, investigator, and baseline FEV_1 (study baseline or visit predose). Table 74 is a summary of the peak percent change in FEV_1 averaged over the double-blind period (primary endpoint) and the peak percent change in FEV_1 at Visit 2, Visit 4, and Visit 6 (secondary endpoints) for each treatment group in Study 051-354 [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 94-95].

Table 74 Peak Percent Change FEV_1 from Visit Pre-dose for Study 051-354 Modified ITT Population

Peak Percent Change in FEV_1	Levalbuterol HFA 90mcg n = 74	Racemic Albuterol HFA 180mcg n = 38	Placebo HFA-134a n = 33
Averaged over Double-Blind Period[1] (Primary EP)			
LS Mean (SE)	25.63 (1.34)	21.81 (1.83)	16.75 (1.94)
Pairwise p-value vs. Placebo[2]	<0.001	0.057	
Pairwise p-value vs. Racemic Albuterol[2]	0.086		
Visit 2[3]			
LS Mean (SE)	33.14 (2.51)	29.56 (3.43)	17.77 (3.64)
Pairwise p-value vs. Placebo[4]	<0.001	0.019	
Pairwise p-value vs. Racemic Albuterol[4]	0.390		
Visit 4[3]			
LS Mean (SE)	20.52 (1.92)	18.46 (2.62)	20.05 (2.71)
Pairwise p-value vs. Placebo[4]	0.886	0.671	
Pairwise p-value vs. Racemic Albuterol[4]	0.519		
Visit 6[3]			
LS Mean (SE)	22.41 (1.53)	19.25 (2.02)	11.30 (2.19)
Pairwise p-value vs. Placebo[4]	<0.001	0.009	
Pairwise p-value vs. Racemic Albuterol[4]	0.208		

1 Peak percent change in FEV1 from visit predose averaged over the double-blind period was calculated by first taking the difference in peak FEV1 recorded during the serial spirometry day (Visits 2, 4, and 6) and the visit predose FEV1. This result was then divided by visit predose FEV1 and multiplied by 100. The three peak percent change values were then averaged.

2 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.

3 Peak percent change in FEV1 from visit predose refers to the maximum FEV1 recorded during the visit minus the FEV1 observed at visit predose, divided by the visit predose FEV1 and multiplied by 100.

4 Pairwise tests of treatment effect were conducted using ANCOVA with treatment, investigator effects, and visit predose FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.

Source: [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 95]

Levalbuterol HFA was statistically superior to placebo based upon the primary endpoint. The mean peak percent increase in FEV_1 in the levalbuterol HFA treatment group was 25.6%. Levalbuterol HFA was also statistically superior to placebo for the peak percent change in FEV_1 at Visits 2 and 6. Racemic albuterol HFA was statistically superior to placebo at Visit 2 and Visit 6, but not averaged over the double blind period. There was no statistical difference between levalbuterol HFA and racemic albuterol HFA for the primary endpoint.
Reviewer's Comment: The lack of a statistically significant difference in the racemic albuterol HFA and placebo group may be due to the small number of subjects.

The peak percent change in FEV1 was greatest for all three treatment groups at Visit 2 and declined at subsequent visits. The reason for the decrease in response as the study progressed appears to be primarily explained by an increase in visit predose FEV1. A review of the peak percent change in FEV1 from study baseline at Visit 2, 4, and 6 showed that the mean peak percent change FEV1 did not change significantly from Visit 2 to Visit 6, which suggests that the visit predose FEV1 increased as the study progressed. The LS mean increase in %FEV1 in the levalbuterol HFA , racemic albuterol HFA, and placebo group from study baseline to predose Visit 6 was 8.96%, 9.69%, and 8.18%, respectively [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 257-260 & 101].

Reviewer's Comment: The Division's statistician also analyzed the primary endpoint without the data from the four study sites (33 subjects)found to be noncompliant with GCP. Without sites 1000, 0902, 1685, 0953, levalbuterol HFA was still statistically superior to placebo for the primary endpoint. Using the ITT population, there is no statistical difference between any of the treatment groups for the primary endpoint. The Modified ITT population excludes 3 subjects with FEV1>200%. Two of the subjects were in the placebo group and one was in the racemic albuterol HFA group. Because of the small number of subjects, including those subjects with such large FEV1 values affects the results of the study. That being said, the exclusion of the data from those subjects is reasonable.

10.1.3.2.2.2 Secondary

Secondary efficacy parameters included the following [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 855]:

- Percent change in FEV1 from study baseline
- Peak change in FEV_1 from predose baseline at each visit
- Peak percent of predicted FEV_1
- AUC FEV1
- Peak change and percent change in $FEF_{25-75\%}$ from predose baseline
- Asthma Symptom Scores
- Peak expiratory flow rate
- Pediatric Asthma Quality of Life Questionnaire and SF-36 Health
- Global Evaluation as measured by the subject and physician at end of treatment.

10.1.3.2.2.2.1 Spirometry

Table 75 summarizes spirometry secondary efficacy endpoints for Study 051-354.

Table 75 Additional Spirometry Endpoints for Study 051-354
(Modified ITT Population)

	Levalbuterol HFA 90mcg n = 74	Racemic Albuterol HFA 180mcg n = 38	Placebo HFA-134a n = 33
AUC for FEV_1 Percent Change from visit predose[1], (DBAvg)			
LS Mean (SE) %-hr	90.33 (8.51)	84.35 (11.62)	42.73 (12.34)
Pairwise p-value vs. Placebo[2]	0.001	0.010	
Pairwise p-value vs. Racemic Albuterol[2]	0.672		
AUC for FEV_1 Percent Change[1] from visit predose, (Visit 2)			
LS Mean (SE) %-hr	116.15 (12.86)	110.23 (17.55)	50.73 (18.65)
Pairwise p-value vs. Placebo[2]	0.004	0.02	
Pairwise p-value vs. Racemic Albuterol[2]	0.781		
AUC for FEV_1 Percent Change[1] from visit predose, (Visit 6)			
LS Mean (SE) %-hr	60.34 (7.18)	56.28 (9.52)	25.90 (10.31)
Pairwise p-value vs. Placebo[2]	0.007	0.032	
Pairwise p-value vs. Racemic Albuterol[2]	0.730		
Peak Change FEF 25-75% from visit predose (DB Avg)			
LS Mean (SE)	0.657 (0.035)	0.661 (0.049)	0.395 (0.051)
Pairwise p-value vs. Placebo[4]	<0.001	<0.001	
Pairwise p-value vs. Racemic Albuterol[4]	0.945		
Peak % Change FEF 25-75% from visit predose (DB Avg)			
LS Mean (SE)	63.06 (3.30)	61.28 (4.57)	39.41 (4.81)
Pairwise p-value vs. Placebo[4]	<0.001	0.001	
Pairwise p-value vs. Racemic Albuterol[4]	0.748		
Peak % Predicted FEV_1 (DB Avg)			
LS Mean (SE)	92.08 (1.41)	90.11 (1.91)	85.64 (2.04)
Pairwise p-value vs. Placebo	0.01	0.396	
Pairwise p-value vs. Racemic Albuterol	0.109		
Visit 2 Peak % Predicted FEV_1[6]			
LS Mean (SE)	93.37 (1.88)	90.66 (2.55)	83.45 (2.73)
Pairwise p-value vs. Placebo	0.003	0.385	
Pairwise p-value vs. Racemic Albuterol	0.053		
Visit 6 Peak % Predicted FEV_1[6]			
LS Mean (SE)	92.20 (1.66)	90.44 (2.19)	85.27 (2.39)
Pairwise p-value vs. Placebo	0.019	0.517	
Pairwise p-value vs. Racemic Albuterol	0.113		

1 Area under the FEV1 percent change curve averaged over the double-blind period was calculated by first applying the linear trapezoidal method to the FEV1 percent change from baseline (visit predose or study baseline) obtained during Visits 2 and 6. These two AUC values were then averaged.

2 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEV1 as the covariate. The tests were performed using a one degree of freedom contrast.

3 Peak change in FEF 25-75% from visit pre-dose averaged over the double-blind period was calculated by first taking the difference between the peak FEF 25-75% recorded during the serial spirometry day (Visits, 2, 4 and 6) and the visit pre-dose FEF 25-75%. The three peak changes from visit pre-dose values were then averaged.

4 Pairwise tests of treatment effect were conducted using ANCOVA with treatment and investigator effects and study baseline FEF 25-75% as the covariate. The tests were performed using a one degree of freedom contrast.

5 Peak percent change in FEF 25-75% from visit pre-dose averaged over the double-blind period was calculated by first taking the difference between the peak FEF 25-75% recorded during the serial spirometry day (Visits, 2, 4 and 6) and the visit pre-dose FEF 25-75%. This result was then divided by visit pre-dose FEF 25-75% and multiplied by 100. The three peak percent changes from visit pre-dose values were then averaged

6 Peak percent of predicted FEV1 was calculated by dividing the peak FEV1 recorded during a serial spirometry day (Visits 2, 4, and 6) by the predicted FEV1 determined at Screening (Visit 1), and then multiplying by 100. For the double-blind average, the three resulting peak percent of predicted values were averaged.

Source: [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 96, 97, 298, 303, 305, 474, 478]

As shown in Table 75, the peak percent change in FEF 25-75% and FEV_1 percent change AUC, averaged over the double-blind period were significantly greater for levalbuterol HFA and racemic albuterol HFA compared to placebo. The levalbuterol HFA group and racemic albuterol HFA group showed similar results for peak percent change in FEF 25-75% and FEV_1 percent change AUC. As noted with the peak FEV1 percent change, the FEV1 percent change AUC declined from Visit 2 to Visit 6 for both levalbuterol HFA and racemic albuterol HFA. The peak percent of predicted FEV1 was significantly greater for levalbuterol HFA compared to placebo, but was not significantly greater for racemic albuterol HFA compared to placebo. The mean peak percent predicted FEV1 was similar between levalbuterol HFA and racemic albuterol HFA at each visit [N21730\N_000\2004-05-11\ clinstat\pediatricasthma\051-354.pdf, p 103].
Reviewer's Comment: The reason that a statistical difference between racemic albuterol HFA and placebo was not noted on some endpoints may be the small number of subjects in those treatment groups.

The Applicant determined the number of responders, which were defined as subjects experiencing ≥ 15% improvement in FEV1 from visit predose. The number of responders was greater in the levalbuterol HFA and racemic albuterol HFA treatment groups when compared to the placebo group. The number of responders was similar between the levalbuterol HFA and racemic albuterol HFA treatment groups except Visit 6 where the levalbuterol HFA treatment group had a higher percentage of subjects responding than racemic albuterol HFA group. The percent of responders decreased as the study progressed, which the Applicant attributed to the increase in predose FEV1 over time [N21730\N_000\2004-05-11\ clinstat\pediatricasthma\051-354.pdf, p 106].

Table 76 Responders in Study 051-354 (Modified ITT Population)

	Levalbuterol HFA 90mcg n = 74	Racemic Albuterol HFA 180mcg n = 38	Placebo HFA-134a n = 33
Visit 2	61 (82%)	31 (82%)	17 (52%)
Visit 4	38 (54%)	19 (53%)	13 (39%)
Visit 6	43 (66%)	19 (54%)	8 (28%)

Source: [N21730\N_000\2004-05-11\clinstat\051-354.pdf, p 368]

Time to peak change in FEV_1 from visit predose was analyzed for Visits 2, 4, and 6 and was similar between levalbuterol HFA and racemic albuterol HFA. The median time to peak change for levalbuterol HFA ranged from 61-78 minutes, which was similar to the results for racemic albuterol HFA [N21730\N_000\2004-05-11\pediatricasthma\051-354.pdf, p 297, 102]. The median times to 15% increase FEV1 were significantly shorter for the active treatment groups compared to placebo and were 4.5 and 4.9 minutes for levalbuterol HFA and racemic albuterol HFA, respectively at Visit 2 and 40.1 and 102.1 minutes, respectively at Visit 6. The Applicant attributed the increase in median time at Visit 6 to an increase in predose FEV1 [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 107].
Reviewer's Comment: The median time to 15% increase in FEV1 was much longer in the racemic albuterol treatment group than the levalbuterol HFA group at Visit 6.

The duration of response was defined as the amount of time during which there was a ≥ 15% increase in FEV1 relative to the visit predose value. The median duration of 15% response was 186 minutes with levalbuterol HFA, 261 minutes with racemic albuterol HFA and 70 minutes with placebo at Visit 2 and was 76, 103, and 54 minutes, respectively at Visit 6 [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 394].
Reviewer's Comment: The duration of 15% increase in FEV1 response was much longer in the racemic albuterol HFA group.

10.1.3.2.2.2.2 Peak Expiratory Flow (PEF)

The Applicant reported the results of the PEF measured at the clinic visits. PEF was measured at each clinic visit pre-dose and 15 minutes post-dose. The highest of 3 maneuvers at each time period was recorded. The percent change in PEF was higher in the two active treatment groups compared to placebo [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 109].

10.1.3.2.2.2.3 Pediatric Asthma Questionnaire Symptom Scores

Asthma symptom scores were recorded by the parent/guardian throughout the study. There were lower total asthma symptom scores in the active groups, but no difference between the active groups [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 499-506].

10.1.3.2.2.2.4 Pediatric Asthma Quality of Life

The Pediatric Asthma Quality of Life Questionnaire (AQLQ) was administered at Visit 2 (Week 0) and Visit 6 (Week 4). Domains were scored on a scale of 1 to 7, in which higher scores indicate a higher quality of life. For all treatment groups, the mean scores increased from Visit 2 to Visit 6 except the Emotional Function Score of racemic albuterol HFA treated subjects decreased from Visit 2 to Visit 6 from 5.74 to 5.69. Although the Applicant did not perform a statistical comparison between the groups, there appeared to be no significant differences [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 507-510].

10.1.3.2.2.2.5 Global Evaluation

At Visit 6 (Week 4), the physician completed a global assessment of asthma symptoms based on the overall study period. Overall from the beginning of the study, investigators rated the subjects' symptoms improved 65-67% in all treatment groups. In addition, the parent/guardian evaluated the child's symptoms and rated symptoms improved to some degree in 71-80% of the subjects in all treatment groups. A statistical comparison was not performed [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 110].

10.1.3.2.2.2.6 Spacer Use

Spacer user/nonuser subgroup analysis was performed. Spacer users consisted of all subjects who used a spacer when administering double-blind study medication during the in-clinic dosing visit. Because only a few subjects utilized spacers (11 in levalbuterol, 4 in racemic albuterol, 5 in placebo) during the study, the subgroup analysis is likely not meaningful. However, there does not appear to be a significant difference between spacer users and non spacer users for the primary endpoint.

10.1.3.2.3 Pharmacokinetic Endpoint Outcomes

PK samples for (R)- and (S)-albuterol were collected on a subset of subjects. Of the subjects who had PK samples obtained predose at Visit 2, over half had detectable (R)-albuterol levels and many had measurable (S)-albuterol levels [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 110].

The Applicant provided the mean and median (R) and (S)-albuterol concentrations measured at Visit 2 and Visit 6 for each treatment group. (S)-albuterol was detectable in the levalbuterol HFA treatment group, but was measured at much higher levels in the racemic albuterol HFA treatment group. Levels of (R)-albuterol were higher in the racemic albuterol HFA group than in the levalbuterol HFA treatment group. Median and mean (R) and (S)-albuterol levels increased at Visit 6, following multiple dose administration. In general, the plasma concentrations of (R) and (S)-albuterol were highly variable [N21730\N_000\2004-05-11\clinstat\pediatricasthma051-354.pdf, p 119-120].

The Applicant presented two scatterplots comparing the (R)-albuterol levels and the serum potassium and glucose. There appeared to be little change in the potassium and glucose levels across the range of observed (R)-albuterol levels [N21730\N_000\2004-05-11\clinstat\pediatricasthma051-354.pdf, p 121].

10.1.3.2.4 Safety

The safety findings from this study, along with the safety data from the other clinical studies, will be reviewed in depth in the Integrated Review of Safety section of this review. A brief summary of the safety findings from this study follows. Safety analyses were performed on the ITT population.

The average number of days of exposure was 27 days for the active treatment groups. The mean daily dose of levalbuterol was 350 mcg versus 699 mcg in the racemic albuterol group. [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 123].
Reviewer's Comment : Because the levalbuterol group was dosed 90mcg QID (360mcg daily) and the racemic albuterol groups was dosed 180mcg QID (720mcg daily), the mean daily dose suggests a high level of compliance.

10.1.3.2.4.1 Adverse Events

Adverse events were reported in 40-50% of the subjects in each treatment group. In general, a larger percentage of subjects reported AEs in the placebo and racemic albuterol HFA groups than in the levalbuterol HFA group. The incidence of asthma adverse events was less in the levalbuterol HFA group compared to the other treatment groups. There were no deaths or SAEs. Table 77 displays a summary of adverse events reported in ≥ 2% of subjects in each of the treatment groups, as reported by the Applicant [N21730\N_000\2004-05-11\clinstat\pediatricasthma051-354.pdf, p 124-125].

Table 77 Summary of Adverse Events (AEs) Reported in ≥ 5% Subjects in Study 051-354
ITT Population During the Double-Blind Period

	Levalbuterol HFA 90mcg (n=76)	Racemic Albuterol HFA 180mcg (n=39)	Placebo HFA-134a (n=35)
Any adverse event	33 (43.4)	22 (56.4)	18 (51.4)
Discontinued due to AE	1 (1.3)	1 (2.6)	3(8.6)
Serious adverse event	0	0	0
Asthma adverse events	**8 (10.5)**	**5 (12.8)**	**5 (14.3)**
Vomiting	8 (10.5)	3 (7.7)	2 (5.7)
Asthma	**8 (10.5)**	**5 (12.8)**	**5 (14.3)**
Asthma Attack*	**7 (9.2)**	**4 (10.3)**	**4 (11.4)**
Accidental Injury	7 (9.2)	4 (10.3)	2 (5.7)
Fever	6 (7.9)	2 (5.1)	3 (8.6)
Headache	5 (6.6)	3 (7.7)	5 (14.3)
Pharyngitis	5 (6.6)	5 (12.8)	2 (5.7)
Cough increased	4 (5.3)	2 (5.1)	2 (5.7)
Viral infection	3 (3.9)	8 (20.5)	3 (8.6)
Diarrhea	3 (3.9)	1 (2.6)	2 (5.7)
Abdominal Pain	2 (2.6)	1 (2.6)	2 (5.7)
Pain	2 (2.6)	2 (5.1)	2 (5.7)
Rhinitis	1 (1.3)	2 (5.1)	3 (8.6)
Epistaxis	0	1 (2.6)	2 (5.7)
Ear pain	0	2 (5.1)	2 (5.7)

* An asthma attack was a subcategory of asthma AES that required one of the following four criteria: 1)hospitalization; 2) an ER visit; 3) intervention with an oral burst or parenteral corticosteroids; or 4) an unscheduled clinic visit to treat acute asthma symptoms.
Source: [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 125].

Headaches, asthma, vomiting and viral infection were the most common AEs. Asthma was the most commonly reported AE, with the highest incidence in the placebo group. AEs more common in the levalbuterol HFA group were vomiting and accidental injury. The racemic albuterol group HFA had a higher incidence of viral infections than the other two treatment groups.

Eighteen subjects had an asthma AE during the double blind treatment period. Fifteen of these subjects met the criteria for an asthma attack, which required one of the following four criteria: 1)hospitalization; 2) an ER visit; 3) intervention with an oral burst or parenteral corticosteroids; or 4) an unscheduled clinic visit to treat acute asthma symptoms. The incidence of asthma attacks was similar less in the levalbuterol HFA group than in the racemic albuterol HFA or placebo group.

The Applicant analyzed potential beta mediated adverse events, such as chest pain, palpitations, tachycardia, dyspepsia, nausea, leg cramps, dizziness, hypertension, insomnia, tremor, QT prolongation and nervousness. Overall potential beta mediated side effects were infrequent and slightly less in the levalbuterol HFA group (1.3%) than in the racemic albuterol HFA group (2.6%) and placebo group (2.9%). The only potential beta mediated adverse events was chest pain/tightness [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 124, 129].

Five subjects had AEs that led to discontinuation of treatment during the double-blind period: 1 (1.3%), 1 (2.6%), and 3 (8.6%) in the levalbuterol HFA, racemic albuterol HFA, and placebo groups, respectively. The most common AE leading to discontinuation was asthma alone or in combination with another respiratory system event (bronchitis, rhinitis) [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 132].

10.1.3.2.4.2 Laboratory Evaluations

Serum potassium and glucose levels were measured predose and post-dose (1 hour) at Visit 2 and Visit 6. Minimal changes in potassium and glucose were noted during the treatment period. Then mean change in potassium at Visit 6 was -0.16, -0.19, and -0.05 mEq/L in the levalbuterol HFA, racemic albuterol HFA, and placebo groups, respectively. The largest serum potassium decrease was -1.9 mEq/L in the levalbuterol HFA group. The mean change in glucose at Visit 6 was 4.95, 7.55, and -2.69 mg/dL in the levalbuterol HFA, racemic albuterol HFA, and placebo groups, respectively. The Applicant analyzed the change in potassium and glucose by shift tables. Only one subject in the racemic albuterol HFA group shifted from normal to low potassium value. None were noted in the levalbuterol HFA and placebo groups. No subjects shifted from normal to high glucose. However 3.9%, 5.1%, and 11.4% of the subjects in the levalbuterol HFA, racemic albuterol HFA, and placebo groups, respectively shifted from normal to a low glucose value [N21730\N_000\2004-05-11\clinstatpediatricasthma\051-354.pdf, p 154].

There were no significant changes from Visit 1 to Visit 6 for the remaining chemistry and hematology parameters. Only one subject in the levalbuterol HFA group experience an elevation in ALT and AST during the treatment period. A 7 year old male had an increase in ALT from 39 to 79 U/L and AST from 40 to 72 U/L [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 154-155].

10.1.3.2.4.3 Vital Signs and Physical Examinations

Vital signs were collected pre-dose and at 20 minute intervals for the first hour post-dose for Visits 2 through 6. No significant change in mean heart rate, blood pressure or physical examination was noted among the treatment groups during the double blind period. More subjects experienced an increase in heart rate > 20 bpm in the levalbuterol group than in the other two treatment groups. However, the levalbuterol HFA group had a smaller percentage of subjects with increase in SBP>20mmHg and DBP >10mmHg [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 156-157, 194].

Table 78 Summary of Changes in Heart Rate and Blood Pressure in Study 051-354
ITT Population During the Double-Blind Period

	Levalbuterol HFA 90mcg (n=76)	Racemic Albuterol HFA 180mcg (n=39)	Placebo HFA-134a (n=35)
Subjects with ↑HR>20bpm	24 (32%)	9 (23%)	7 (20%)
Subjects with ↑ SBP >20mm Hg	9 (11%)	8 (21%)	5 (14%)
Subjects with ↑ DBP >10mm Hg	28 (37%)	17 (44%)	19 (54%)

Source: [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 156-157].

10.1.3.2.4.4 Electrocardiograms

ECGs were collected predose and 30 minutes post dose during Visits 2 through 6. All ECGs were overread at a central laboratory. No significant change in mean heart rate was noted among the treatment groups. No consistent significant change in QT_{c-F} was noted among the treatment groups. The largest mean increase in the QT_{c-F} was in the levalbuterol HFA group at Visit 2 with an increase of 4.0ms, although the placebo group showed at mean increase of 3.0ms. Prolongation of the QT_{c-F} interval >450 ms occurred in 0%, 5.1%, and 2.9% of subjects in the levalbuterol HFA, racemic albuterol HFA, and placebo treatment groups, respectively. The percentage of subjects with a change in the QT_{c-F} of 30-60ms was 6.6%, 12.8%, and 2.9% in the levalbuterol HFA, racemic albuterol HFA, and placebo treatment groups, respectively. No subjects experienced a change in the QT_{c-F} of >60ms from visit predose to post-dose or had a QT_{c-F} >500ms. Two subjects with abnormal ECGs in the single-blind run-in period withdrew from the study [N21730\N_000\2004-05-11\clinstat\pediatricasthma\51-354.pdf, p 158-162].
Reviewer's Comment: The levalbuterol HFA group had less subjects with QT_{c-F} >450ms than the other two treatment groups. The levalbuterol HFA group had a lower percentage of subjects with QT_{c-F} change 30-60ms than the racemic albuterol HFA group.

10.1.3.2.4.5 Rescue Medication, Paradoxical Bronchoconstriction

Subjects in the active treatment groups demonstrated a greater decrease in rescue medication use (when compared to the single-blind run-in period) compared to the placebo group. The largest decreases in rescue medication use were noted in the last two weeks of the study [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 164-165].

Paradoxical bronchospasm was defined as a ≥ 15% decrease in FEV1 within one hour of clinic dosing. During the serial spirometry the percent of subjects with paradoxical bronchoconstriction at any time during the double-blind period was 10.8%, 7.9%, and 9.1% for the levalbuterol HFA, racemic albuterol HFA, and placebo treatment groups, respectively. No subject required rescue medication. The Applicant indicated some cases of paradoxical bronchospasm may in part be due to poor-quality spirometry, as 53% of the events occurred at four sites in which data collection and reporting methods for spirometry did not meet minimum quality standards [N21730\N_000\2004-05-11\clinstat\pediatricasthma\051-354.pdf, p 166-167].

10.1.3.3 Discussion and Conclusions

10.1.3.3.1 Efficacy

Study 051-354 demonstrated that 90 mcg levalbuterol HFA was superior to placebo on the pre-specified primary efficacy endpoint: the peak percent change in FEV1 from visit predose averaged over the double-blind period. The mean peak percent change in FEV1 from visit predose average over the double-blind period was 25.63% in the levalbuterol HFA group versus 16.75% in the placebo group. Racemic albuterol HFA was also superior to placebo on the pre-specified primary efficacy endpoint.

Efficacy was supported by statistically significant improvements in the levalbuterol HFA group as compared to the placebo group in the following secondary endpoints:

- AUC for FEV1 percent change from visit predose averaged over the double-blind period
- Peak change and peak percent change in $FEF_{25-75\%}$ from visit predose.
- Peak percent predicted FEV_1 averaged over the double-blind period.

In general, none of the non-spirometric outcome variables demonstrated a statistically significant benefit in the levalbuterol HFA group. Significant treatment group differences were not observed for the PAQ, asthma quality of life questionnaire, modified CHQ, physician or subject global evaluation.

This study did not demonstrate that levalbuterol HFA was superior to racemic albuterol on the pre-specified primary endpoint, secondary spirometry endpoints, or quality of life scores. However, the levalbuterol HFA group demonstrated numerically higher values than racemic albuterol HFA for the primary endpoint and most secondary endpoints.

10.1.3.3.2 Safety

In Study 051-354, the rates of AEs were less in the levalbuterol HFA treatment group. Common AEs in the levalbuterol HFA treatment group were vomiting, asthma (including asthma attacks), and accidental injury. Although asthma was the most common AE overall, the incidence of asthma was less in the levalbuterol HFA treatment group than in the other two groups. A lower percentage of subjects in the levalbuterol HFA group discontinued treatment due to an adverse event. Levalbuterol HFA was not associated with significant changes in vital signs, laboratories, physical examination, or changes in ECG.

10.1.3.3.3 Pharmacokinetics

Some subjects in the levalbuterol HFA treatment group had measurable levels of (S)-albuterol during the study; however, (S)-albuterol concentrations were much higher in the racemic albuterol HFA treatment group. The levels of (R)-albuterol were much higher in the racemic albuterol group HFA compared to the levalbuterol HFA group. There was a large degree of inter-subject variability in (R) and (S)-albuterol concentrations.

10.1.4 Study 051-356

Study 051-356 is an ongoing, randomized, open-label, active-controlled, multicenter, parallel-group study evaluating the safety of 90 mcg levalbuterol HFA and 180mcg racemic albuterol HFA. The primary objective is to evaluate the safety of levalbuterol 90 mcg (45mcg per

actuation), as compared to racemic albuterol 180 mcg (90 mcg per actuation) during a 12-month period of chronic dosing of adolescent and adult subjects with asthma. A secondary objective is to assess device performance [N21730\N_000\2004-05-11\clinstat\other\051-356.pdf, p 8].

The study was conducted in subjects 12 years of age and older with asthma. Subjects completing studies 051-353 and 051-355 were eligible to participate (rollover subjects) and were randomized to treatment at Visit 1. New subjects (de novo) completed a one week placebo run in period and were randomized to treatment at Visit 2. All subjects were randomized in a 2:1 ratio to levalbuterol HFA MDI 90mcg (2 actuations, 45 mcg each) QID or racemic albuterol HFA MDI 180 mcg (2 actuations, 90 mcg each) QID for a duration of 12 months. Open label Pirbuterol (0.2mg per actuation) was used as rescue medication throughout the study. Subjects had 10 clinic visits throughout the study approximately every 8 weeks [N21730\N_000\2004-05-11\clinstat\other\051-356.pdf, p 9].

The Applicant estimates approximately 240 subjects will participate as rollover subjects. Subjects must have a baseline FEV1 $\geq$ 50% and $\leq$ 80% of predicted in addition to $\geq$ 12% reversibility of airflow. To account for attrition, up to 400 new subjects will need to be randomized to obtain 6 months of levalbuterol exposure data in at least 300 subjects and 12 months of levalbuterol exposure in at least 100 subjects. Therefore, the Applicant estimates a total of 650 subjects will be needed for randomization [N21730\N_000\2004-05-11\clinstat\other\051-356.pdf, p 10].

10.1.4.1.1 Materials

Subjects were randomized to the following two treatment groups for Study 051-356:

- Levalbuterol HFA MDI 90mcg (2 actuations, 45 mcg each)
- Racemic Albuterol HFA MDI 180 mcg (2 actuations, 90 mcg each).

All subjects were provided a supply of Pirbuterol to be used as needed for rescue medication. Stable doses of cromolyn, nedocromil, inhaled corticosteroids ($\leq$ 600mcg of fluticasone/day or $\leq$ 800 mcg of beclomethasone), and leukotriene inhibitors were allowed during the study [N21730\N_000\2004-05-11\clinstat\other\051-356.pdf, p 11].

10.1.4.1.2 Amendments

Although several amendments to the protocol were made, the most relevant was Amendment 4, dated November 18, 2003, which was implemented after 338 subjects were randomized. Amendment 4 specified the following[N21730\N_000\2004-10-29\update\clinsum.pdf, p 16]:

- A secondary objective to assess device performance was added
- Daily diary card assessing difficulties with device were added
- A Call Center was established for subjects to contact when having difficulties with device
- Subject instructions for regular washing of the actuator were added.

10.1.4.2 Results

Study 051-356 is an ongoing safety study, which was initiated January 21, 2003. The Applicant submitted updated results of the study in the October 29, 2004, 120 Day Safety Update

submission. According to the Applicant, data submitted in the safety update is all the safety information available as of July 1, 2004. The interim study results are as follows.

10.1.4.2.1 Subject Disposition

As shown below, 547 subjects have been enrolled in Study 051-356 as of July 1, 2004. Almost half the subjects enrolled have discontinued the study. A similar percentage of subjects discontinued due to AEs from the levalbuterol HFA (7.4%) and racemic albuterol HFA (7.6%) treatment groups.

Table 79 Study 051-356 Subject Disposition as of July 1, 2004

	Treatment Group		Single-Blind Placebo Only*	Total
	Levalbuterol N (%)	Racemic Albuterol N (%)	N (%)	N (%)
No. Subjects Enrolled	297	157	93	547
No. Subjects Ongoing	156 (52.5)	95 (60.5)	4 (4.3)	255 (46.6)
No. Subjects Completed	30 (10.1)	13 (8.3)	---	43 (7.9)
No. Subjects Discontinued	111 (37.4)	49 (31.2)	89 (95.7)	249 (45.5)
No. Subjects Discontinued Due to AE	22 (7.4)	12 (7.6)	8 (8.6)	42 (7.7)

* Subjects received single-blind placebo only (i.e., they were not randomized to the active treatment groups).

Source: [N21730\N_000\2004-10-29\update\clinsum.pdf, p 18]

Reviewer's Comment: The Applicant has noted some inconsistencies in CRF for the reported termination due to AEs and AEs that led to discontinuation. The Applicant intends to query the sites to rectify the final database [N21730\N_000\2004-10-29\update\clinsum.pdf, p 17].

10.1.4.2.2 Baseline Characteristics and Demographics

Table 80 Demographics and Baseline Characteristics in Study 051-356 as of July 1, 2004		
	Levalbuterol HFA n = 297	**Racemic Albuterol HFA n = 157**
Gender		
Male	99 (33.3%)	53 (33.8%)
Female	198 (66.7%)	104 (66.2%)
Age		
Mean	39.5	41.1
Range	12-79	12-77
Race		
Caucasian	208 (70%)	115 (73%)
Black	57 (19%)	32 (20%)
Hispanic	23 (7.7%)	8 (5.1%)
Asian	8 (2.7%)	1 (0.6%)
Other	1 (0.3%)	1 (0.6%)
FEV_1 Percent Predicted		
Mean	68%	69%
Range	40-100%	19-92%

Source: [N21730\N_000\2004-10-29\update\clinsum.pdf, p 19]

Reviewer's Comment: The treatment groups are similar with respect to baseline characteristics.

10.1.4.2.3 Safety

There have been no deaths noted in Study 051-356 thus far. Twenty-two SAEs have been reported after randomization and there is a slightly higher incidence in the racemic albuterol HFA group (9/157, 5.7%) than in the racemic albuterol HFA group (13/297, 4.4%). SAEs in the levalbuterol HFA group included: regressive ischemic neurological disorder, malignant melanoma (2), appendicitis, umbilical hernia, asthma (4), BPH, breast carcinoma, allergic reaction/chest pain, and mood disorder. The incidence of asthma SAEs (1.3%) was similar in both treatment groups [N21730\N_000\2004-10-29\update\clinsum.pdf, p 25-28].

The incidence of discontinuation due to AEs post randomization is, thus far, similar between treatment groups. The AEs leading to discontinuation in the levalbuterol HFA group are: asthma (9), asthma/bronchitis, asthma/viral infection, asthma/cough increased, hypertension (2), headache/insomnia, depression, migraine, breast carcinoma, viral infection, pharyngitis, and urticaria. The most common AE leading to discontinuation in both treatment groups is asthma with 4% in the levalbuterol group and 3.8% in the racemic albuterol group [N21730\N_000\2004-10-29\update\clinsum.pdf, p 41].

Table 81 displays the most common AEs in Study 051-356. More AEs have been reported in the levalbuterol HFA group. The most common AEs in the levalbuterol group are asthma and viral infection, while rhinitis, asthma, and viral infection are the most common AEs in the racemic albuterol group.

Table 81 Summary of Post-Randomization Adverse Events (AEs) Reported in ≥ 2% Subjects in Study 051-356
As of July 1, 2004

	Levalbuterol HFA (n=297)	Racemic Albuterol HFA (n=157)
	n (%)	n (%)
Any adverse event	105 (35.4)	42 (26.8)
BODY AS A WHOLE	48 (16.2)	15 (9.6)
Headache	22 (7.4)	3 (1.9)
Accidental injury	11 (3.7)	0
Pain	10 (3.4)	5 (3.2)
Fever	6 (2.0)	3 (1.9)
Abdominal pain	4 (1.3)	4 (2.5)
Chest pain	3 (1.0)	4 (2.5)
RESPIRATORY SYSTEM	74 (24.9)	33 (21.0)
Viral infection	35 (11.8)	11 (7.0)
Asthma	34 (11.4)	11 (7.0)
Rhinitis	15 (5.1)	13 (8.3)
Pharyngitis	14 (4.7)	4 (2.5)
Sinusitis	11 (3.7)	7 (4.5)
Bronchitis	10 (3.4)	5 (3.2)
Cough increased	9 (3.0)	8 (5.1)
Dyspnea	1 (0.3)	4 (2.5)

Source: [N21730\N_000\2004-10-29\update\clinsum.pdf, p 21]

The incidence of asthma AES is more common in the levalbuterol group than in the racemic albuterol group. Table 82 displays more details regarding the asthma AEs in Study 051-356. The incidence of severe asthma AEs and discontinuation due to asthma AEs are similar in both treatment groups.

Table 82 Asthma AEs in Study 051-356
As of July 1, 2004

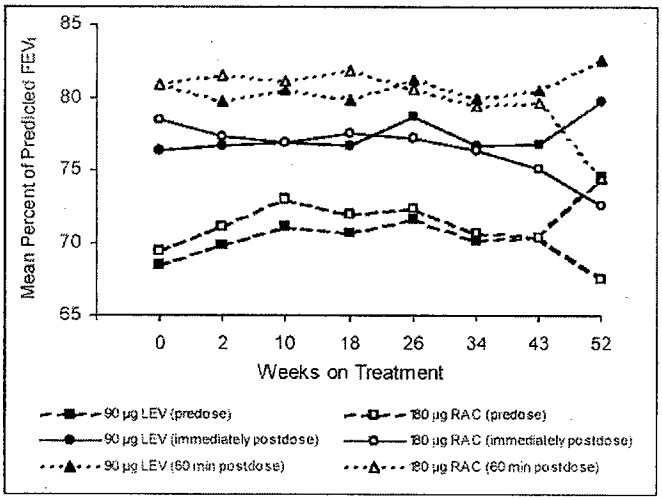
	Levalbuterol (n=297)	Racemic Albuterol (n=157)
	n (%)	n (%)
Any adverse event	105 (35.4)	42 (26.8)
Discontinued due to AE	22 (7.4)	12 (7.6)
Serious adverse event	13 (4.4)	9 (5.7)
Asthma adverse events	34 (11.4)	11 (7.0)
SAE – asthma	4 (1.3)	2 (1.3)
Asthma leading to discontinuation	12 (4.0)	6 (3.8)
Asthma AEs assessed as severe	10 (3.4)	6 (3.8)

Source: [N21730\N_000\2004-10-29\update\clinsum.pdf, p 22]

Tolerance

The Applicant assessed the interim data for evidence of tolerance over time. As shown in Figure 14, the percent predicted FEV1 does not clearly show a meaningful decline in the pre-dose or post-dose values for either levalbuterol HFA or racemic albuterol HFA. Thus, tolerance does not appear to be a problem.

Figure 14 Percent predicted FEV1 predose & post-dose at clinic visits during Study 051-356



Source: [N21730\N_000\2004-10-29\update\clinsum.pdf, p 56]

Reviewer's Comment: Although the racemic albuterol group shows a decrease in percent predicted FEV1 at the end of the treatment period, the Applicant points out that there are very few subjects tested at the end of the dosing period, thereby limiting the interpretation of the finding.

10.1.4.2.4 Device Performance

The Applicant had not collected device performance data in the Phase 2 and Phase 3 clinical studies. Thus, Study 051-356 was amended (Amendment 4) on November 18, 2003 to collect device performance data. At the time the study was amended, 338 subjects had been enrolled. The Division requested in vitro analysis of all the complaint devices. In vitro testing requested included: appearance, DCU, shot weight, particle size, water content, and microscopic evaluation.

Reviewer's Comment: Because the only prospective device performance data is in Study 051-356, there is no device performance data for children aged 4-11 years.

Reviewer's Comment: For Proventil HFA complaint devices, the Applicant observed the device and tested DCU, using the levalbuterol HFA method, which was not validated for use with Proventil HFA. No additional testing was done [N21730\N_000\2004-10-29\update\clinsum.pdf, p 64].

In addition to the in use device performance data, the Division requested the Applicant perform in vitro testing on at least 100 non-complaint devices that have 35-50 actuations remaining (near the end of life. Finally, for analysis of the device performance data, the Division requested the incidence of device-malfunction be calculated as follows [January 5, 2004, Teleconference Meeting Minutes]:

(# of complaint devices confirmed as malfunctioning by in-vitro analysis +
# of non-complaint devices confirmed as malfunction by in-vitro analysis)
Number of Devices Used by Patients

In addition to the prospective collection of device performance, the Applicant attempted to identify complaint devices prior to Amendment 4 and perform in vitro testing.

Complaint Devices

Of the post amendment devices used, over 85% reportedly were used for 3 weeks. As shown in Table 83, the number of prospectively collected complaint devices as of July 1, 2004, in Study 051-356 was 57, 39 of which were levalbuterol HFA. The complaint rate for levalbuterol post amendment 4 was 0.024 (39/1626) versus 0.017 (16/967) for racemic albuterol. Although the Applicant presented data on a few retrospectively collected complaint devices, the focus will be on the prospective complaint devices. Of the subjects in Study 051-356 who registered a device complaint, none reported a SAE, discontinued from the study, or experienced any AE that could be related to the device complaint, according to the Applicant.

Table 83 Number of Complaint Devices

	Devices used	Original NDA (March 12, 2004 cut-off date)	Additional Data from Safety Update (July 1, 2004 cut-off date)	Total
Prospective Study 051-356 Post Amend No. 4	1626 Lev 967 RA	16 Lev 7 RA 2 Pirb (rescue)	23 Lev 9 RA 0 Pirb	39 Lev 16 RA 2 Pirb
Retrospective Study 051-356 Pre Amend No. 4	1143 Lev 614 RA	5 Lev	0	5 Lev
Retrospective Studies 051-353, 051-354, 051-355	1793 Lev 818 RA 759 PBO	7 Lev 3 RA 3 PBO 6 rescue medication	0	7 Lev

Source: [N21730\N_000\2004-10-29\update\clinsum.pdf, p 71-90]

Reviewer's Comment: The number of complaint devices increases significantly after amendment number 4.

Table 84 displays the analyses of the complaint devices. By far the most common complaints are clogging related (85% of levalbuterol complaint devices, 81% or racemic albuterol complaint devices). Many complaint canisters were initially out of specifications on in vitro analysis; however, with proper cleaning the in vitro analyses were within specifications. Thus proper cleaning appears to be very important in maintaining a functional MDI. Three canisters with abnormal in vitro analysis all had no propellant; however, one of those devices was found by a retrospective collection of complaints. Thus two (5%) of the 39 prospectively collected levalbuterol complaint devices were found to be in vitro failures.

Table 84 Analyses of Complaint Devices

	Complaint Devices	Complaints	In vitro analysis
Prospective Study 051-356 Post Amend No. 4	39 Lev 16 RA 2 Pirb	Lev: 33 clog-related Lev: 5 empty/no spray RA: 13 clog-related RA: 3 no spray; defective, unknown Pirb: defective, broken	Lev: 8/33 clog related – initial DCU outside specs 4/33 clog related – within specs after wash 21/33 clog related – within specs as received Lev: 3/5 empty – c/w depleted canister **Lev: 1/5 empty – no propellant** **Lev: 1/5 no spray – propellant loss, crimp loose** RA: 4/13 clog related – initial DCU outside specs; ok w/ wash RA: 4/13 clog related – within specs RA: 4/13 clog related – within specs as received
Retrospective Study 051-356 Pre Amend No. 4	5 Lev	Lev: 4 clog related Lev: 1 defective	Lev: 4/4 clog related – blocked actuator, initial DCU outside specs; within specs after wash **Lev: 1/1 defective – no propellant**
Retrospective Studies 051-353, 051-354, 051-355	7 Lev	Lev: 3 broken; 1 missing actuator; 2 empty; 1 not working	Lev: only 2 tested and within specs

Source: [N21730\N_000\2004-10-29\update\clinsum.pdf, p 71-90]

Reviewer's Comment: Of the 3 in vitro device failures, one was placed in luggage in the cargo of a plane, one was left on the dash in a car in warm conditions, while the third (pre amend 4) is unknown as it was simply labeled as defective by the subject.

Reviewer's Comment: The in vitro analyses of racemic albuterol will not be discussed in detail because the testing was quite limited and not validated for Proventil HFA.

Non-Complaint Devices

As stated above, the Division requested the Applicant perform in vitro testing on at least 100 non-complaint devices that have 35-50 actuations remaining (near the end of life.) The Applicant actually tested 180 non-complaint devices (114 post-amendment 4, 66 pre-amendment 4). None of the 180 non-complaint devices selected were failures on the basis of in vitro testing.

10.1.4.3 Discussion and Conclusions

Study 051-356 does not provide evidence of a new safety signal for levalbuterol HFA. In general, the reported AEs are quite similar between levalbuterol HFA and racemic albuterol HFA and are similar to AEs reported in the Phase 3 studies. More asthma AEs were noted in the levalbuterol group (11.4%) than in the racemic albuterol HFA group (7%). However the discontinuation rate due to asthma, asthma SAEs, and severe asthma AEs were similar between the two groups.

The Applicant amended the protocol to prospectively collect device performance data. Study 051-356 provides the only device performance data for levalbuterol HFA. In general, the device complaint rate was low. The complaint rate for levalbuterol was 0.024 compared to 0.017 for racemic albuterol. The most common complaints were related to clogging. In vitro testing of the complaint devices indicated DCU was occasionally out of specs, but returned within specs after proper washing. Thus, proper washing of the device is important for reliable performance. Two complaint canisters were confirmed device failures by in vitro testing (no propellant). A sample of 180 non complaint devices did not fail in vitro analyses. The device failure rate is 0.0118 with

a 95% confidence interval for the failure rate of (0, 0.0028). The limitation of Study 051-356 is that it does not provide device performance data for children age 4-11 years. However, the device complaints in the adult studies were generally clog-related, which leads this reviewer to believe device complaints in the pediatric population would also be clog related.
Reviewer's Comment: The device failure rate was calculated as follows: 2 in vitro failures / (1626 levalbuterol canisters used post amend 4 + 66 pre amend 4 non complaint canisters selected for in vitro testing).

Because Study 051-356 is a long term study the Applicant assessed for tolerance to levalbuterol HFA. The interim data for the percent predicted FEV1 does not provide evidence of tolerance to levalbuterol.

10.1.5 Dose Ranging EIB Studies (Study 051-308 and Study 051-312)

10.1.5.1 Study Design

Study 051-308 was a randomized, double blind, active controlled, multicenter, parallel treatment crossover study of the dose response and pharmacodynamics of levalbuterol and racemic albuterol HFA MDI in subjects 12 years of age and older with asthma, while Study 051-312 was similar design except in children aged 4-11 years. Subjects were enrolled and underwent a baseline period during which subjects underwent two exercise challenges following administration of placebo. Eligible subjects were randomized to receive 3M manufactured levalbuterol HFA (45mcg, 90mcg, and 180mcg) or racemic albuterol HFA (90mcg, 180mcg, and 360mcg) in random order. Subjects were administered study medication at clinic visits prior to an exercise challenge test. There was approximately a five day washout between medication dosing. All medication was administered via a plastic spacer [redacted] in Study 051-308. Spacers were not used in Study 051-312.
Reviewer's Comment: Exercise induced bronchospasm is a model. The dose that prevents EIB may not necessarily be the optimal clinical dose. However, the studies can be used to compare the study medication with an approved product. Unfortunately, this comparison was compromised in the adult studies because of the use of spacers.

The primary efficacy variable was FEV1 which was obtained pre-dose, post dose, and serially post exercise challenge. In Study 051-308, the primary efficacy parameter was the AUC for percent decrease from visit post-dose/pre-challenge FEV curve. For Study 051-312, the primary efficacy parameter was the maximum percent decrease in FEV1 from visit post-dose/pre-challenge FEV1. Other secondary efficacy parameters included the maximum percent FEV1 decrease from visit pos-dose/pre-challenge FEV1 (Study 051-308), FEV1 $AUC_{0\text{-}60min}$, time to FEV1 recover to pre-challenge and to predose levels, FVC, and $FEF_{25\text{-}75\%}$.

All subjects in Study 051-308 had serial PK samples measured for (R) and (S)-albuterol PK parameters. Safety monitoring included adverse events, vital signs, physical examinations, ECGs, potassium and glucose levels, and laboratories.

[N21730\N_000\2004-05-11\clinstat\adultasthma\051-308.pdf, p 4-8 and N21730\N_000\2004-05-11\hpbio\hupharm\051-312.pdf, p 4-6]

10.1.5.2 Efficacy Results Study 051-308

The primary population for analysis excluded subjects randomized incorrectly at site 621 due to non-compliant findings during an audit (Correctly Randomized population). Table 85 displays the results for the primary endpoint for Study 051-308. The 180mcg dose of levalbuterol was more bronchoprotective than the 45 mcg dose, which indicates a dose response. However, the difference was not statistically significant. According to Table 85, the 90mcg and 180mcg dose of levalbuterol produced a similar response. The dose response relationship was not as clear with levalbuterol as with racemic albuterol HFA.

Table 85 Study 051-308 Percent Decrease from Visit Post-dose/Pre-challenge FEV1 AUC (Primary EP)
Correctly Randomized Population Excluding Site 621

	Levalbuterol			Racemic Albuterol		
	45 mcg (n=23)	90mcg (n=23)	180mcg (n=22)	90mcg (n=25)	180mcg (n=27)	360mcg (n=25)
Mean (SD)	267 (296)	169 (270)	174 (280)	192 (249)	153 (249)	109 (201)
LS Mean (±)	264 ± 66		171 ± 67	184 ± 48		109 ± 48
	Lev 45mcg vs. Lev 180mcg p=0.164			Rac 90mcg versus Rac360mcg p=0.07		

Secondary endpoints (such as, maximum % decrease from visit post-dose/pre-challenge FEV1, % decrease from visit predose FEV1 AUC, and mean time to recovery) also suggested a dose response with levalbuterol. In general the 180mcg dose was more bronchoprotective than the 45 mcg dose, but the difference was not statistically significant. In addition, the 90mcg appeared to be more bronchoprotective than the 45 mcg dose. Racemic albuterol also demonstrated a dose response and appeared to be more potent that levalbuterol. The Applicant concluded that levalbuterol and racemic albuterol MDIs, when used with spacers, were not clinically comparable [N21730\N_000\2004-05-11\clinstat\adultasthma\051-308.pdf, p 73-103].

The results of Study 051-308 suggest that the 90mcg levalbuterol HFA dose is an appropriate dose; however, the study was complicated by the use of spacers.

10.1.5.3 Efficacy Results Study 051-312

The efficacy analyses utilized the EVAL population, which was all randomized subjects who received at least one dose of double-blind study medication to which they were correctly randomized, subjects who were incorrectly randomized yet received a valid treatment sequence, and subjects who were re-randomized to treatment. Of interest, no black subjects were randomized to the levalbuterol treatment group; however, only four black subjects were randomized to the racemic albuterol treatment group. Table 86 displays the results for the primary endpoint, the maximum percent decrease in FEV1 from visit post-dose/pre-challenge.

Table 86 Study 051-312 Maximum percent decrease in FEV1 from visit post-dose/pre-challenge (Primary EP) EVAL population						
	Levalbuterol			Racemic Albuterol		
	45 mcg (n=16)	90mcg (n=16)	180mcg (n=16)	90mcg (n=16)	180mcg (n=16)	360mcg (n=16)
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	0.92, 6.70	2.81, 12.33	1.35, 9.13	0.69, 8.37	1.13, 4.25	0.78, 6.65

In general, there was no dose response for either levalbuterol or racemic albuterol. However, at baseline following exercise challenge in this subject population the decrease in FEV1 was on average approximately 27%. Thus, as shown above, the lowest dose of levalbuterol and racemic albuterol were bronchoprotective. Secondary endpoints (such as FVC) also suggested a lack of dose response with either treatment, but suggested some protection against exercise induced bronchoconstriction with either treatment N21730\N_000\2004-05-11\hpbio\hupharm\051-312.pdf, p 78-82].

The results of Study 051-312 suggest that 90mcg levalbuterol is an appropriate dose for bronchoprotection. However, the study also suggests that the 45mcg levalbuterol HFA dose may also be effective.

10.1.5.4 Safety Results Study 051-308 and Study 051-312.

There were no deaths or SAEs in either study. The incidence of AEs did not appear to increase with an increase in dose of study medication. More AEs were noted in the racemic albuterol treatment groups. The most frequently reported AE in the levalbuterol group was pharyngitis in the adult study and viral infection in the pediatric study. One subject in each treatment group in Study 051-308 discontinued due to asthma. In Study 051-312, one subject in each treatment group discontinued secondary to sinusitis. Because these studies were exercise challenge studies, an increase in heart rate, blood pressure and respiratory rate were considered related to the exercise challenges. No significant change was noted in the mean potassium concentration in any of the treatment groups. There did not appear to be any significant changes in the mean potassium or glucose levels. ECG findings were attributed to the exercise challenges [N21730\N_000\2004-05-11\clinstat\adultasthma\051-308.pdf, p 103-121 and N21730\N_000\2004-05-11\hpbio\hupharm\051-312.pdf, p 82-96].

10.1.6 Cumulative Dose Studies (051-309, 051-310, 051-311)

[N21730\N_000\2004-05-11\hpbio\hupharm\051-309.pdf, p 4-9, N21730\N_000\2004-05-11\hpbio\hupharm\051-310.pdf, p 4-9].

These three studies were randomized, double (or modified) blind, active-controlled, multicenter crossover cumulative dose studies of levalbuterol HFA and racemic albuterol HFA in adults/adolescents with asthma (051-309 and 051-310) and children age 4 to 11 years (051-311). The studies were primarily safety and tolerability studies, but did investigate efficacy with secondary endpoints. Eligible subjects were randomized to either levalbuterol or racemic

albuterol treatment groups. Subjects were dosed up to 16 cumulative actuations in the adult studies and 8 cumulative actuations in the pediatric study as follows: 1 puff at 0 and 30 minutes, two puffs at 60 minutes, four puffs at 90 minutes, and eight puffs at 120 minutes. After an approximate 7 day washout period, subjects were dosed with the other study medication. Study 051-310 was performed with a plastic spacer (— Study 051-311 was performed with two cohorts of pediatric subjects: with — spacer and without spacer.

Safety monitoring included heart rate, blood pressure, potassium and glucose levels, AEs, ECGs, physical examinations, laboratories, rescue medication use and asthma attacks. A discussion of the safety results of the cumulative dose studies will be included in the integrated summary of efficacy.

Efficacy endpoints (secondary) included FEV1, FVC, $FEF_{25-75\%}$ and the percent change from visit predose to 25 minutes after each cumulative dose. For the efficacy analyses, the following table demonstrates the percent change in FEV1 from visit predose to 25 minutes post each cumulative dose.

Table 87 Percent change in FEV1 from visit predose to 25 minutes post-each cumulative dose (ITT Population)

	Study 051-309		Study 051-310		Study 051-311			
	No Spacers		Spacers		Spacer Cohort		No Spacer Cohort	
LS Mean ± SE or mean (SD)	Levalbuterol N=47	Racemic Albuterol N=45	Levalbuterol N=31	Racemic Albuterol N=31	Levalbuterol N=12	Racemic Albuterol N=12	Levalbuterol N=19	Racemic Albuterol N=19
Post 1X Dose	20.7 ±2.3	20.8 ±2.3	17.1 ± 3.2	19.6 ± 3.2	11.4 (14.0)	13.6 (13.0)	6.8 (9.5)	12.6 (15.1)
Post 2X Dose	24.6 ±2.4	23.9 ±2.5	22.5 ± 3.9	23.9 ±3.9	17.2 (12.7)	17.9 (13.8)	9.0 (13.4)	14.9 (16.7)
Post 4X Dose	28.5 ±2.6	27.1 ±2.6	25.3 ± 4.4	27.5 ±4.4	20.1 (11.8)	20.9 (17.2)	10.9 (13.1)	15.1 (16.1)
Post 8X Dose	32.3 ±2.8	30.2 ±2.8	28.6 ± 4.9	30.7 ±4.9	20.0 (10.9)	23.6 (13.8)	14.3 (8.9)	16.1 (19.5)
Post 16X Dose	36.2 ±3.0	33.4 ±3.1	30.7 ± 4.9	32.8 ± 4.9				

Source: N21730\N_000\2004-05-11\hpbio\hupharm\051-309.pdf, p 97; N21730\N_000\2004-05-11\hpbio\hupharm\051-310.pdf, p 136-137; N21730\N_000\2004-05-11\hpbio\hupharm\051-311.pdf, p196-197

Dose dependent increases in mean percent change in FEV1 were noted. The relative potency of levalbuterol and racemic albuterol in Study 051-309 was similar. However, in Study 051-310, levalbuterol was less potent than racemic albuterol and were thus not considered to have comparable efficacy. The Applicant attributed this difference to the increase in exposure noted with racemic albuterol with unconditioned spacer use. The Applicant performed Anderson Cascade Impactor studies with both levalbuterol and racemic albuterol without a spacer and in the presence of a conditioned and unconditioned spacer. The fine particle distribution was similar between each drug without a spacer; however, in the presence of an unconditioned spacer, racemic albuterol HFA had an increase in FPD compared to levalbuterol HFA. The difference was not as prominent in the presence of a conditioned spacer [N21730\N_000\2004-05-11\hpbio\hupharm\051-310.pdf, p 93-94].

In Study 051-311, the Applicant included a cohort with and without spacers. As shown above in Table 87, the spacer cohort demonstrated a similar dose-dependent increase in FEV1 with cumulative doses. In the cohort without spacers, the increase in FEV1 was lower for both treatment groups; however, the racemic albuterol group had a greater increase in FEV1 than the levalbuterol group.

10.2 Line-by-Line Labeling Review

The Division's proposed labeling recommendations were conveyed to the Applicant during the review period. At the time of finalization of this review, labeling negotiations were ongoing with the Applicant.

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

/s/

Sally Seymour
2/25/05 02:35:10 PM
MEDICAL OFFICER

Eugene Sullivan
2/25/05 02:40:27 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA # 21-730	**TRADE NAME:**	Xopenex HFA
Applicant:	Sepracor Inc.	**USAN NAME:**	Levalbuterol tartrate
MEDICAL OFFICER:	Sally Seymour, MD		
DEPUTY DIRECTOR:	Eugene J. Sullivan, MD, FCCP	**CATEGORY:**	Beta agonist
REVIEW DATE:	July 1, 2004	**ROUTE:**	Oral inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
May 11, 2004	May 12, 2004	Original NDA	Electronic Submission

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY: This NDA is a 505(b)(2) application for a levalbuterol HFA Inhalation Aerosol. The Applicant, Sepracor, requests approval of an HFA MDI containing 59 mcg of levalbuterol tartrate (equivalent to 45 mcg levalbuterol in propellant) per actuation. The reference product is Proventil HFA Inhalation Aerosol (3M Corporation). The proposed indication is the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease. The proposed dose is two inhalations (90mcg) every 4 to 6 hours. The Applicant has proposed the trade name Xopenex HFA™ Inhalation Aerosol for the drug product.

The reference product is Proventil HFA Inhalation Aerosol (3M Pharmaceuticals), which is currently approved for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in adults and children 4 years of age and older.

This application is supported by two randomized double-blind, placebo-controlled, active-controlled, 8 week studies in adults/adolescents 12 years of age and older with asthma. In addition, the application is supported by one randomized double-blind, placebo-controlled, active-controlled, 4 week study in children age 4 to 11 years with asthma. These studies are appropriately indexed and organized to allow review. A 12 month safety study (051-356) is currently ongoing.

The Applicant did not prospectively address device performance in the Phase III studies. The ongoing safety study (051-356) was amended in November of 2003 to include collection of device performance data. Although the limited device performance data submitted in this NDA is not a filing issue, the adequacy of the device performance database to support approval of levalbuterol HFA will be a review issue.

The submission is adequate to allow full, in-depth clinical review. The submission is fileable. A DSI audit will be requested. Comments will be conveyed to the Sponsor.

OUTSTANDING ISSUES: 1) A DSI audit will be requested.

2) Comments will be conveyed to the Sponsor.

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	____	**SAFE TO PROCEED**	____	**CLINICAL HOLD**		
NDA/SUPPLEMENTS:	X	**FILEABLE**	____	**NOT FILEABLE**		
	____	**APPROVAL**	____	**APPROVABLE**	____	**NOT APPROVABLE**
OTHER ACTION:						

I. General Information

This NDA is a 505(b)(2) application for a levalbuterol HFA Inhalation Aerosol. The Applicant, Sepracor, requests approval of an HFA MDI containing 59mcg of levalbuterol tartrate (equivalent to 45 mcg levalbuterol in propellant) per actuation. The proposed indication is the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease [N21730\labeling\proposed.pdf]. The proposed dose is two inhalations (90mcg levalbuterol) every 4 to 6 hours [N21730\labeling\proposed.pdf]. The Applicant has proposed the trade name Xopenex HFA™ Inhalation Aerosol for the drug product. The Applicant has submitted the NDA in electronic format.

The reference product is Proventil HFA Inhalation Aerosol (3M Pharmaceuticals), which is currently approved for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in adults and children 4 years of age and older.

Levalbuterol is a β_2-receptor agonist, which is the (R)-isomer of racemic albuterol. Racemic albuterol is a mixture of two stereoisomers, the (R)- and the (S)-isomers. The Applicant purports that the (R)-isomer is responsible for the reversal of bronchoconstriction and the (S)-isomer may potentially oppose the beta agonist bronchodilation of the (R)-isomer [N21730\summary.pdf, page 38]. Levalbuterol Inhalation Solution in a unit dose vial is currently marketed by Sepracor for the treatment or prevention of bronchospasm in subject six years of age and older with reversible obstructive airway disease. In this NDA application, Sepracor has developed levalbuterol HFA Inhalation Aerosol as a more convenient drug delivery system.

Reviewer's Comment: Levalbuterol tartrate is the drug substance in Xopenex HFA, while levalbuterol hydrochloride is the drug substance in Xopenex Inhalation Solution.

This application is submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of the approved reference product and a comparison of the bioavailability and bioequivalence of the proposed new drug to those reference products. The Applicant's drug development program is based upon data from three pivotal Phase III clinical studies, two studies in adults and adolescents and one pivotal study in children ages 4 and older. The Applicant has also conducted multiple Phase II supportive clinical studies. In addition, the Applicant is referencing the long-term clinical safety data for Proventil HFA Inhalation Aerosol (NDA# 20-503, 3M Pharmaceuticals) and all relevant data for Xopenex Inhalation Solution (NDA# 20-837, Sepracor Inc.).

II. Regulatory and Foreign Marketing History

A. Regulatory History

The following is a brief summary of the regulatory history of levalbuterol.

- Sepracor submitted NDA# 20-837 for Xopenex (levalbuterol HCl) Inhalation Solution in a unit dose vial (UDV) on June 30, 1997.
    - The application was approved March 25, 1999, for the treatment or prevention of bronchospasm in adults and adolescents 12 years of age and older with reversible obstructive airway disease [NDA#20-837, Approval Letter].
    - In January 2002, a pediatric supplement for Xopenex UDV (NDA# 20-837 S006) was approved for the treatment and prevention of bronchospasm in patients 6 years of age and older with reversible obstructive airway disease.
- Sepracor submitted
- Sepracor submitted IND# 62,906 on July 11, 2001, for the Xopenex HFA MDI.
- In late 2001, 3M provided Sepracor the right of reference to the 3M Proventil® HFA MDI non-clinical and clinical safety database submitted in NDA# 20-503 [N21730\other\reghistory.pdf, page 2].
- Several meetings and teleconferences were held between the FDA and Sepracor to discuss the development of Xopenex HFA. However, an EOP-2 meeting was not held. The following is a list of some of the meetings with pertinent clinical discussion points.
    - Type C meeting on February 19, 2002
        - Device performance in actual clinical use needs to be addressed
        - A long-term safety study would not be required if the Sponsor can cross-reference existing data. However, any differences between the products must be supported.
        - The Division stated that it is open to the length of the proposed study as long as the length could be justified.
            - 4 week study not long enough to look at life of device
            - 12 week study would provide adequate device exposure
            - 8 week study is possible provided device performance issue is adequately supported in the overall clinical program.
        - Rescue therapy in studies should be same as treatment medication.
        - PK/PD dose-ranging studies with 3 doses of Proventil HFA MDI and Xopenex HFA MDI in adults and children should be performed.
        - A cumulative dose study comparing Proventil HFA MDI and Xopenex HFA MDI should be performed.
    - Type C Meeting October 29, 2003
        - Exercise challenge studies performed in dose ranging studies

- The Division questioned whether the Sponsor had acceptable data on device performance.
- The Division indicated that all data the Sponsor feels is necessary to support the safety data should be submitted at the time they submit the NDA.
- The Division indicated the Sponsor's proposed dose selection of 90 mcg appears appropriate.

- Type A Meeting (teleconference) January 5, 2004
  - Device performance incorporation into 12 month safety study (051-356) was discussed
    - The Division agreed with the plan for the Sponsor to test at least 100 non-complaint samples that have 35-50 actuations remaining.
    - The Division stated that incidence of device malfunction should be the sum of all of the devices that malfunction on in-vitro testing divided by the number of devices used by patients in the study.
  - The Division stated if the entire device performance database is not submitted with the NDA, whether the data submitted is adequate to support the approval of the drug product will become a review issue.

- On May 11, 2004, Sepracor submitted NDA# 21-730 for Xopenex HFA Inhalation Aerosol.

B. Foreign Marketing History

According to the Applicant, Xopenex HFA is not currently commercially marketed in any country and there have not been any foreign regulatory actions on Xopenex HFA [N21730\summary.pdf, page 39].

Reviewer's Comment: The foreign marketing history of Xopenex Inhalation Solution may provide additional information regarding the safety database of Xopenex HFA.

III. Items Required for Filing

The Applicant has provided the following necessary elements (21 CFR 314.50) in this submission.

Table 1 Necessary Elements

Item	Type	Status	Location (paper/*electronic*)
	Application Form (FDA 356h)	Present	N21730\356h.pdf
1	Index / Table of Contents	Present	N21730\ndatoc.pdf
2	Samples and Labeling Proposed Package Insert Proposed Label Proposed Medication Guide	Present	 N21730\labeling\proposed.pdf N21730\labeling\contain.pdf
3	Summary		

Item	Type	Status	Location (paper/*electronic*)
	Labeling		N21730\labeling\proposed.pdf
	Marketing History	Present	N21730\summary\summary.pdf (section 3)
	Chemistry, Manufacturing, & Controls (CMC)	Present	N21730\summary\summary.pdf (section 4)
	Nonclinical Pharmacology and Toxicology	Present	N21730\summary\summary.pdf (section 5)
	Human Pharmacokinetics and Bioavailability	Present	N21730\summary\summary.pdf (section 6)
	Clinical	Present	N21730\summary\summary.pdf (section 8)
	Benefits vs. Risks	Present	N21730\summary\summary.pdf (section 9)
4	CMC	Present	N21730\cmc\
	Environmental Impact statement	Present	N21730\cmc\environ.pdf
5	Nonclinical Pharmacology and Toxicology	Present	N21730\pharmtox\
6	Human Pharmacokinetics and Bioavailability	Present	N21730\hpbio\
8	Clinical	Present	N21730\clinstat\
8.5	Controlled studies	Present	N21730\clinstat\
8.7	Uncontrolled studies	N/A	
8.8	Integrated Summary of Effectiveness (subsets for age, gender, and race)	Present	N21730\clinstat\ise\ise.pdf
8.9	Integrated Summary of Safety	Present	N21730\clinstat\iss\iss.pdf
	Potential for Abuse		
8.11	Benefits vs Risks	Present	N21730\clinstat\riskben\riskben.pdf
8.12	Statements of Good Clinical Practice:		
	Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures	Present	Volume 1
	Auditing information		
9	Safety Updates	N/A	
10	Statistics	Present	N21730\clinstat\
11	Case Report Tabulations	Present	N21730\crt\
12	Case Report Forms (for patients who died or did not complete studies)	Present	N21730\crf\
13	Patent Information	Present	N21730\other\patinfo.pdf
14	Patent Certification	Present	N21730\other\patcert.pdf
16	Investigator Debarment Certification	Present	N21730\other\debar.pdf
17	Field copy certification (if applicable)	Present	N21730\other\fieldcer.pdf
18	User Fee Cover Sheet	Present	N21730\other\userfee.pdf
19	Financial Disclosure	Present	N21730\other\financial.pdf
20	Other		
	Claimed Marketing Exclusivity	Present	Volume 1
	Pediatric Waiver	Not Present	

Reviewer's Comment: The Applicant did not address the Pediatric Research Equity Act. The Division will defer the pediatric requirement and request the Applicant submit a pediatric development program for children < 4 years of age.

IV. Clinical Studies

A. Pivotal Studies

This application includes two pivotal Phase III studies in adults/adolescents and one pivotal Phase III study in pediatric subjects. The pivotal studies will be addressed in further detail; however, a change in actuator and manufacturers during the clinical development is worth noting at this time. In Phase II Studies 051-305 and 051-306, the levalbuterol HFA product was manufactured at — with an actuator orifice diameter of — mm. However, this product produced a lower respirable dose when compared with the racemic albuterol comparator product. For subsequent studies, the actuator orifice diameter was modified to — mm so that performance characteristics, including respirable dose, better matched the racemic albuterol MDI products. Initially, the product with the — mm orifice was manufactured by — Subsequently it was manufactured by 3M, the proposed commercial manufacturer [N21730\clinstat\clinsum.pdf, page 60].

During the pivotal trials, two different manufacturers of the levalbuterol HFA product were utilized. Both manufacturers incorporated the final actuator orifice diameter of —. Throughout the discussion of the clinical studies, the different manufacturers will be referred to as follows:

- Levalbuterol HFA-**A** manufactured at 3M
  - proposed commercial manufacturer
  - final actuator orifice diameter of — mm
- Levalbuterol HFA-**B** manufactured at —
  - final actuator orifice diameter of — mm

Reviewer's Comment: Because different manufacturers were utilized during the pivotal studies, any significant differences between levalbuterol HFA-A and levalbuterol HFA-B will need to be taken into consideration during the review process.

The three pivotal studies are very similar in design and are summarized in Table 2 below. A more detailed description of the pivotal studies follows.

Table 2 Summary of Pivotal Studies

Study #	Study Type	Subjects	Design	Treatment Groups
051-353	Efficacy & Safety Adults/Adolescents	445 subjects 12 years and older with asthma	R, DB, PC, AC, MC, // 8 weeks	Levalbuterol HFA-B 90 mcg QID Proventil HFA180 mcg QID Placebo 2 actuations QID
051-355	Efficacy & Safety Adults/Adolescents	303 subjects 12 years and older with asthma	R, DB, PC, AC, MC, // 8 weeks	Levalbuterol HFA-A 90 mcg QID Levalbuterol HFA-B 90 mcg QID Proventil HFA 180 mcg QID Placebo 2 actuations QID
051-354	Efficacy & Safety Pediatric	150 subjects 4-11 years of age with asthma	R, DB, PC, AC, MC, // 4 weeks	Levalbuterol HFA-A 90 mcg QID Proventil HFA 180 mcg QID Placebo 2 actuations QID

R = randomized, DB = double blind, PC = placebo controlled, AC = active controlled, MC = multicenter, // = parallel group

Reviewer's Comment: Study 051-355 is the only pivotal study conducted with the levalbuterol HFA product produced by the proposed commercial manufacturer.

Study 051-353 [N21730\clinstat\ise.pdf, page 29-30]

Study 051-353 was a randomized, double-blind, placebo- and active controlled, multicenter, parallel group study in adults/adolescents with asthma of approximately nine weeks duration. A total of 445 males and females at least 12 years of age with a history of non-life-threatening asthma, FEV_1 between 45 and 75% of predicted, and a $\geq$12% reversibility of airflow obstruction were randomized. A screening visit was followed by a one-week single-blind placebo period. Subjects were randomized to one of the following three treatment groups in a 2:1:1 ratio, respectively.

- Levalbuterol HFA-B 90 mcg (2 actuations of 45 mcg) QID
  - 219 subjects
- Proventil HFA 180 mcg (2 actuations of 90 mcg) QID
  - 119 subjects
- Placebo-vehicle only HFA MDI (2 actuations) QID
  - 107 subjects

All study medication was administered four times per day (QID) for eight weeks. Levalbuterol-B HFA treated subjects were given double-blind levalbuterol-B HFA for use as rescue medication, while the Proventil and placebo treated subjects were given double-blind racemic albuterol CFC for use as rescue medication.

The primary efficacy endpoint was the peak percent change from visit predose in FEV_1 averaged over the 8 week double-blind period. The key secondary efficacy endpoint was the area under the FEV_1 percent change from visit predose curve averaged over the double-blind period. Other secondary efficacy endpoints included the peak percent change in FVC from visit predose, peak percent change in $FEF_{25-75\%}$ from visit predose, number and percent of responders, time to onset of response, duration of response, and asthma symptom scores. (R) and (S)-albuterol plasma concentrations and pharmacokinetic parameters were also assessed.

Study 051-355 [N21730\clinstat\ise.pdf, page 30-31]

Study 051-355 was a double-blind, randomized, placebo- and active-controlled, multicenter, parallel-group study in adults/adolescents with asthma of approximately nine weeks duration. A total of 303 males and females at least 12 years of age with a history of non-life threatening asthma, baseline FEV_1 between 45 and 75% of predicted and a >12% reversibility of airflow obstruction were randomized. A screening visit was followed by a one week single blind placebo period. Subjects were then randomized to the following treatment groups in a 2:1:1:1 ratio, respectively.

- Levalbuterol-A HFA 90 mcg (2 actuations of 45 mcg) QID
  - 122 subjects
- Levalbuterol-B HFA 90 mcg (2 actuations of 45 mcg) QID
  - 62 subjects
- Proventil HFA 180 mcg (2 actuations of 90 mcg) QID
  - 60 subjects
- Placebo-vehicle only HFA MDI (2 actuations) QID
  - 59 subjects

All study medication was administered QID for 8 weeks. Pirbuterol acetate (0.2 mg/actuation) was used as rescue medication.
Reviewer's Comment: The Division had requested in the February 19, 2002, meeting with the Applicant that the rescue medication be the same as the treatment medication.

The primary efficacy endpoint was the peak percent change from visit predose in FEV_1 averaged over the double-blind period. The key secondary efficacy endpoint was the area under the FEV_1 percent change from visit predose curve averaged over the double-blind period. Other secondary efficacy endpoints included the peak percent change in FVC from visit predose, peak percent change in $FEF_{25-75\%}$ % from visit predose, number and percent of responders, time to onset of response, duration of response, and asthma symptom scores. (R) and (S)-albuterol plasma concentrations and pharmacokinetic parameters were also assessed.

Adverse Events for Studies 051-353 and 051-355 [N21730/clinsum.pdf, page 103 - 107]
The Applicant pooled the safety data for the multiple dose controlled studies in adolescents/adults (051-353, 051-355, 051-305). The most common adverse events reported were headache, respiratory viral infection, asthma, pharyngitis, rhinitis, accidental injury and pain. The most common adverse event leading to discontinuation of treatment was asthma. No deaths were reported in any of the studies in adults/adolescents. The following SAEs were reported in the levalbuterol treatment groups

- Levalbuterol 90 mcg
  - Ovarian cyst
  - Accidental injury – left knee ACL reconstruction, medial meniscus repair
  - Accidental injury – concussion and lumbar fracture
  - Asthma
  - Hypertension.

Study 051-354 (Pediatric Pivotal Study) [N21730\clinstat\ise.pdf, page 37]
Study 051-354 was a double-blind, randomized, placebo and active-controlled, multicenter, parallel-group study in pediatric subjects with asthma of approximately 6 weeks duration. A total of 150 subjects age 4 to 11, with a history of non-life-threatening asthma, FEV_1 between 45 and 80% of predicted and $\geq$ 12% reversibility of airflow obstruction were randomized. A screening visit was followed by a one week single-blind placebo period. Eligible subjects were then randomized into the following treatment groups in a 2:1:1 ratio, respectively.

- Levalbuterol HFA-A 90 mcg (2 actuations of 45 mcg) QID
  - 76 subjects
- Proventil HFA 180 mcg (2 actuations of 90 mcg) QID
  - 39 subjects
- Placebo MDI (2 actuations) QID
  - 35 subjects

All study medication was administered QID for four weeks. Based upon randomized treatment, subjects were given either double-blind levalbuterol UDV (1.25mg) or double-blind racemic albuterol UDV (2.5mg) for use, as rescue medication.

The primary efficacy endpoint was the peak percent change from visit predose in FEV_1 averaged over the double-blind period. The key secondary efficacy endpoint was the area under the FEV_1 percent change from visit predose curve averaged over the double-blind period. Other secondary efficacy endpoints included the peak percent change in FVC from visit predose, peak percent change in $FEF_{25-75\%}$ from visit predose, number and percent of responders, time to onset of response, duration of response, and asthma symptom scores.

The Applicant pooled the safety data in the controlled pediatric clinical studies (051-354 and 051-306) [N21730\clinstat\clinsum.pdf\page 137-140]. The most common AEs reported were headache, asthma, vomiting, and accidental injury. Two SAEs (gastroenteritis, constipation) occurred in the double blind treatment period in pediatric subjects. Both SAEs were in the racemic albuterol group. The most common AE leading to subject discontinuation was asthma. No deaths were reported in any study conducted in pediatric subjects.

B. Supportive Studies

Table 3 is a brief overview of the supportive studies for this application. Two early studies are not listed (051-301 and 051-304) because these studies were conducted with the levalbuterol CFC formulation and will not support this application. Study 051-356, which is an ongoing 12 month safety study, is not completed at the time of the NDA submission. Study 051-356 is discussed in more detail following Table 3.

Table 3 Overview of Supportive Studies

Study #	Study Type	Subjects	Design	Treatment Groups
051-305	Efficacy, Safety, Tolerability Adults/Adolescents	Males and females 12 years or older with asthma N = 162	R, MC, DB, PC, AC, // 4 weeks	Levalbuterol HFA-B 90 mcg Levalbuterol HFA-B 180 mcg Ventolin CFC 180 mcg Placebo **(early actuator design — nm actuator orifice)**
051-306	Efficacy, Safety, Tolerability Pediatric	Males and females 4 to 11 years of age with asthma N=127	R, DB, PC, AC, MC, // 4 weeks	Levalbuterol HFA-B 90 mcg Levalbuterol HFA-B 180 mcg Ventolin CFC 180 mcg Placebo **(early actuator design — nm actuator orifice)**
051-308	Dose Ranging EIB Adults/Adolescents	Males or females 12 years or older with asthma N=62	R, Modified-blind, AC, MC, //, 3x3 CO (5 +/- 2 day w/o) 3 weeks	Levalbuterol HFA-A 45 mcg Levalbuterol HFA-A 90 mcg Levalbuterol HFA-A 180 mcg Proventil HFA 90 mcg Proventil HFA 180 mcg Proventil HFA 360 mcg
051-309	Cumulative Dose Safety/Tolerability Adults/Adolescents	Males or females 12 years or older with asthma N=49	R, Modified-blind, AC, MC, 2 way CO 3 weeks	Levalbuterol HFA-A 16 cumulative actuations then Proventil HFA 16 cumulative actuations Proventil HFA 16 cumulative actuations then Levalbuterol HFA-A 16 cumulative actuations
051-310	Cumulative Dose Safety/Tolerability Adults/Adolescents	Males or females 12 years or older with asthma N=32	R, Modified-blind, AC, MC, 2 way CO 3 weeks	Levalbuterol HFA-A 16 cumulative actuations then Proventil HFA 16 cumulative actuations Proventil HFA 16 cumulative actuations then Levalbuterol HFA-A 16 cumulative actuations
051-311	Cumulative Dose Safety/Tolerability Pediatric	Males and females 4 to 11 years of age with asthma N=31	R, DB, AC, MC, two treatment, two period CO 3 weeks	Spacer (—) Cohort and No Spacer Cohort Levalbuterol HFA-A 8 cumulative actuations then Proventil HFA 8 cumulative actuations Proventil HFA 8 cumulative actuations then Levalbuterol HFA-A 8 cumulative actuations
051-312	Dose Ranging EIB Pediatric	Males and females 4 to 11 years of age with asthma N=33	R, DB, AC, MC, //, 3x3 CO (5 +/- 2 day w/o) 4 weeks	Levalbuterol HFA-A 45 mcg Levalbuterol HFA-A 90 mcg Levalbuterol HFA-A 180 mcg Proventil HFA 90 mcg Proventil HFA 180 mcg Proventil HFA 360 mcg
051-356 **(Ongoing)**	Safety Study Device Performance	Males or females 12 years or older with asthma N=369 (As of January 29, 2004) N= 650 (goal)	R, open-label, AC, MC, // 12 months	Levalbuterol HFA-A 90mcg Proventil HFA 180 mcg

R = randomized, DB = double blind, PC = placebo controlled, AC = active controlled, MC = multicenter, // = parallel group, CO = crossover
EIB = exercise induced bronchospasm, w/o = washout

Reviewer's Comment: Studies 051-308 and 051-310 were conducted with spacers. However, the Applicant found that the PK and PD were inconsistent with Study 051-355 (pivotal study using levalbuterol HFA-A). Therefore, the Applicant conducted Study 051-309 without the use of spacers.

Study 051-356 [N21730\clinstat\clinsum.pdf, page 163-170; N21730\clinstat\other\051-356.pdf]

Study 051-356 is a long term safety study of levalbuterol HFA and racemic albuterol in subjects 12 years of age and older with asthma. The study is a randomized, open-label, active controlled, multicenter, parallel group study comparing 90 mcg levalbuterol HFA and 180 mcg racemic albuterol HFA. New subjects and subjects completing pivotal studies 051-353 and 051-355 were eligible. The protocol specifies approximately 650 subjects will be randomized.

In addition to adverse events, lung function, vital signs, ECGs, glucose and potassium levels, the protocol was amended (Amendment No. 4) on November 25, 2003, to collect prospective subject-reported MDI device performance during the course of the study. The amendment was implemented on December 5, 2003, after 338 subjects were randomized into the study. Amendment No. 4 implemented the following:

- A new daily dosing diary card to query for MDI device performance.
- A Call Center was established so that subjects with reported MDI device problems could complete an operator-assisted questionnaire detailing the nature of the complaint.
- All subject-reported complaint devices were sent to an analytical laboratory for *in vitro* testing to characterize the performance of the device to determine the probable cause of the subject's complaint. *In vitro* testing included:
    - Appearance of contents and components of canister
    - Dose content uniformity (DCU)
    - Shot weight
    - Aerodynamic particle size by Anderson Cascade Impaction (ACI)
    - —
    - Microscopic evaluation of particle size and shape.
- Specific cleaning instructions were provided [N21730\cmc\product.pdf, page 1996].

A cut-off date of March 12, 2004, was established for retrieval of subject-reported complaint MDI devices from Study 051-356. According to the Applicant, a total of 1906 levalbuterol canisters (763 post-amendment and 1143 pre-amendment) were used from the start of Study 051-356 until the March 12, 2004, cut-off date. Thirty complaint devices were identified from the study initiation until the March 12, 2004, cut-off date. The following list provides some detail about the device complaints. The *in vitro* data for the complaint devices is included in the application.

- 25 post-amendment devices
    - 22 subjects
    - 16 levalbuterol devices, 7 Proventil HFA devices, 2 rescue (pirbuterol) devices
    - Most common complaints
        - Less spray than usual – 5
        - Canister was clogged – 3

  - No spray came out – 4
  - Canister/device empty – 3
  - Spray would not work - 1
- 5 pre-amendment devices

Reviewer's Comment: The number of complaints increased significantly post amendment from 5 to 25 complaints.

Reviewer's Comment: The Applicant plans to submit additional device performance data obtained from study 051-356 with the 120 day safety update.

Device Performance

The Applicant also included the following device performance data in this submission:

- 101 non-complaint MDI devices with ≤ 50 actuations remaining were identified for *in vitro* testing from Study 051-356. The 101 non-complaint canisters included 66 pre-amendment canisters and 35 post-amendment canisters.

Reviewer's Comment: Interpretation of the data from the 66 pre-amendment non-complaint canisters will be limited because the determination of "non-complaint" was based upon a retrospective review of CRFs. It is unclear if subjects were asked about device performance/complaints prior to the amendment.

- Retrospective *in vitro* testing and analysis of complaint devices identified prior to Amendment No. 4 (November 25, 2003) for Study 051-356 and from previously completed Phase III studies.

Reviewer's Comment: Interpretation of the data from the retrospective analysis will be limited due to concerns of reliability.

Table 4 is a summary of the device performance data included in this submission.

Table 4 Summary of Device Performance Data

	NDA Submission	120 Day Safety Update
Prospective Complaint Devices Study 051-356 Post Amendment No. 4 (N=763 devices)	25 complaint devices	Additional 1000 devices used
Non-Complaint Devices by *in vitro* ≤ 50 actuations remaining Post Amendment No. 4 (N=763 devices)	35 devices	
Non-Complaint Devices by *in vitro* ≤ 50 actuations remaining Pre Amendment No. 4 (N=1143 devices)	66 devices	
Retrospective Complaint Devices Study 051-356 Pre Amendment No. 4	5 devices	
Retrospective Complaint Devices Studies 051-353, 051-354, 051-355 (N=1793 devices)	7 devices	

For analysis of the device performance data, the incidence of device-malfunction was calculated as follows:

$$\frac{\text{(\# of complaint devices confirmed as malfunctioning by } \textit{in-vitro} \text{ analysis + \# of non-complaint devices confirmed as malfunction by } \textit{in-vitro} \text{ analysis)}}{\text{Number of Devices Used by Patients}}$$

Reviewer's Comment: The calculation of the incidence of device malfunction is consistent with the Division's request in the January 5, 2004, teleconference.

Reviewer's Comment: The Division had requested the entire device performance data be submitted with the NDA. Although the limited device performance data submitted in this NDA is not a filing issue, the adequacy of the device performance database to support approval of levalbuterol HFA will be a review issue.

V. DSI Review / Audit

To determine whether a DSI audit should be performed and the location, the financial interest of the investigators and the number of subjects at each center in the pivotal trials were evaluated.

In the 3 pivotal trials (051-353, 051-354, 051-355), only 3 investigators reported a financial interest and all 3 participated in trial — [N21730\other\financial.pdf]

- — > $25,000
  - Enrolled 1 subject [N21730\clinstat\051-353.pdf, page 216-220]
- — >$25,000
  - Enrolled 3 subjects [N21730\clinstat\051-353.pdf, page 216-220]
- — >$25,000
  - Enrolled 15 subjects [N21730\clinstat\051-353.pdf, page 216-220]

For Study 051-353, the largest number of subjects enrolled by a single investigator was 28 by Investigator William Rees, MD (site #0201) [N21730\clinstat\051-353.pdf, page 216-220]. For Study 051-355, the largest number of subjects enrolled by a single investigator was 27, by Investigator William Rees, MD (site #0201) [N21730\clinstat\051-355.pdf, page 193-195]. For the pediatric pivotal study (051-354), the largest number of subjects enrolled by a single investigator was 13 by investigator Kenneth Kim, MD (site # 0027) [N21730\clinstat\051-354.pdf, page 189-192].

Reviewer's Comment: None of the investigators with financial interests contributed a significant number of patients to the studies. Dr. William Rees enrolled 55 subjects in the pivotal studies and, therefore, will be a reasonable investigator/site to audit. A DSI audit will be requested of Dr. William Rees.

VI. Brief Review of Proposed Labeling

The Applicant submitted proposed labeling [N21730\labeling]. The product label is very similar to the Xopenex (levalbuterol HCl) Inhalation Solution product label. However, the

Xopenex HFA label contains preclinical information regarding the propellant HFA-134a. In addition, the Pharmacokinetics, Information for Patients, Geriatrics, Adverse Reactions, Dosage and Administration, as well as the How Supplied sections have all been updated.

A detailed label review will be performed later in the course of review of this NDA.

VII. Timeline for Review

Table 5 displays the estimated timeline for review of this submission.

Table 5 Timeline for Review

Milestone	Target Date for Completion
Stamp Date	May 13, 2004
Filing Date	July 11, 2004
Study	September 1, 2004
Draft Review	November 30, 2004
Label Review	December 30, 2004
Wrap-up Meeting	January 26, 2005
Due Date (Division)	February 26, 2005
PDUFA Date	March 12, 2005

VIII. Summary

This NDA is a 505(b)(2) application for a levalbuterol HFA Inhalation Aerosol. The Applicant, Sepracor, requests approval of an HFA MDI containing 200 metered actuations of 59 mcg of levalbuterol tartrate (equivalent to 45 mcg levalbuterol in propellant). The reference product is Proventil HFA Inhalation Aerosol (3M Corporation). The proposed indication is the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease. The proposed dose is two inhalations (90mcg) every 4 to 6 hours. The Applicant has proposed the trade name Xopenex HFA™ Inhalation Aerosol for the drug product.

The reference product is Proventil HFA Inhalation Aerosol (3M Pharmaceuticals), which is currently approved for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in adults and children 4 years of age and older.

This application is supported by two randomized double-blind, placebo-controlled, active controlled, 8 week studies in adults/adolescents 12 years of age and older with asthma. In addition, the application is supported by one randomized double-blind, placebo-controlled, active controlled, 4 week study in children age 4 to 11 years with asthma. These studies are

appropriately indexed and organized to allow review. A 12 month safety study (051-356) is currently ongoing.

The Applicant did not prospectively address device performance in the Phase III studies. The ongoing safety study (051-356) was amended in November of 2003 to include collection of device performance data. Although the limited device performance data submitted in this NDA is not a filing issue, the adequacy of the device performance database to support approval of levalbuterol HFA will be a review issue.

The submission is adequate to allow full, in-depth clinical review. The submission is fileable. A DSI audit will be requested. Comments will be conveyed to the Applicant.

IX. Decision

The submission appears adequate to allow a full, in-depth clinical review; therefore, the application is fileable.

X. Comments to Applicant

The following comments will be conveyed to the Applicant.

Submit a brief foreign marketing history of levalbuterol hydrochloride inhalation solution.

Although the limited device performance data submitted in this NDA is not a filing issue, the adequacy of the device performance database to support approval of levalbuterol HFA will be a review issue.

Please submit a pediatric development program for this product.

Reviewed by:

Sally Seymour, M.D.

Medical Officer, Division of Pulmonary and Allergy Drug Products

Eugene J. Sullivan, M.D.

Deputy Director, Division of Pulmonary and Allergy Drug Products

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