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*APPLICATION NUMBER:*  
**21-912**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Established Name Arformoterol  
(Proposed) Trade Name   Brovana  
Therapeutic Class Long-acting Beta-2 adrenergic agonist  
Applicant Sepracor, Inc.

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Priority Designation S

Formulation Inhalation Solution  
Dosing Regimen Q 12 hours  
Indication Treatment of bronchoconstriction associated  
with chronic obstructive pulmonary disease  
Intended Population Adults

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

From a clinical perspective, the data submitted in this NDA provide support for Approval. The adequate and well-controlled clinical studies demonstrated that the proposed dose of 15 µg of arformoterol tartrate inhalation solution delivered by nebulization twice daily provides a statistically significant degree of bronchodilation over placebo in study subjects with chronic obstructive pulmonary disease (COPD). 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 appropriate secondary endpoints.

Given its documented clinical efficacy, the safety profile of arformoterol tartrate inhalation solution is acceptable. In the clinical studies conducted for this application, arformoterol tartrate was well-tolerated. Adverse events attributable to the drug were generally non-serious and likely related to the systemic Beta adrenergic effects of arformoterol. In this application, the safety of arformoterol tartrate is also supported by the Agency's previous finding of the safety of racemic formoterol (Foradil<sup>®</sup>) at a comparable dose.

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

Long-acting Beta-2 agonists (LABAs) as a class, while efficacious, may increase the incidence of severe asthma exacerbations and asthma-related deaths in patients with asthma who use them. Insufficient data exist to know whether similar safety issues are present in patients with COPD who use LABAs.

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#### Required Phase 4 Commitments

On August 25, 2006, a Regulatory Briefing was held in order to provide guidance to DPAP regarding safety concerns of arformoterol. The Panel agreed with DPAP's concerns as to both the long-term safety of arformoterol in the COPD population and its likely off label use to treat patients with asthma, especially children. As a result of these concerns, additional studies, including the possibility of a randomized, large simple trial to assess the long term safety of

arformoterol in patients with COPD, and to evaluate the safety of arformoterol use in patients in which a nebulized LABA would be attractive, including children with asthma in an acute care setting, will be required as Phase 4 commitments.

A concern of DPAP regarding this NDA previously conveyed to the Applicant has been the lack of safety and efficacy data in non-Caucasian populations, specifically African-Americans. The clinical development program for arformoterol contains < 5% African-Americans. The Applicant is currently conducting study 091-061, a 6-month safety study which will have increased African-American representation. No further commitments for the conduct of studies in minority populations will be sought from the Applicant.

### 1.2.2 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 arformoterol tartrate. Arformoterol is the (R,R)-enantiomer of racemic formoterol and is a long-acting Beta-2-adrenergic receptor agonist (LABA). The Applicant has submitted the names "Brovana" and  $\text{L}^{\text{A}}\text{R}$  as possible trade names. Arformoterol tartrate is supplied as 15  $\mu\text{g}$  of arformoterol in a 2 mL volume of buffered solution packaged in unit dose vials. The drug is to be delivered by nebulization. Throughout the clinical program, arformoterol solution was delivered via a PARI LC PLUS nebulizer and a PARI Dura-neb 3000 compressor.

The Applicant's proposed indication is the treatment of  $\text{L}^{\text{A}}\text{R}$  associated with COPD. The proposed dosing regimen is 15  $\mu\text{g}$  by nebulization (one 2mL vial) twice daily.

The Applicant conducted two pivotal Phase 3 clinical studies, three supportive studies including Phase 2 single and multiple dose dose-ranging studies and a Phase 3 long term safety study, twelve additional Phase 1 and 2 studies in normal subjects, special populations, and asthma patients to support the efficacy and safety of arformoterol. In addition, there is one ongoing safety study. In the pivotal Phase 3 studies, a total of 1456 subjects were enrolled. There were a total of 595.7 person-years of exposure data to arformoterol in the COPD clinical program. Specifically, there were 342 subjects exposed to arformoterol 15  $\mu\text{g}$  BID for up to 12 weeks, 345 COPD subjects exposed to arformoterol 25  $\mu\text{g}$  BID for up to 12 weeks, 383 COPD subjects received arformoterol 50  $\mu\text{g}$  QD for at least six months, and 308 subjects received arformoterol 50  $\mu\text{g}$  QD for one year. In the Phase 3 studies, arformoterol was administered at doses of 15  $\mu\text{g}$  twice daily, 25  $\mu\text{g}$  twice daily, and 50  $\mu\text{g}$  once a day for 12 weeks in adults with moderate to severe COPD. 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 to support the safety and efficacy of arformoterol inhalation solution.

One issue is worth noting about the clinical development program for this application. Reportedly for safety reasons, the Applicant intentionally unblinded the treatment codes for 24 subjects in the pivotal Phase 3 studies. The unblinding, however, did not have the potential to affect the outcome of the pivotal trials. This issue is addressed in detail in Section 4 of this review.

### 1.3.2 Efficacy

The two pivotal Phase 3 studies support the efficacy of arformoterol tartrate by demonstrating a statistically significant degree bronchodilation over placebo in subjects with COPD. The studies were adequate, well-controlled and identical in design; multicenter, randomized, double-blind, parallel group, and both placebo and active controlled. The two studies enrolled subjects 35 years of age and older with COPD and FEV1  $\leq$  65% predicted but  $>$  0.70 liters. The diagnosis of COPD was made by the presence of obstructive lung disease in adult subjects with chronic bronchitis and/or emphysema in the absence of other pulmonary disease who also had at least a 15 pack-year history of cigarette smoking. Subjects were treated with study medication for twelve weeks duration. The study design, study population, and study duration were found to be acceptable by DPAP.

For the primary efficacy variable, the Applicant chose FEV1, which is a well-established efficacy variable to assess the treatment of bronchospasm, determined at the end of the dosing interval. Serial spirometry during which FEV1 was measured was performed at each clinic study visit. As the specific primary efficacy endpoint, the Applicant determined the percent change from study baseline FEV1 to that at the end of the dosing interval over the 12 week double-blind treatment period. Pertinent secondary efficacy endpoints included the % change in FEV1 AUC, both from visit pre-dose and study baseline values over 12 and 24 hours, peak % predicted FEV1, and peak % change in FEV1. Non-spirometry based secondary endpoints included at-home and in-clinic peak expiratory flow rate (PEFR), supplemental ipratropium bromide and racemic albuterol MDI use, exacerbations of COPD, COPD Symptom Ratings, St. George's Hospital Respiratory Questionnaire (SGRQ), dyspnea indices, and six-minute walk.

The results of the clinical studies support the efficacy of arformoterol for the treatment of bronchoconstriction associated with COPD. Efficacy was established by the demonstration that arformoterol, at all doses tested, resulted in statistically significant improvements over placebo in FEV1 at the end of the dosing interval over the course of the 12 week studies. All secondary analyses of the FEV1 data, including area under the FEV1 curve analyses from 0-12 hours post dose and peak FEV1 established that arformoterol is superior to placebo. Other than the six-minute walk test, most other non-spirometry based secondary efficacy variables, including morning and evening home peak flow measurements and "rescue" albuterol and ipratropium bromide use, also generally supported the efficacy of arformoterol in COPD patients. In addition, all doses of arformoterol tested achieved comparable bronchodilation to that of the active comparator, the approved LABA, salmeterol.

### 1.3.3 Safety

The safety of arformoterol tartrate inhalation solution is supported by the Applicant's clinical studies and the Agency's previous determination of safety for racemic formoterol.

In the clinical programs, the size of the safety database is approximately 2722 subjects representing 1968 unique subjects, including subjects with COPD, subjects with asthma, and healthy volunteers. The great majority of subjects in the safety database participated in the Phase 3, multiple dose COPD studies which lasted 12 weeks (pivotal studies 091-050 and 091-051) and one year (safety study 091-060). The majority of the safety data for this review comes from the multi-dose pivotal Phase 3 studies because they are placebo-controlled, have more subjects, provide exposure to 3 different dose/dosing regimens of arformoterol, and have an active control as well. The long-term safety study provides additional safety data which assesses the safety of long-term use of a higher dose of arformoterol (50 µg once daily) than the proposed 15 µg twice daily dose.

The results of the clinical studies indicate that arformoterol, at a dose of 15 µg twice daily was well-tolerated. Beta adrenergic agonists have been studied extensively and have the potential to produce certain adverse events related to Beta adrenergic receptor stimulation, such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, arrhythmias, and worsening hypertension. Dose-related beta mediated adverse events were noted in the studies; however, the incidences were low. COPD related adverse events, including exacerbations, were less common in the 15 µg BID treatment group than the placebo group with other active treatment groups being similar to placebo.

Hypokalemia and hyperglycemia are also considered systemic Beta adrenergic effects. Small, generally clinically insignificant, changes in the mean concentrations of glucose and potassium were noted in the clinical studies. However, dose dependent increases in serum glucose and decreases in serum potassium concentrations were noted in the clinical trials.

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. The data from the multiple dose clinical studies demonstrated no consistent mean change in ECG measures, including QT prolongation. In addition, the rates of new, treatment emergent arrhythmia events was the same for subjects who received arformoterol 15 µg twice daily as that for those who received placebo. Despite the older age and the presence of cardiovascular co-morbidities in many subjects, cardiovascular adverse events in the clinical studies were uncommon in any treatment group. There were, however, more subjects who discontinued due to cardiovascular adverse events in all active treatment groups compared to placebo.

### 1.3.4 Dosing Regimen and Administration

The proposed dosing regimen of arformoterol tartrate inhalation solution is 15 µg by nebulization twice daily. The proposed dosing interval is sufficiently supported by the clinical

efficacy data as the primary efficacy variable (trough FEV1), through which efficacy was established, was a measurement taken at the end-of-dosing interval.

Multiple doses and both daily and twice daily dosing regimens, including the proposed dose, all administered were studied in Phase 2 dose-ranging and pivotal Phase 3 studies. Those studies demonstrated a dose-response both in terms of efficacy and tolerability of the known effects of increasing Beta adrenergic receptor stimulation, especially tremor and nervousness. Doses of 25 µg twice daily were slightly more effective than the 15 µg twice daily dose, but were associated with a greater incidence of increased Beta agonist side effects. The increased Beta agonist side effects seen at the 25 µg dose is indicative of a relatively narrow therapeutic index for this particular LABA and highlights the point that if the nebulizer used to deliver the marketed arformoterol product is more efficient than the PARI LC PLUS used in the clinical trials, increased Beta agonist mediated side effects may occur. A 50 µg once daily dose had even greater Beta agonist effects as well as a decrease in efficacy towards the end of the daily dosing interval.

#### 1.3.5 Drug-Drug Interactions

The effect of inhibition of the liver enzyme CYP2D6 on arformoterol pharmacokinetics was evaluated and no dosage adjustments are necessary when the arformoterol is given concomitantly with other drugs that are known to be CYP2D6 enzyme inhibitors. In the product label, the Applicant has included appropriate warnings regarding Beta agonist drug interactions that are known to occur with Beta blockers, diuretics, xanthine derivatives, monoamine oxidase inhibitors, steroids, tricyclic antidepressants, and drugs that prolong the QT interval.

#### 1.3.6 Special Populations

Special dosing is not recommended for arformoterol tartrate inhalation solution based upon gender, age, cardiac, renal, hepatic, or respiratory disease. While safety and efficacy analyses aimed at detecting possible race interactions did not reveal evidence of such interactions, because very few patients in the Phase 3 studies were non-Caucasian, no firm conclusions can be drawn. Subjects with hepatic   have increased systemic exposure to arformoterol and the proposed product label appropriately states that arformoterol should be used cautiously in these patients. Also, because of the potential for Beta agonist mediated adverse effects, the proposed product label cautions use in patients with cardiovascular disorders, convulsive disorders, or in individuals with

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Arformoterol tartrate has not been studied in pregnant women; therefore, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Similarly, it is not known if arformoterol 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 Applicant, Sepracor, Inc., submitted NDA 21-912 on December 8, 2005 for a nebulized inhalation solution containing only the (R,R) enantiomer of the long-acting Beta-2 agonist (LABA) formoterol (arformoterol) to be indicated for the long-term maintenance treatment of  associated with COPD. b(4)

The molecular structure of formoterol contains two chiral centers. Thus, formoterol may exist as a mixture of up to 4 enantiomers, (R,R), (S,S), (R,S), and (S,R). While the marketed formoterol LABA, Foradil<sup>®</sup>, contains an equal mixture of the (R,R) and (S,S) enantiomers, studies have shown that it is the (R,R) enantiomer of formoterol that possesses the Beta-agonist activity and therapeutic bronchodilation of the molecule. It is approximately 1000-fold more potent as a Beta-agonist than the (S,S) enantiomer based on receptor stimulation, smooth muscle relaxation and inhibition of spasmogen responses. Arformoterol, like racemic formoterol, exhibits a relatively rapid onset of action, with the proposed dose of 15 µg producing significant bronchodilation within minutes of inhalation and has a long duration of effect after a single dose which supports a twice daily dosing schedule. As would be expected, by containing only the active enantiomer of formoterol, on a stoichiometric basis, it is twice as potent as racemic formoterol. The Applicant has proposed two trade names, Brovana and  with a stated preference for . b(4)

The trade name review is ongoing at the time of this clinical review.

### 2.2 Currently Available Treatment for Indications

The formoterol product, Foradil<sup>®</sup>, is marketed in Europe and the United States for treatment of bronchospasm in asthma and COPD.

Currently, there are other several Beta-2 adrenergic receptor agonists available in a variety of formulations in the United States for the treatment of bronchospasm associated with COPD. They include the short-acting Beta-2-adrenergic agonists (e.g. albuterol, pirbuterol, bitolterol, metaproterenol, and terbutaline) and two LABAs (salmeterol and formoterol). These LABAs, marketed alone as Serevent<sup>®</sup> and Foradil<sup>®</sup> and in a combination product which includes an inhaled corticosteroid, Advair<sup>®</sup>, are in the same drug class as arformoterol, with Foradil representing the same molecule, albeit the racemic mixture of enantiomers. Arformoterol, however, would be the only LABA available as an inhalation solution for nebulization. Other approved bronchodilators for COPD are short-acting and long-acting anti-cholinergic agents (ipratropium and tiotropium, respectively), and theophylline.

### 2.3 Availability of Proposed Active Ingredient in the United States

Arformoterol is not marketed in the United States or any foreign country. Racemic formoterol, which contains arformoterol, is marketed in the United States as Foradil<sup>®</sup>.

## 2.4 Important Issues With Pharmacologically Related Products

The LABAs, salmeterol (Serevent<sup>®</sup>) and racemic formoterol (Foradil<sup>®</sup>) are marketed world-wide for the relief of bronchospasm in both patients with COPD and those with asthma. The safety of chronic use of LABAs, especially for the control of asthma symptoms has been an issue of concern in recent years. Salmeterol was first approved in the United States for use in patients with asthma in 1994. Shortly thereafter, reports in the literature suggested that chronic usage of salmeterol may make asthma worse. Due to accumulating concerns regarding the safety of chronic, regular use of salmeterol, the FDA worked with GlaxoSmithKline (GSK), the makers of Serevent<sup>®</sup> to have them conduct a large, controlled prospective safety study to address this issue. As a result, GSK initiated the Salmeterol Multicenter Asthma Research Trial (SMART) in 1996. The SMART was a randomized, double-blind study that enrolled patients with asthma not currently using LABAs to assess the safety of salmeterol (42 mcg twice daily for 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). The study was prematurely terminated in January 2003 after a total of approximately 30,000 patients had been enrolled because a planned interim analysis suggested that salmeterol may be associated with an increased risk of severe asthma exacerbations including death, particularly in African Americans. While no controlled study large enough to assess this safety issue has ever been conducted for Foradil<sup>®</sup>, prior to approval in 2001, there were also safety concerns with asthma exacerbations seen consistently across the pivotal phase 3 studies when a dose of 24 µg of formoterol was used, a dose subsequently not approved. As a result of the findings described above, the safety of LABAs was the topic of discussion at a July 13, 2005, Pulmonary Allergy Drugs Advisory Committee Meeting. Subsequent to the meeting, in November, 2005, the FDA released a Public Health Advisory to alert healthcare professionals and patients that LABAs may increase the chance of severe asthma episodes, and death when those episodes occur, and that even though LABAs decrease the number of asthma episodes, they may increase the chances of a severe asthma episode when they do occur. The existing product labels have been revised and now include a Boxed Warning and a Medication Guide for both marketed LABA products.

The safety studies described above pertain to the use of LABAs for treatment of asthma. Until recently, no information was available to know whether there are similar concerns when LABAs are used for COPD. However, the pharmaceutical company, GlaxoSmithKline, has funded a large clinical study (TORCH) which evaluated the effect of the LABA, salmeterol, and the inhaled corticosteroid, fluticasone, on all-cause mortality in 6,100 patients with COPD. The data are currently being analyzed by GlaxoSmithKline.

Both salmeterol and formoterol are indicated for use in COPD and asthma patients and both labels contain a Boxed Warning and Medication Guide concerning the safety risks in asthma. The fact that arformoterol will be indicated for treatment of patients with COPD and not asthma raises some unique safety concerns. It is likely that arformoterol, even though approved for use in COPD only, will be used "off-label" in patients with asthma, the population in which the risk of severe exacerbations has been shown to be increased with the use of other LABAs. In addition, because of the lack of safety studies such as SMART in patients with COPD, the

question regarding safety of LABAs in patients with COPD remains unanswered. On August 25, 2006, a Regulatory Briefing was held in order to provide guidance to DPAP regarding the above-mentioned safety concerns of arformoterol. Concerns were raised as to both the long-term safety of arformoterol in the COPD population and its likely off label use to treat patients with asthma, especially children. DPAP has similar concerns and, as a result, believes that a Boxed Warning and Medication Guide should be required for arformoterol even though it will be indicated for use in COPD and not asthma. In addition, DPAP considers both the accumulation of additional long-term safety data of arformoterol in the COPD population, including the possibility of a randomized, large simple trial, and establishing the safety profile of arformoterol in patients with asthma as essential components of post-marketing risk management activities. See Sections 8.7 and 9.3 of this review for further discussion of these safety issues.

## **2.5 Presubmission Regulatory Activity**

The following are pertinent regulatory milestones for the development of arformoterol tartrate inhalation solution including pertinent DPAP comments

### **Pre-IND Meeting**

On January 14, 1998, Sepracor discussed development plans and a new IND submission for Arformoterol Tartrate Inhalation Solution. Subsequently, IND 55,302 was submitted on February 20, 1998. Comments included:

- General toxicity studies and at least one carcinogenicity study should be investigated using the inhalation route while reproductive toxicology studies could employ the oral route, provided that no important ADME differences between these routes were found.
- An NDA for Arformoterol Tartrate Inhalation Solution would be categorized as a 505(b)(1) NDA submission,
- Heart rate alone is not the only index for Beta-agonist tolerance. Other parameters are clinical chemistry, pathology, histology evaluation and clinical observations to determine the Beta agonist tolerance level.

### **ECAC Meeting**

The proposed inhalation carcinogenicity study in rats was submitted to the ECAC for review on July 23, 1999. The committee recommended a 13-week toxicology dose-ranging study to increase confidence on the dose selected for the carcinogenicity study. In addition, DPAP suggested that the range of particle size be defined, organ weights be recorded, systemic exposure by plasma drug levels be assessed, EKGs be monitored, and for statistical analysis, tests be run with each control group and the means be combined.

### **End-of-Phase 2 Meeting**

On September 06, 2001, an End-of-Phase 2 meeting was held to discuss the proposed Phase 3 development program. Comments included:

- A pediatric waiver would likely be granted for a COPD indication.

- Even though arformoterol is likely metabolized in the same manner as racemic formoterol, primarily by conjugation and secondarily by CYP450 isozymes, documentation of the proposed mechanism would be required.
- A 90-day inhalation study using the most appropriate species was suggested for the qualification of degradants exceeding 1.0% and impurities exceeding 0.1%. DPAP also noted that qualification could also be achieved with the 6-month rat study, 13-week dog study, or 9-month dog study.
- Sepracor's plan to characterize the PK profile of arformoterol was acceptable
- It was recommended that Sepracor perform a genotype PK study of arformoterol in CYP2D6 poor metabolizers, if it were discovered from in vitro metabolism studies that arformoterol is metabolized by CYP2D6.
- DPAP cautioned that the patient population studied in the Phase 3 trials would become part of the indication for the drug with regard to including nonreversible subjects in the pivotal studies.
- DPAP suggested additional spirometry time point assessments to adequately characterize the response over the QD dosing interval.
- It was stated that FEV1 measured over time (FEV1 AUC<sub>0-12</sub> or AUC<sub>0-24</sub>) would be a more acceptable primary clinical endpoint for the maintenance therapy of a bronchodilator rather than peak percent FEV1.
- DPAP recommended additional dose ranging studies with clinically relevant endpoints, including the determination of a no-effect dose.
- For a 505(b)(1) submission with at least 1500 patients exposed to the drug, the DPAP confirmed that the 300 patients exposed for 6 months and the 100 patients exposed for 12 months would be acceptable for filing, as long as the exposure was to the dose that is to be approved, or one that is higher.

### **Special Protocol Assessment**

Following the End-of-Phase 2 meeting, Sepracor requested a Special Protocol Assessment for a Phase 3 protocol 091-051 was submitted on November 02, 2001. DPAP comments included:

- The primary efficacy should be the statistical separation of groups by trough FEV1.
- For twice daily dosing-inhaled bronchodilators, FEV1 AUC<sub>0-12</sub> hourly or every other hour measured in all subjects over the entire 12-hour interval should be collected.
- Long-term maintenance treatment would need to be assessed for the potential induction of tachyphylaxis associated with long term dosing with regard to FEV1 response and serious COPD exacerbations.
- Validation of the global evaluation and baseline/transitional dyspnea indices would be required if they were to be used to support approval.

### **FDA Request for Information Concerning Intentional Unblinding**

On April 24, 2003 Sepracor notified DPAP of a limited unblinding of safety data from a total of 24 subjects participating in Studies 091-050 and 091-051 who experienced serious cardiac or respiratory adverse events. On August 21, 2003, Sepracor received a request for additional

information regarding this unblinding. Sepracor submitted the requested information on December 23, 2003 and noted that any additional questions that the FDA might have could be addressed in an upcoming Type C meeting held on February 09, 2004. At that meeting:

- DPAP provided guidance on relevant information that would need to be submitted in the NDA to address the unblinding of safety data and that the conclusion regarding the integrity of the pivotal data subsequent to this unblinding could not be reached until the review of the NDA.
- DPAP also noted that, to adequately assess potential arformoterol effects on cardiac repolarization in Study 091-026, serial ECGs obtained at steady state and overread by a central ECG vendor were required. Correction for heart rate should utilize QTcB and QTcF correction formulae in addition to QTcM (subject-specific correction formula).
- DPAP noted that the number of subjects in the safety database appeared acceptable and should be complete at the time of NDA submission.

#### **Pre-NDA Meeting**

A Type B pre-NDA meeting with the DPADP was held on March 07, 2005.

- DPAP stated that the summary data provided in the briefing package supported using the 15 µg BID dose in the pivotal clinical studies, but determining whether this is the optimal dose would be a review issue.
- It was noted that the clinical program was not constructed to support a titrated dosing regimen, i.e., the clinical studies did not employ escalating doses for patients who did not respond to an initial dose, the clinical dose was not defined for a proposed dose titration, and the methods used for differentiating doses have not been evaluated.
- It was confirmed that the overall safety database is minimal, but acceptable and that adequate data for the highest dose would support lower doses.
- DPAP found the proposal for pooling data reasonable noting that presentation of safety data in the package insert should be supported by the analyses presented in the ISS.
- Sepracor explained that approximately 95% of the subjects in the pivotal studies were Caucasian, 3-3.5% were black, and the remaining 1-1.5% were Hispanic, Asian, or other. DPAP gave further consideration to this issue following the meeting, and determined that the lack of racial and ethnic subgroup data in the pivotal studies, resulting in under-represented subgroups, could be problematic to Sepracor's NDA application. On 10 June 2005, Sepracor requested clarification regarding the statement that the lack of racial and ethnic subgroup data in the pivotal studies may be problematic to the NDA application. DPAP responded by noting that it did not anticipate concerns with filing or potential approval of the NDA based on the racial/ethnic representation in the clinical studies alone.
- DPAP commented that the issue of breaking the treatment blind for some patients in the pivotal studies is not closed and that a convincing case must be provided in the NDA. It was agreed at the meeting that the information should be included as an appendix to NDA Section 8 with hyperlinks from each relevant CSR to this section.

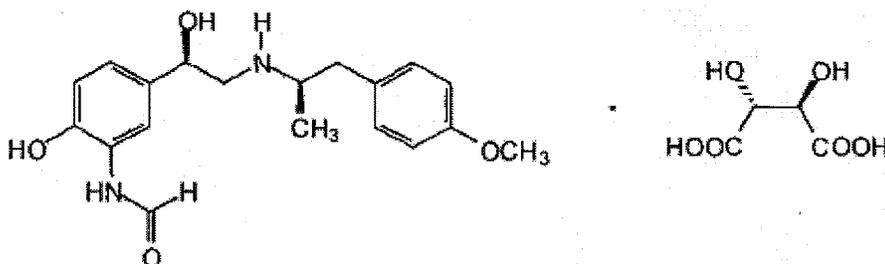
## 2.6 Other Relevant Background Information

Arformoterol has not been marketed in any other country and there have not been any foreign regulatory actions on arformoterol.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### 3.1 CMC (and Product Microbiology, if Applicable)

Arformoterol tartrate is designated chemically as (-)-N-[2-hydroxy-5-[(1R)-1-hydroxy-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide (2R,3R)-2,3-dihydroxybutanedioate. Arformoterol tartrate is not a new molecular entity manufactured by Sepracor Canada Ltd. Formoterol has two chiral centers with arformoterol possessing the (R,R) stereochemical configuration. The chemical structure and molecular formula for arformoterol tartrate are shown below:



The manufacturing process for arformoterol tartrate is a

The structure of arformoterol was elucidated by a variety of analytical and spectrophotometric techniques, including elemental analysis, UV and IR spectroscopy, NMR (<sup>1</sup>H and <sup>13</sup>C) spectroscopy, mass spectrometry, and X-ray crystallography. Arformoterol tartrate is a white to off-white solid which melts at approximately

b(4)

The proposed drug product is manufactured by

Arformoterol tartrate inhalation solution is formulated as isotonic, preservative-free, sterile aqueous solution consisting of arformoterol tartrate in a citrate-buffer saline solution (pH 5.0). All excipients are USP/NF grade. The composition and components of the inhalation solution (15 µg/2 mL) are listed in the following Table.

b(4)

### Arformoterol Inhalation Solution Composition

Component	Quality Standard	Function	Amount/Unit
Arformoterol Tartrate <sup>a</sup>	USP	Active	0.6967 gm
Citric Acid	USP	Buffer Component	
Sodium Citrate	USP	Buffer Component	
Sodium Chloride	USP	Isotonic	
<b>E</b>			
<b>Total</b>			2 mL

b(4)

<sup>a</sup>: 0.6967 gm of Arformoterol free base = 1.0 gm Arformoterol Tartrate

<sup>b</sup>: The amount in the table is the theoretical for the batch

Arformoterol Tartrate Inhalation Solution is filled in LDPE vials which are then over wrapped in foil pouches.

At the time of finalization of this review, Dr. Chien-Hua Niu, the Division's CMC reviewer, recommends Approval for this application.

### 3.2 Animal Pharmacology/Toxicology

Discussions with Pharmacology/Toxicology reviewer, Dr. Timothy Robison, during the course of this review failed to reveal any outstanding Pharmacology/Toxicology issues. Data presented below were obtained from information provided by the Applicant [Section 5, summary/summary.pdf] and from the Pharm/Tox review performed by Dr. Robison.

Arformoterol has been extensively characterized in standard in vivo and in vitro models and has been shown to exhibit preferential binding to the  $\beta_2$ -adrenergic receptor. It has a two-fold greater potency than racemic formoterol and has full agonist activity at the  $\beta_2$ -adrenergic receptor. The S,S enantiomer of formoterol, is 1000-fold less potent than (R,R)-formoterol as a  $\beta_2$ -agonist, based on receptor binding. Arformoterol was broadly screened for activity at a variety of other receptors, ion channels and enzymes and was found to be devoid of significant activity for any of the sites tested. A table listing all primary and secondary studies, including significant results can be found in Section 2.6 of the pharmacology/toxicology summary found in the NDA [Section 2.6/pharmtox/pharmsum.pdf].

Following oral administration, the absolute bioavailability of arformoterol in mice and rats was low (5 to 10%) but was more than 50% in the dog. After oral or intravenous administration, arformoterol was rapidly and widely distributed throughout mouse, rat and dog tissues. The apparent volume of distribution ( $V_{ss}$ ) in rats and dogs was 5.6-11.5 L/kg following an intravenous dose. Arformoterol was found to be moderately to weakly bound to plasma proteins in humans (52-65%), mice (28-34%), rats (37-49%) and dogs (36-48%). Following inhalation administration of arformoterol to mice, rats, or dogs, absorption was rapid with peak plasma concentrations typically observed in less than one hour. No consistent gender-specific differences in systemic exposure were observed in mice, rats, or dogs.

The inhalation NOAEL of 800  $\mu\text{g}/\text{kg}/\text{day}$  arformoterol in mice resulted in systemic exposures were approximately 500-fold or higher than the human exposure (0.069  $\text{ng}\cdot\text{h}/\text{mL}$ ) at the

maximum anticipated dosage (15 µg BID). The inhalational NOAEL in rats was 100 µg/kg/day. This NOAEL corresponded to systemic exposures that were 42- to 58-times higher than human exposure at the maximum anticipated dosage of 15 µg BID. The arformoterol systemic exposure threshold in dogs was 29-fold higher for AUC and 58-fold higher for C<sub>max</sub> than the human exposures after the maximum anticipated dosage of 15 µg BID

Arformoterol was not genotoxic based on the negative findings of an in vitro mutagenicity study in bacterial cells, in vitro chromosomal aberration assay in CHO cells, and in vivo micronucleus study in mouse bone marrow.

Carcinogenicity studies with arformoterol tartrate in rats showed no increase in treatment related tumors in animals who received 40 µg/kg/day, which is approximately 35.9-55.5 times the systemic exposure for the proposed clinical dose of 15 µg BID. At higher doses (100-200 µg/kg/day), increased incidences of thyroid C-cell adenoma and carcinoma in female rat treatment groups was seen [*Pharm/Tox Review/ Carcinogenicity Study Review/Timothy Robison*].

An arformoterol dose of 10 mg/kg/day was considered a NOAEL for reproductive performance and early embryonic development in the rats. Based on a body surface area comparison, this NOAEL was at least 2,857-fold higher than the maximum anticipated human dosage of arformoterol at 15 µg BID. The NOAEL for both maternal and developmental toxicity in the rabbit was 20 mg/kg/day arformoterol. The systemic exposure on gestation day 20 in rabbits at the NOAEL was at least 8,400-fold higher than the human exposure. Based on the body surface area comparison, the arformoterol NOAEL was approximately 12,000-fold higher than the maximum anticipated dosage of 15 µg BID in humans.

In a developmental study in rabbits, arformoterol at 80 mg/kg/day was compared to racemic formoterol at 160 mg/kg/day. Maternal rats exhibited decreased defecation after receiving racemic formoterol at 160 mg/kg/day. Findings in the racemic formoterol and arformoterol groups, at comparable (R,R)-enantiomeric dosage, consisted of fluctuations in maternal body weights and food consumption, and developmental effects of post-implantation loss, decreased fetal viability, decreased weights, and presence of malformations (spina bifida, malpositioned kidney, bulbous aorta, interventricular septal defect, and malaligned sternbrae) and variation (sternbrae with thread-like attachment). Additional fetal malformations with racemic formoterol included craniorrhachischisis, gastroschisis, sternoschisis, fused sternum, ectrodactyly, and brachydactyly. This study suggests that both racemic formoterol and arformoterol, at comparable doses, elicit fetal malformations and skeletal variations. These developmental effects are consistent with those that have been cited in the literature with other β-adrenergic agonists in animals when evaluated at high doses.

Reproductive and developmental findings with arformoterol were consistent with other β-adrenergic agonists that carry a Pregnancy Category C classification. Based on the review of comprehensive reproductive and developmental information, a Pregnancy Category C classification for arformoterol is justified.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The clinical data submitted in support of this NDA are derived from the studies performed as part of the Applicant's clinical development program. The application does not rely on reports in the medical literature or other sources of data.

### 4.2 Tables of Clinical Studies

The following tables provide a summary of the pivotal, supportive, and other clinical studies in this application.

#### Pivotal Phase 3 Clinical Trials 091-050 and 091-051 for NDA 21-912

Study Number (Report #)	Study Type	Treatment Groups	Location	Duration	Design	Number of Subjects	Primary Endpoint
091-050	Safety/Efficacy	Arformoterol 15mcg bid Arformoterol 25mcg bid Arformoterol 50mcg qd Salmeterol 42mcg bid Placebo bid	US	12 weeks	R, DB, DD, PC, AC, PG	717	% change in trough FEV1 from study baseline to the end of the dosing interval (12 or 24 hr)
091-051	Safety/Efficacy	Same as above	US	12 weeks	Same as above	739	Same as above

#### Supportive Clinical Trials 091-021, 091-026, and 091-060 for NDA 21-912

Study # Country/ Dates	Design	Treatments	Duration	# of Subjects	Population	Primary Endpoint	Relevance to Review
091-021 USA 10/00-4/01	Dose-ranging R, PC, cross-over	Arformoterol: 9.6mcg qd 24mcg bid 48mcg qd 96mcg qd placebo	Single Dose	75	COPD	Safety and tolerability	Dose Ranging Safety
091-026 USA 10/03-5/04	Dose-ranging R, DB, PG 2 part	Part A Arformoterol 5, 15, 25mcg bid Part B Arformoterol 15, 25, 50mcg qd Placebo	Part A 14 Days Part B 14 Days	Part A 215 Part B 191	COPD	Explore airway function endpoints	Dose-Ranging Cardiac Safety
091-060 USA 6/02-12/04	Safety R, OL, AC, PG	Arformoterol 50mcg qd Salmeterol 42mcg bid	1 year	793	COPD	Long-term safety	Safety of Higher doses of arformoterol

**Other Clinical Studies Conducted with Arformoterol for NDA 21-912**

Study No. Report No.	Description of Study	Total No. Subjects	Country	Relevance to Review
091-001	Tolerability and pharmacokinetics of single increasing doses in normal volunteers (6-96 mcg).	16	USA	Safety
091-002	Tolerability and pharmacokinetics of single increasing doses in subjects with mild to moderate asthma (6-96 mcg).	6	USA	Safety
091-007	Evaluation of the impact of P450 2D6 and UGT1A1 metabolism on the PK of arformoterol inhalation solution (poor vs extensive CYP2D6 metabolizers, single 50mcg dose)	40	USA	Safety Metabolism
091-012	Metabolism and pharmacokinetics of a single oral radio-labeled dose in normal volunteers (50mcg po dose)	8	USA	ADME Study
091-013	Tolerability and pharmacokinetics after a single 50mcg dose in healthy elderly subjects	48	USA	Safety in elderly
091-014	Tolerability and pharmacokinetics of a single 50mcg dose in subjects with mild to severe renal insufficiency	40	USA	Safety in renal failure population
091-015	Tolerability and pharmacokinetics of a single 50mcg dose in subjects with mild to severe hepatic insufficiency	40	USA	Safety in hepatic failure population
091-016	Pharmacokinetics of single increasing dose arformoterol compared to racemic formoterol in subjects with mild to moderate asthma (15 and 50mcg arf/12 and 100mcg for)	23	USA	Safety and PK
091-018	Drug interaction study of multiple dose arformoterol concomitantly with multiple dose paroxetine (inhibitor of P450 2D6) in normal volunteers (50mcg arf/20 mg par qd)	34	USA	Safety, Drug interaction
091-019	Multiple-dose, 3-way crossover study to compared the PK profile of arformoterol inhalation solution dose of 15 µg BID to Foradil DPI (12 µg and 24 µg BID) in subjects with COPD	39	USA	Safety, PK, PD comparison to marketed racemic formoterol
091-003	Single-dose 6-way crossover study in the reversal of bronchoconstriction in adults with asthma (dose-response study with 12, 24, 48, 72mcg of arformoterol, 2.5mg albuterol, and placebo)	49	USA	Safety
091-004	Safety, efficacy, and tolerability of multiple once-daily doses in subjects with asthma (24, 48, 72mcg)	357	USA	Safety

**4.3 Review Strategy**

The two pivotal, Phase 3 studies (091-050 and 091-051) shown in the table above are the primary basis in this review to support the efficacy of arformoterol tartrate inhalation solution. Each of the studies is reviewed individually in detail in the Appendix. The studies had identical designs and in the Integrated Review of Efficacy (Section 6), the efficacy results for the studies are pooled.

In addition to safety, following is a summary of the review strategy for the supporting studies listed the table above:

- Studies 091-021 and 091-026 are single and multiple-dose, dose-ranging studies which support dose selection. In addition, study 091-026 included extensive ECG and Holter monitoring in order to assess for the QT prolongation and the arrhythmogenic potential of arformoterol. Both studies are reviewed individually in the Appendix of this review.
- Study 091-060 is the one year, open-label safety study with the approved LABA, salmeterol as an active comparator. The study has limited use because it used a higher dose and different dosing regimen of arformoterol than the proposed dose. Long-term safety data with the higher dose, however, were useful in determining if unforeseen safety issues not consistent with the Beta-2 agonist class could be detected. The study is also reviewed individually in the Appendix.

Studies in subjects with asthma and normal volunteers were briefly reviewed for safety, however, since asthma and COPD patient populations are very different and the asthma studies were generally short, the safety assessment added little to the review. Other studies listed above contributed to the safety review in special populations (elderly, renal, and hepatic failure) or to assessment of drug metabolism and pharmacokinetics.

There is one ongoing study that is not listed in the tables above, a 6-month safety study (091-061) comparing arformoterol 15 and 25 µg BID by nebulization to the marketed product Foradil Aerolizer (racemic formoterol) 12 µg BID via dry powder inhaler. An update on the study is included in the safety update submitted by the Applicant, however, since only 45 subjects have been randomized and the study remains blinded, no significant conclusions can be made concerning safety.

#### **4.4 Data Quality and Integrity**

Review of the data from the pivotal studies by the Biometrics reviewer (Dr. Ted Guo) did not show any evidence of treatment-by-site interaction. DPAP did not request audits by the Division of Scientific Investigation. This decision is based on the facts that the molecular entity is not a new molecular entity but is the active enantiomer of the well-characterized LABA, racemic formoterol, which is already approved for the treatment of both asthma and COPD, the efficacy data are robust and as would be expected for the product, and the sponsor is not making any novel claims for the product.

It should be noted that during the pivotal trials, 091-050 and 051, the Applicant unblinded itself and the DMSB to 24 patients who had adverse events related to either cardiac or respiratory systems. When informed, the Division noted its concern that this unblinding could undermine the integrity of the pivotal studies and notified the Applicant at a Pre-NDA meeting on March 07, 2005 that full explanation of blind breaking must be made in the NDA. The reason stated for the internal unblinding of study participants was that in the monitoring of the open-label safety study, 091-060, it appeared that there was a higher incidence of cardiac and respiratory AEs in the group receiving 50 µg of arformoterol QD than the group receiving the active comparator

salmeterol at 42 µg BID. The course of events surrounding the unblinding and the possible impact on the outcome of the trials has been reviewed and it is apparent that the unblinding of safety data for these 24 subjects would not impact the study outcomes [Section 2.4.2, *clinstst\clinsum.pdf*]. This conclusion was reached for the following reasons: 1) unblinding information was not conveyed to participants, investigators, or study site staff, 2) at the time of the unblinding 96% of the subjects had already completed the study, 3) removal of these 24 subjects had no effect on primary/key secondary analyses, 4) no efficacy data were unblinded, and 5) no changes were made to protocols, databases, or analyses as a result of the unblinding.

#### 4.5 Compliance with Good Clinical Practices

The Applicant has indicated that all clinical trials were conducted in accordance with accepted ethical standards [Section 1.4, *clinstat\clinsum.pdf*].

During the course of studies 091-050 and 051 there was limited unblinding of safety data. This issue is discussed in Section 2.4, *clinsum.pdf* of this NDA application and is summarized above in Section 4.4 of this review. After review of the unblinding issue, while improper, it would not have significant effects on the study outcome.

#### 4.6 Financial Disclosures

Section 19 of the NDA addresses the Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators. The Applicant certifies that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study (Category 1), that no investigator received significant payments (Category 2), that none of the investigators disclosed a proprietary interest in the product (Category 3), or possessed a significant equity interest in the Applicant (Category 4) as defined in 21 CFR 54 with the following exceptions. Three investigators were noted to receive significant payments from the Applicant > \$25,000 (Category 2), [ ] possessed a significant equity interest of > [ ] \$50,000. [ ]

[ ] [ ] Based on this information, as well as the multi-center nature of the pivotal clinical studies, it is unlikely that financial interests could have influenced or biased the results of these studies.

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### 5 CLINICAL PHARMACOLOGY

Pertinent pharmacokinetic, pharmacodynamic, and dose-exposure relationships are summarized below. Significant findings include:

- Arformoterol does not inhibit common CYP enzymes.

- Systemic exposure of arformoterol increased 1.3-2.4-fold in subjects with hepatic impairment.
- Dose-ranging studies found that doses of 5 µg BID were not efficacious over the entire dosing period and that doses > 50 µg/day did not add appreciably to efficacy.
- Clinical studies demonstrated a clear dose-related decrease in serum potassium levels and increase in glucose levels with increasing doses of arformoterol (changes generally clinically insignificant).
- Analyses from study 091-026 demonstrated no correlation between change in QT<sub>C-M</sub> values at t<sub>max</sub> and peak arformoterol plasma concentrations.
- Pivotal studies demonstrated a transient dose-response with regard to QT prolongation after the first dose of study drug only at Week 0 when QT<sub>C-F</sub> increased from 2.38 to 3.15 to 4.71ms compared to 0.60ms in the placebo group, in the arformoterol 15 µg BID, 25 µg BID, and 50 µg QD groups, respectively.
- AEs reported in the arformoterol groups that appeared to have a dose response included asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor with nervousness and tremor showing the strongest dose-response relationship. Rates of these AEs in the arformoterol proposed 15 µg BID dose did not differ significantly from rates in the placebo group except for tremor (1.4% vs 0.3%).
- Holter monitoring findings from study 091-026 showed more ventricular ectopic beats in a 24 hour period in the higher dose arformoterol groups (25 µg BID in Part A and 50 µg QD in Part B) than in lower dose groups, however, this difference did not translate into an increased number of subjects with nonsustained (3-9 beat run) or sustained (≥ beat run) ventricular tachycardia.
- In the pivotal studies the rates of arrhythmia events not present at baseline over the double-blind period were slightly higher in the higher dose arformoterol 25 µg BID and 50 µg QD groups and salmeterol group, (37.6, 40.1, and 39.6%, respectively). The rates in subjects in the placebo and arformoterol 15 µg groups with new, treatment emergent arrhythmias was the same (approximately 33-34%).

## 5.1 Pharmacokinetics

Arformoterol appeared within 10 minutes in the systemic circulation following administration of nebulized doses in subjects with COPD. The median t<sub>max</sub> was approximately one half hour and the terminal-phase half-life was approximately 26 hours over the administered dose range. Systemic exposure to arformoterol increased linearly with dose in COPD subjects following arformoterol doses of 5, 15, or 25 µg twice daily for 2 weeks or 15, 25, or 50 µg once daily for 2 weeks. Steady-state PK parameters are presented in the Table below.

### Steady State Plasma Arformoterol Pharmacokinetic Parameters After Administration of Arformoterol 15 mcg BID for 14 Days in COPD Patients

Parameter	Arformoterol 15 µg BID
Mean C <sub>max</sub> (pg/mL)	4.3
Mean AUC <sub>0-12</sub> (pg*hr/mL)	34.5

Median $t_{max}$ (hr)	0.57
Mean $t_{1/2}$ (hr)	25.6

### Absorption

Systemic exposure to arformoterol may be primarily ascribed to pulmonary absorption. In COPD subjects administered 15 µg arformoterol every 12 hours for 14 days, a mean steady-state peak arformoterol plasma concentration of 4.3 pg/mL was observed approximately one half hour after drug administration.

### Distribution

Arformoterol is moderately bound (52-65%) to human plasma proteins.

### Metabolism

In vitro profiling studies in hepatocytes and liver microsomes have shown that arformoterol is primarily metabolized by direct conjugation (glucuronidation) and secondarily by O demethylation. At least five human uridine diphosphoglucuronosyltransferase (UGT) isozymes catalyze arformoterol glucuronidation in vitro. Two cytochrome P450 isozymes (CYP2D6 and secondarily CYP2C19) catalyze the O-demethylation of arformoterol. Arformoterol did not inhibit CYP1A2, CYP2A6, CYP2C9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11 enzymes.

Arformoterol was almost entirely metabolized following oral administration of 35 µg of radiolabeled arformoterol in eight healthy subjects. Direct conjugation of arformoterol with glucuronic acid was the major metabolic pathway. Most of the drug-related material in plasma and urine was in the form of glucuronide or sulfate conjugates of arformoterol. O-Desmethylation and conjugates of the O desmethyl metabolite were relatively minor metabolites accounting for less than 17% of the dose recovered in urine and feces.

These investigations suggest that arformoterol does not inhibit common CYP enzymes [Section 5, *pharmtox/pharmsum.pdf*]. To confirm these findings, the Phase 1 studies 091-007 and 091-018 were performed in healthy subjects to evaluate the pharmacokinetics of arformoterol tartrate inhalation solution in subjects classified as poor versus extensive CYP2D6 metabolizers, or with reduced uridine diphosphate glycosyl transferase 1 polypeptide A1 (UGT1A1) activity and to evaluate the effects of paroxetine, a potent inhibitor of CYP2D6, on the pharmacokinetic profile of arformoterol at steady state in healthy subjects. Results confirmed that CYP2D6 is not an important component of the metabolism of arformoterol and that a drug-drug interaction with any CYP2D6 inhibitor would not be likely [Study 091-007 and 018 Clinical Study Reports].

### Elimination

After administration of a single oral dose of radiolabeled arformoterol to eight healthy male subjects, 63% of the total radioactive dose was recovered in urine and 11% in feces within 48

hours. A total of 89% of the total radioactive dose was recovered within 14 days, with 67% in urine and 22% in feces. Approximately 1% of the dose was recovered as unchanged arformoterol in urine over 14 days. In COPD subjects given 15 µg inhaled arformoterol twice a day for 14 days, the mean terminal half-life of arformoterol was 26 hours.

### Special Populations

Pharmacokinetic analyses indicated that there were no effects of gender, age, or race upon the pharmacokinetics of arformoterol. It must be noted, however, that there were very few African-American or other races who participated in the clinical trials ( $\leq 5\%$ ).

The pharmacokinetic profile of arformoterol was assessed in 24 subjects with mild, moderate and severe hepatic impairment. The systemic exposure ( $C_{max}$  and AUC) of arformoterol increased 1.3 to 2.4-fold in subjects with hepatic impairment compared to 16 healthy control subjects.

The impact of renal disease upon the pharmacokinetics of arformoterol was studied in 24 subjects with mild, moderate, or severe renal impairment. There was no difference in systemic exposure (AUC and  $C_{max}$ ) between subjects with renal impairment compared with healthy control subjects.

The pharmacokinetics of arformoterol has not been studied in pediatric subjects.

### 5.2 Pharmacodynamics

The Applicant conducted 2 dose-ranging studies, 091-021 and 091-026 which are reviewed individually in the Appendix of this NDA review. These studies found that doses of 5 µg BID were not efficacious over the entire dosing period and that doses  $> 50$  µg/day did not add appreciably to efficacy. Instead of attempting to select one dose used in the dose-ranging studies to take into the pivotal trials, the Applicant used 3 different doses, including a once daily dose (15 and 25 µg BID and 50 µg QD).

In addition to early dose-ranging studies, the pharmacodynamic relationship between mean time-matched plasma concentrations of (R,R)-formoterol and percent change in FEV1 from study baseline ( $\% \Delta FEV1$ ) was assessed in study 091-019, a Phase 2, open-label, randomized, multiple-dose, 3-way crossover, multicenter study compared the PK profile of arformoterol inhalation solution at the proposed clinically indicated dose of 15 µg BID to Foradil DPI (12 µg and 24 µg BID) in 39 male and female subjects with COPD. Results demonstrated that the  $\% \Delta FEV1$  from study baseline increased with plasma (R,R)-formoterol concentrations in all three treatments after 14 days. There appears to be a correlation between systemic exposure to (R,R)-formoterol and FEV1 in subjects with COPD (see Section 7.2.9, Safety Update, in this review for further discussion).

In the pivotal studies, there was a clear dose-related decrease in serum potassium levels with increasing doses of arformoterol both at the beginning and end of the treatment period with the effect was greatest at the 2 hour post-does time point [Table 6.8.1.2.2-1, clinstat\iss.pdf]. Dose-

related increases in serum glucose were also evident at two hours post-dose and persisted at six hours post-dose.

With regard to QT prolongation, in order to assess a possible PK/PD relationship, time-matched individual  $QT_{C-M}$  interval change from baseline by  $t_{max}$  plasma concentration was also analyzed for Study 091-026. The analyses demonstrated no correlation between change in  $QT_{C-M}$  values at  $t_{max}$  and peak arformoterol plasma concentrations. This study included a dose (50  $\mu\text{g}$  QD) which is >3-fold higher than the proposed single dose (15  $\mu\text{g}$ ). In addition, there were no clinically meaningful changes in other ECG intervals (PR, QRS, or QT) [Tables 6.9.1.1.1-1 and 6.9.1.1.1-2, *clinstat/liss/liss.pdf*]. However, in the pivotal studies, there is a hint of a dose-response with regard to QT prolongation after the first dose of study drug at Week 0 when  $QT_{C-F}$  increased from 2.38 to 3.15 to 4.71ms compared to 0.60ms in the placebo group, in the arformoterol 15  $\mu\text{g}$  BID, 25  $\mu\text{g}$  BID, and 50  $\mu\text{g}$  QD groups, respectively. The effect is not clinically significant nor was it maintained at later time points (Weeks 6 or 12).

### 5.3 Exposure-Response Relationships

This section will focus on the relationship between exposure and safety. A more complete presentation of safety findings, including possible exposure-related safety findings can be found in Section 7, Integrated Review of Safety.

While the overall incidence of treatment emergent AEs in the pivotal studies was very similar across treatment groups, AEs reported in the arformoterol groups that appeared to have a dose response included asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor with nervousness and tremor showing the strongest dose-response relationship. Rates of these AEs in the arformoterol proposed 15  $\mu\text{g}$  BID dose did not differ significantly from rates in the placebo group except for tremor (1.4% vs 0.3%).

Holter monitoring findings from study 091-026 showed more ventricular ectopic beats in a 24 hour period in the higher dose arformoterol groups (25  $\mu\text{g}$  BID in Part A and 50  $\mu\text{g}$  QD in Part B) than in lower dose groups, however, this difference did not translate into an increased number of subjects with nonsustained (3-9 beat run) or sustained ( $\geq$  beat run) ventricular tachycardia. [Tables 6.9.2.1-1 and 6.9.2.1-2, *clinstat/liss/liss.pdf*]. In the pivotal studies the rates of arrhythmia events not present at baseline over the double-blind period were slightly higher in the higher dose arformoterol 25  $\mu\text{g}$  BID and 50  $\mu\text{g}$  QD groups and salmeterol group, (37.6, 40.1, and 39.6%, respectively). The rates in subjects in the placebo and arformoterol 15  $\mu\text{g}$  groups with new, treatment emergent arrhythmias was the same (approximately 33-34%) [Table 6.9.2.2-4, *clinstat/liss/liss.pdf*].

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## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

Many patients with COPD have an element of reversible bronchoconstriction that responds to Beta-2 agonist and anti-cholinergic bronchodilator agents and the use of these agents has been shown to improve symptoms of airway obstruction. The Applicant is thus seeking an indication for use of the LABA, arformoterol, as twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. This is the standard indication that bronchodilator agents for the treatment of patients with COPD have been typically approved for.

#### 6.1.1 Methods

Conclusions regarding the efficacy of arformoterol tartrate inhalation solution (15µg BID) were arrived at following detailed review of the efficacy findings of each of the two individual pivotal Phase 3 studies. The studies (091-050 and 091-051), outlined in the table below were identical 12-week, double-blind, double-dummy, placebo- and active-controlled, randomized multi-center, parallel group studies that evaluated the safety and efficacy of arformoterol at doses of 15 µg BID, 25 µg BID and 50 µg QD versus placebo and salmeterol 42 µg BID over in subjects with COPD.

**Pivotal Clinical Studies 091-050 and 091-051** /Table 4-1, *clinstat/ise/ise.pdf*

Study No. No. of Centers Status (Start and Completion Dates)	Phase, Study Design, and PK Sampling Strategy	Diagnosis and Criteria for Inclusion	Duration of Treatment	Dose, Route, and Dosage Form		Criteria for Evaluation	Formulation and Lot No.
				Arformoterol	Comparator		
091-050 60 centers 27 Feb 2002 to 18 Jun 2003	Phase 3 Study Design: DB, randomized, PBO- and active-controlled, multicenter, parallel-group study of arformoterol in subjects with COPD  N= 724 (Randomized population) N= 717 (ITT population)  PK Sampling Strategy (only on a subset of subjects): Blood: Predose and post-first dose at 10 min and 2 and 6 h at Visits 3, 5, and 7 (Weeks 0, 6, and 12, respectively)	M:F (>35 years) with a primary diagnosis of COPD, including components of chronic bronchitis and/or emphysema; MRC Dyspnea Scale Score ≥2; baseline FEV <sub>1</sub> ≤65% of predicted normal value and >0.70 L; FVC ratio ≤70%.	12 weeks	Arformoterol: 50 µg QD (N=146), 25 µg BID (N=143), 15 µg BID (N=141) Nebulization (2 mL solution)	Placebo Nebulization (2 mL solution) (N=143)  Salmeterol (Serevent®) MDI 42 µg BID Inhalation (N=144)	Primary Endpoint: % change in trough FEV <sub>1</sub> from study baseline to the end of the dosing interval (12 h post-second dose for the BID treatment groups and 24 h postdose for the QD treatment group). Key Secondary Endpoint: FEV <sub>1</sub> nAUC <sub>0-12h</sub> . Safety: AEs, vital signs, physical examination findings, ECG findings, 24-h Holter monitoring.	Arformoterol tartrate inhalation solution; Lot Nos. 03501A (15µg/2mL); 03501B (25µg/2mL); 03501C (50µg/2mL); Placebo; Lot No. 02301A; Salmeterol MDI (Serevent®); 13g canister/120 actuations; Lot Nos. 1ZP1729 and 2ZP1391; Ipratropium MDI (Atrovent®); 14g canister/200 actuations; Lot Nos. 010719W & 020077W; Racemic albuterol (Ventolin®); 17g canister/200 actuations; Lot Nos. 1ZP0791, ZP1204
				Rescue med = racemic albuterol (Ventolin®)			
				Supplemental med = ipratropium MDI (Atrovent®)			

Study No. No. of Centers Status (Start and Completion Dates)	Phase, Study Design, and PK Sampling Strategy	Diagnosis and Criteria for Inclusion	Duration of Treatment	Dose, Route, and Dosage Form		Criteria for Evaluation	Formulation and Lot No.
				Arformoterol	Comparator		
091-051  64 centers  16 April 2002 to 08 Mar 2004	Phase 3 Study Design: DB, randomized, PBO- and active-controlled, multicenter, parallel-group study  N= 741 (Randomized population) N=739 (ITT population)  PK Sampling Strategy (only on a subset of subjects): Blood: Predose and post-first dose at 10 min and 2 and 6 h at Visits 3, 5, and 7 (Weeks 0, 6, and 12, respectively)	M/F (≥35 years) with a primary diagnosis of COPD, including components of chronic bronchitis and/or emphysema; MRC Dyspnea Scale Score ≥2; baseline FEV <sub>1</sub> ≤65% of predicted normal value and ≥0.70 L; FVC ratio ≤70%.	12 weeks	Arformoterol: 50 µg QD (N=147), 25 µg BID (N=149), 15 µg BID (N=147) Nebulization (2 mL solution)	Placebo Nebulization (2 mL solution) (N=150)  Salmeterol (Serevent®) MDI: 42 µg BID Nebulization (N=146)	Primary Endpoint: % change in trough FEV <sub>1</sub> from study baseline to the end of the dosing interval (12 h post-second dose for the BID treatment groups and 24 h postdose for the QD treatment group).  Key Secondary Endpoint: FEV <sub>1</sub> nAUC <sub>0-12h</sub>  Safety: AEs, vital signs, physical examination findings, ECG findings, 24-h Holter monitoring, and clinical laboratory parameters (including glucose and potassium).	Arformoterol tartrate inhalation solution; Lot Nos. 03501A and 00902B (15µg/2 mL); 03501B and 00902C (25µg/2 mL); 03501C and 00902D (50 µg/2 mL); Placebo; Lot Nos. 05301B and 000902A, Salmeterol MDI (Serevent®) 13.0g canister/120 actuations; Lot No. 1ZP1966; Ipratropium MDI (Atrovent®); 14g canister/200 actuations; Lot No. 010584W; Racemic albuterol (Ventolin®); 17g canister/200 actuations; Lot Nos. 1ZP1205
				Rescue med = racemic albuterol (Ventolin®)			
				Supplemental med = ipratropium MDI (Atrovent®)			

### 6.1.2 General Discussion of Endpoints

Currently approved medications for COPD are indicated for the relief of bronchospasm due to COPD. As such, the basis for approval of these drugs has been adequate and well controlled studies demonstrating bronchodilator efficacy. Consistent with this traditional approach, the 2 pivotal clinical studies in this NDA specified as the primary variable an established measure of bronchodilator activity (FEV<sub>1</sub>). In addition, numerous secondary variables supporting bronchodilator activity were employed as well as use of rescue medications and quality of life indices. This Integrated Review of Efficacy will discuss the efficacy findings of the pivotal clinical studies primarily in regard to the bronchodilator efficacy of the drug and will also comment on the other non-pulmonary function endpoints.

### 6.1.3 Study Design

The pivotal Phase 3 trials supporting efficacy consisted of two identical, multi-center, randomized, double-blind, double-dummy, placebo- and active-controlled parallel-group studies of arformoterol in the treatment of subjects with chronic obstructive pulmonary disease over a 12 week treatment period (Studies 091-050 and 091-051). The active comparator in the trials was salmeterol, a LABA approved for use in the United States under the name Serevent® for the treatment of bronchoconstriction associated with both asthma and COPD. The dose of salmeterol used was the recommended inhaled dose of 42 µg BID. While an argument could be made that racemic formoterol (the approved LABA, Foradil®) would have been the optimal active comparator, the use of salmeterol was acceptable.

Detailed reviews of studies 091-050 and 091-051 are located in the Appendix to this review. In these studies, a total of 1465 patients with COPD were, following a 2-week single-blind placebo

run-in period, randomized 1:1:1:1 between placebo, salmeterol MDI 42 µg BID, and arformoterol 15 µg BID, 25 µg BID, and 50 µg QD. Arformoterol solution was delivered via a PARI LC PLUS nebulizer and a PARI Dura-neb 3000 compressor. Eligible patients had a history of COPD, a smoking history of  $\geq 15$  pack-years, age  $\geq 35$  years, FEV1  $\leq 65\%$  of predicted and  $> 0.70$  L, and an FEV1/FVC  $\leq 70\%$ . These inclusion criteria are appropriate and define a population of study subjects with moderate to severe COPD. Baseline bronchodilator reversibility was assessed but subjects were not included/excluded from the studies on the basis of reversibility. Spirometry was performed every 3 weeks throughout the 12 week treatment period (Weeks 0, 3, 6, 9, and 12). On Week 0, 6, and 12 testing days spirometry was performed immediately prior to dosing, immediately post-first dose first, at 15 and 40 minutes, and 1, 2, 3, 4, 5, 6, 8, 10, 12, 23, and 24 hours post-first dose. A subset of subjects underwent spirometry at 13, 14, and 16 hours post-first dose on Week 0, 6, and 12 testing days as well. On Week 3 and 9 testing days, spirometry was performed per-dose and at 2 hours post-dose.

Unlike many pivotal Phase 3 programs which assess the safety and efficacy of a single dose level of study drug, in each of their pivotal trials, the Applicant evaluated 3 dose levels of arformoterol, 15 and 25 µg BID and 50 µg QD in the pivotal studies. These doses were arrived at by assessing the bronchodilator action of arformoterol at 5, 15, 24, and 48 µg BID and 9.6, 15, 48, and 96 µg QD in Phase 2 dose-ranging studies (091-021, single dose and 091-026, multiple dose). These studies are reviewed in detail in the Appendix to this review. They demonstrated that doses of 5 µg BID and 9.6 and 15 µg QD did not perform adequately and that doses higher than 25 µg BID (50 µg total daily dose) offered no additional benefit, thus justifying the dose range used in the Phase 3 trials. In addition, they showed a dose-response relationship exists for doses up to 25 µg BID.

The pre-specified primary efficacy endpoint of the pivotal trials was percent change from study baseline FEV1 to the end of the dosing interval (i.e., trough at 12 hours post-second dose for the BID treatment arms and 24 hours post-dose for the QD treatment arm). The maximum FEV1 value from two maneuvers was recorded at each collection time.

A key secondary efficacy endpoint for the study was FEV1 time-normalized area under the percent change from visit predose curve over 12 hours (nAUC<sub>0-12-P</sub>) or, for the q day dosing group over 24 hours (nAUC<sub>0-24-P</sub>). Other secondary endpoints included numerous linked to bronchodilator activity including FEV1 time-normalized area under the % change from study baseline curve over 12 hours (nAUC<sub>0-12-B</sub>), FEV1 time-normalized area under the % change from visit predose curve over 24 hours (nAUC<sub>0-24-P</sub>), FEV1 time-normalized area under the % change from study baseline curve over 24 hours (nAUC<sub>0-24-B</sub>), peak % predicted FEV1, and peak % change in FEV1. Additional FEV1-based endpoints are listed in the individual pivotal study reviews found in the Appendix to this review.

Non-spirometry based secondary endpoints included at-home and in-clinic peak expiratory flow rate (PEFR), relationship between plasma concentration of arformoterol and % change in FEV1, supplemental ipratropium bromide and racemic albuterol MDI use, exacerbations of COPD,

COPD Symptom Ratings, St. George's Hospital Respiratory Questionnaire (SGRQ), subject/investigator global evaluations, dyspnea indices, and six-minute walk.

Study groups were generally well balanced for age, gender, and pulmonary characteristics. Most of subjects in the studies were Caucasian (95%), thus, there was little racial diversity in the studies. In the Pre-NDA meeting minutes dated March 07, 2005, this lack of racial/ethnic subgroups in the pivotal studies was raised as an important potential issue with the NDA. In a post pre-NDA Type B meeting July 26, 2005, the Division stated that it did not anticipate that demographic factors alone would prevent the potential approval of the application. The mean age of subjects was 62-63 years and there were more males (58-60%) than females. At screening, these patients had a mean FEV1 of approximately 1.2-1.3 liters which was 41-43% predicted. Approximately 80% of study subjects displayed FEV1 reversibility of  $\geq 10\%$ .

It should be noted that during the pivotal trials, 091-050 and 051, the Applicant unblinded itself and the DMSB to 24 patients who had adverse events related to either cardiac or respiratory systems. When informed, the Division noted its concern that this unblinding could undermine the integrity of the pivotal studies and notified the Applicant at a Pre-NDA meeting on March 07, 2005 that a convincing case concerning blind breaking must be made in the NDA. The course of events surrounding the unblinding and the possible impact on the outcome of the trials has been reviewed and it is highly unlikely that the unblinding could impact the study outcomes. Refer to Section 4.4 for a discussion of the events leading to the unblinding.

#### 6.1.4 Efficacy Findings

Both studies 091-050 and 091-051 demonstrated that arformoterol, at all dose levels tested, was superior to placebo and comparable to the marketed active comparator LABA, salmeterol, on the pre-specified primary endpoint of per cent change in trough FEV1 from study baseline over the 12-week double-blind treatment period (all p-values  $< 0.001$ , See Table below). The mean trough per cent change in FEV1 response in the 15 and 25  $\mu\text{g}$  BID groups and 50  $\mu\text{g}$  QD group was 16.9, 18.9, and 14.9 in study 091-050 and 15.7, 21.0, and 17.8 in study 091-051, respectively, thus establishing a dose-response relationship between the 15 and 25  $\mu\text{g}$  BID dose groups. The response of the salmeterol active comparator group was not clinically or statistically different to that of the arformoterol arms.

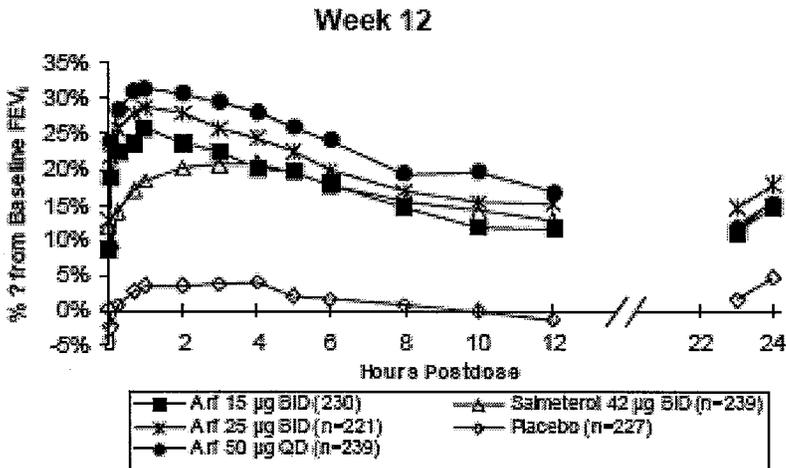
As would be expected, subjects whose airway obstruction was not reversible to the short-acting Beta agonist albuterol (defined as a  $< 10\%$  improvement in FEV1 when tested prior to randomization), improved less than that observed for subjects with  $\geq 10\%$  reversibility. For nonreversible subjects, the overall mean improvement difference relative to placebo was 2.3 to 8.7% for the arformoterol dose groups [Tables 11.4.1.1-2, *clinstat\copd\091-050.pdf* and *clinstat\copd\091-051.pdf*].

**Primary Pulmonary Function Outcomes Over the 12 Week Treatment Period** [Table 3.1.2.1.1-1, *clinstat\copd\ise.pdf*]

	Placebo	ARF 15 µg BID	ARF 25 µg BID	ARF 50 µg QD	Salmeterol 42 µg BID
<b>Primary Endpoint: Percent Change in FEV<sub>1</sub> from Study Baseline at 24-Hour Trough</b>					
Study 091-050					
n	134	138	142	143	138
LS Mean (SE)	6.0 (1.7)	16.9 (1.6)	18.9 (1.6)	14.9 (1.6)	17.4 (1.6)
p-value vs. placebo	-	< 0.001	< 0.001	< 0.001	< 0.001
Study 091-051					
n	141	140	142	138	138
LS Mean (SE)	5.3 (1.6)	15.7 (1.6)	21.0 (1.6)	17.8 (1.6)	17.3 (1.6)
p-value vs. placebo	-	< 0.001	< 0.001	< 0.001	< 0.001

As both pivotal studies were of identical design and both included salmeterol as a positive control, the pooled percent change in FEV<sub>1</sub> data are shown in the following Figure.

**Per Cent Change from Study Baseline FEV<sub>1</sub> (Pooled Studies 091-050 and 091-051)** [Figure 3.1.2.1.1-1, *clinstat\copd\ise.pdf*]



It should be noted that the approximately 11% change in mean trough FEV<sub>1</sub> above placebo seen in the 15 µg BID dose group translates to an increase of approximately 0.14 liters. This is comparable to the 0.11-0.13 liter increase in trough FEV<sub>1</sub> response seen in the tiotropium pivotal trials, the other recent COPD bronchodilator program in which trough FEV<sub>1</sub> response was the primary endpoint.

The Applicant pre-specified assessing FEV<sub>1</sub> nAUC<sub>0-12-P</sub> (time-normalized percent change from visit predose from 0 to 12 hours post-dose) as a key secondary efficacy endpoint which would assess bronchodilation over the 12 hours after dosing, relative to the day's predose value. FEV<sub>1</sub> nAUC<sub>0-12-P</sub> was significantly greater than placebo over the 12-week double-blind period for all arformoterol groups (p < 0.001 for all groups). Improvement over the 12-week double-blind period in FEV<sub>1</sub> nAUC<sub>0-12-P</sub> was also significantly greater for all arformoterol doses compared to salmeterol 42 µg BID (p values range from 0.029 to < 0.001). [Table 9.2.2-1, *clinstat\copd\ise.pdf*]

Other spirometry-based endpoints included FEV1 time-normalized area under the percent change from study baseline curve from 0 to 12 hours post-dose (nAUC0-12-B), peak per cent predicted FEV1, peak per cent change in FEV1 from visit predose, FEV1 peak per cent change from baseline, and FEV1 per cent change from study baseline at visit predose. Arformoterol, at all doses was statistically superior to placebo for all these endpoints over the 12 week treatment period. These data further support the conclusions regarding end-of-dosing interval efficacy that were drawn from the primary efficacy endpoint analysis.

Several pulmonary function secondary endpoints warrant specific commentary. The change in FEV1 peak percent of predicted from Week 0 to Weeks 6 and 12 were analyzed to assess the potential for development of tolerance to arformoterol. Using pooled data from both pivotal studies, there was a slight difference in change (decrease) in FEV1 peak per cent of predicted in any arformoterol or salmeterol treatment group between the Week 0 to 6 and 0 to 12 analyses (approximately 0.2-0.3 per cent predicted decrease in Week 0-12 vs Week 0-6). [Table 8.3, *clinstat/copdlise.pdf*] There was also a small reduction magnitude of bronchodilation as determined by percent improvement in trough FEV1 and FEV1 AUC0-12-P. The reduction was observed by Week 6 and generally remained stable through the Week 12 time point.

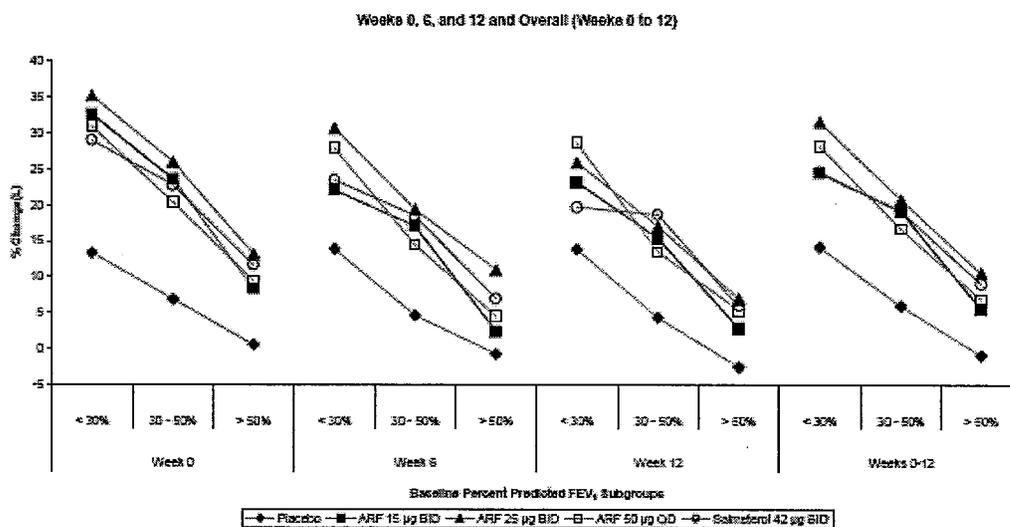
Also of interest is the time to onset of response from visit predose. A responder was defined as a subject who achieved a 10% increase in FEV1 from predose values. There were a large proportion of responders at all weeks ( $\geq 88\%$  at Week 0 and  $\geq 77\%$  at Week 12) in all arformoterol treatment groups. The time to onset was 3-10 minutes at Week 12 for the arformoterol groups versus 142 minutes for the salmeterol group. [Table 9.2.3.7-1, *clinstat/copdlise.pdf*] This difference is consistent with the well-known more rapid onset of action of racemic formoterol compared to salmeterol.

Other evidence in support of the efficacy of arformoterol includes improved (relative to placebo) morning and evening pre-medication peak expiratory flow rates (0.25 - 0.45 L/sec) over that observed for the baseline period (descriptive statistics only). There were small decreases in the reported use of ipratropium bromide and as-needed supplemental albuterol. Dyspnea Index scores improved for all arformoterol groups in both pivotal studies. The studies also included the "disease-specific" health-related quality of life assessment St. George's Hospital Respiratory Questionnaire (SGRQ) An improvement of 4 units in the total score has been considered clinically significant in prior studies. Mean improvements from baseline in total scores measured at Week 6 ranged between 2.6 and 4.4 units compared to 0.2 to 1.2 for placebo. Thus, although scores improved, they generally did not reach clinical significance. There was no difference in the distance walked in 6 minutes between any treatment groups.

Subgroup analyses by age, race, gender, reversibility, current smoking status, baseline percent predicted FEV1 and corticosteroid use were performed on subject data combined from both Phase 3 pivotal studies (091-050 and 091-051) for the primary endpoint (percent change in trough FEV1), and for the secondary endpoints of FEV1 AUC (nAUC0-12-P), FEV1 peak % predicted, and FEV1 peak percent change.

Analyses of these measures of pulmonary function by subgroups exhibited similar trends to that shown for the overall population. All arformoterol doses were efficacious in all subgroups examined. [Section 9.4, *clinstat\copd\ise.pdf*] When analyzed according to disease severity as defined by the GOLD criteria (i.e. GOLD Severe = FEV1 <30% predicted; GOLD Moderate = FEV1 30 - <50% predicted; GOLD Mild = FEV1 ≥50% predicted) the improvement in the percent change in trough FEV1, the improvement in FEV1 from visit predose in the 12 hours after dosing (FEV1 nAUC0-12-P), and the FEV1 peak percent change increased with COPD severity for all treatment groups (see Figure below).

**Mean Per Cent Change in Trough FEV1 from Study Baseline by Baseline Per Cent Predicted Subgroups for Pooled Studies 091-050 and 091-051** [Figure 9.4.6.1-1, *clinstat\copd\ise.pdf*]



### 6.1.5 Clinical Microbiology

Not applicable as there was no clinical microbiology review for this Beta-2 agonist.

### 6.1.6 Efficacy Conclusions

The clinical development program for this drug included two identical 12-week, randomized, double-blind, placebo- and active-controlled, multi-center studies that evaluated the safety and efficacy of arformoterol at 3 different doses (15 µg BID, 25 µg BID and 50 µg QD) versus placebo in subjects with COPD with the approved LABA, salmeterol group serving as an active comparator. The studies primarily focused on establishing substantial evidence of efficacy to support the indication traditionally used for COPD drugs, the relief of  associated with COPD. Thus, in these studies the primary efficacy variable was a measure of bronchodilation, FEV1, specifically trough FEV1 over the course of the 12-week treatment period.

b(4)

The two pivotal clinical studies, supported by Phase 2 dose-ranging studies provided evidence of the bronchodilator efficacy of arformoterol. Primary analyses of the two pivotal studies demonstrate that treatment with arformoterol at all doses tested resulted in statistically and what would be considered to be clinically significant improvements in FEV1 at the end of the dosing interval. All doses of arformoterol tested achieved comparable bronchodilation to that of the active comparator, salmeterol.

In addition, secondary analyses of the FEV1 data, including area under the FEV1 curve analyses from 0-12 hours post dose and peak FEV1 established that arformoterol is superior to placebo. It should be noted that the time to reach peak FEV1 is more rapid with arformoterol than salmeterol (as is racemic formoterol). Finally, other than the 6-minute walk test, most other non-spirometry based secondary efficacy variables, such as morning and evening home peak flow measurements, "rescue" albuterol and ipratropium bromide use, and health-related quality of life assessments also generally supported the efficacy of arformoterol in COPD patients.

## **7 INTEGRATED REVIEW OF SAFETY**

### **7.1 Methods and Findings**

The principal sources of data reviewed to support the safety of arformoterol tartrate inhalation solution included the following: the safety data from the Applicant's Phase 3 pivotal placebo-controlled studies (091-050 and 091-051) and open-label long term safety study (091-060), the safety data from the supporting Phase 2 dose-ranging study (091-026), a literature review provided by the Applicant, and the safety update, which includes the final study report for the Phase 2 study, 091-019, and interim blinded safety data from the ongoing safety study (091-061).

It should be noted that in the long term safety study, 091-060, the dose of arformoterol used was different from the dose ultimately proposed by the Applicant, 50 µg QD vs 15 µg BID, respectively. Since the daily dose used in study 091-060 was higher than the proposed dose, DPAP found this acceptable.

The Applicant presented the safety data as follows:

- Phase 2 multi-dose, dose-ranging study 091-026
- Pooled pivotal studies 091-050 and 091-051
- Long term safety study 091-060

Safety data from the two-week dose ranging study (091-026) and 12-month long-term safety study (091-060) were pooled with the 12-week pivotal studies for selected analyses only (i.e., summaries of AEs adjusted for observation time). Study 091-026 also provided cardiac repolarization (QT) safety data through extensive ECG and Holter monitoring assessments.

Single dose pharmacokinetic studies in special subject populations (renal, 091-014, and hepatic, 091-015, insufficiency, those who were extensive CYP2D6 metabolizers, 091-018, and the elderly, 091-013) were analyzed separately. Studies in the asthma population (091-002, 003, 004, and 016) were also analyzed separately from COPD studies.

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 multi-dose pivotal Phase 3 studies because they have more subjects, provide exposure to 3 different dose/dosing regimens of arformoterol as well as an active control, and are placebo-controlled. The long-term safety study provides additional safety data which assesses the safety of long-term use of a higher daily dose of arformoterol. The approach taken in the following review will generally follow the Applicant's pooling of safety data as outlined above.

### 7.1.1 Deaths

A total of 10 deaths occurred in randomized subjects during the course of all clinical studies performed for the arformoterol clinical development program. In general, the causes of death were consistent with what might be expected in this older patient population with many co-morbid conditions.

There were five deaths during the double-blind periods in the two pivotal studies:

- Subject 0765-S007-5810 (Study 091-051; arformoterol 15 µg BID) was a 66 year old male with a past history of greater than 30 pack year history of smoking, diverticulitis, hypercholesterolemia, mitral valve prolapse, subaortic stenosis, and TIA in 1997 who died due to complications following surgery for diverticulosis-induced rectal bleeding after 66 days on double-blind treatment. The hospital course was complicated by respiratory failure, repeat surgical procedures for repair of ileostomy, and gram + cocci sepsis.
- Subject 0622-S009-0061 (Study 091-050; arformoterol 15 µg BID) was a 45 year old male without any co-morbidities who died due to hepatic lacerations secondary to a motor vehicle accident (single occupant, unrestrained) after 27 days on double-blind treatment. At autopsy, the subject's blood alcohol level was 0.15 and serum drug tests were positive for benzodiazepines.
- Subject 0706-S010-0317 (Study 091-050; arformoterol 15 µg BID) was a 73 year old male with a past medical history significant for COPD, elevated cholesterol, and coronary artery disease (status post 2 vessel CABG  $\leftarrow$   $\rightarrow$ ).who died due to complications following surgery for an abdominal-aortic aneurysm four days after the last dose of double-blind treatment. The diagnosis of was made after a CAT scan performed for bladder irritation showed an aortic aneurysm. Post-operatively, the subject had respiratory difficulty after extubation and became unstable hemodynamically. He developed metabolic acidosis, jaundice, and thrombocytopenia. A CT scan of the head showed diffuse cerebral edema, and probable basilar artery thrombosis. He subsequently developed bradycardia and was pronounced dead the same day.
- Subject 0730-S001-5004 (Study 091-051; arformoterol 25 µg BID) was a 58 year old male with a past history of greater than 100-pack-year history of cigarette smoking,

b(6)

pneumonia x 2 (2000, 2001), non-insulin dependent diabetes, history of ETOH abuse, and cardiovascular disease who died due to disseminated malignancy after 42 days on double-blind treatment. He reportedly presented to the Emergency Department with a 2-week history of progressive right-sided weakness. He also complained of 1 month of right hip pain and urinary incontinence and he had noted a 35-pound weight loss over the previous 3 months. After undergoing a diagnostic work-up, he was hospitalized with a diagnosis of metastatic cancer to the brain, liver, and lungs. He declined chemotherapy and received palliative care at home until his death.

- Subject 0749- S017-5283 (Study 091-051; arformoterol 50 µg QD) was a 66 year old male with a past diverticulitis, and hypercholesterolemia who died due to complications of an aortic dissection after 58 days on double-blind treatment. Initially, Subject reportedly had complained of back pain and was later found unresponsive at home with left hemiparesis on the afternoon of [redacted]. He was transported to the Emergency room where he was intubated. He was diagnosed with a type A dissection of the aorta and a CVA. EKG showed sinus rhythm at 75 and was unremarkable; CK was normal at 102 and troponin I was < 0.08. The subject underwent emergent repair of the aortic arch with aortic valve re-suspension and a Gore-Tex interposition graft. Post-operative complications included compartment syndrome of the left leg, fever, hemodynamic instability, anoxic brain injury, rhabdomyolysis, renal failure, and right cerebral infarct. He remained ventilator dependent. He was placed in hospice care until his death one day later.

b(6)

An additional subject, a 73 year old female from Study 091-050 consented to participation but was a screening failure due to eosinophilia and did not get randomized. During a telephone follow-up, it was learned that the subject had died unexpectedly, apparently during her sleep.

There were 5 deaths in Study 091-60, the one year open label safety study. Of note is that the arformoterol dose used in this study was 50 µg QD. This dose is 40% higher than the 15µg BID dose selected by the Applicant as the indicated dose and, significantly, it was delivered as one single dose.

- Subject 0194-S506 (arformoterol 50 µg QD) was a 67 year old female being treated with oral corticosteroids and methotrexate for psoriatic arthritis who died of cryptococcal meningitis approximately three months after the last dose of study medication. She had successfully completed pivotal trial 091-050 where she had received 25 µg arformoterol BID for 12 weeks.
- Subject 0197-S503 (arformoterol 50 µg QD) was 68 year old male with severe COPD (FEV1 28% predicted), hypercholesterolemia and hypertension who died of a myocardial infarction after 201 days of treatment. Previously, he had successfully completed the pivotal trial 091-050, where he received 50 µg arformoterol QD for 12 weeks. On [redacted] he suffered an acute anterior myocardial infarction. He was transported via EMS to the hospital. A Cardiac catheterization revealed diffuse disease in the coronary arteries including the left main, the circumflex (30-40% stenosis), LAD (70% stenosis), and right (60%). Stent placement was performed in the left anterior descending (LAD) and right coronary arteries. He required aggressive life support measures,

b(6)

including ventilatory support, intra-aortic balloon pump, and 18 defibrillations over two days. Complications during hospitalization included cardiogenic shock, liver failure, and renal failure. The subject died on . [ ]

b(6)

- Subject 0844-S909 (arformoterol 50 µg QD) was a 75 year old male with a past history of hypertension, cigarette smoking left hernia repair, cholecystectomy, renal mass, depression, chronic back pain who died of cardiac ischemia after 309 days of treatment. He had previously had a separate SAE during the study, COPD exacerbation 81 days before this hospitalization (Manufacturer's Control #S091060-030814-1). At that time he had normal cardiac wall motion and an ejection fraction of 54%. He presented to the emergency department with dyspnea and chest pain. Troponin level was 2.1 ng/mL on admission and he had an episode of atrial fibrillation treated with a Beta-blocker. He was treated with Plavix and Lovenox. His hemoglobin decreased necessitating several transfusions of RBCs. He developed hemoptysis and renal failure requiring dialysis. His is angina became more severe and he suffered a cardiac arrest and subsequently died.
- Subject 0254-S507 (salmeterol 42 µg BID) was a 76 year old male with a past history of prostatic cancer who died of lung cancer after 20 days of treatment. The subject had successfully completed the pivotal trial 091-050 in which he received 15 µg arformoterol BID for 12 weeks. He was hospitalized because of complaints of falling. A brain CT scan showed a 2.3 cm mass in the right basal ganglia/thalamus. CT scans of the chest, abdomen, and pelvis conducted on showed a 2 cm spiculated mass in the left apex of the lung. CT-guided needle biopsy of the left lung mass showed a poorly differentiated non-small cell carcinoma. He was diagnosed with lung cancer with a solitary brain metastasis. He received palliative radiation therapy only.
- Subject 0681-S503 (salmeterol 42 µg BID) was a 63 year old male with a tobacco history of 80 pack-years and was a current smoker who died of lung cancer three months after the end of treatment. Prior to participation in this trial, the subject had successfully completed the pivotal trial 091-050, in which he received placebo for 12 weeks. The subject presented with hemoptysis and prolonged pneumonia that was slow to clear on chest x-ray. A CT scan of the chest showed a linear opacity in the left lower lobe of the lung. A flexible laryngoscopy/bronchoscopy was performed and cytopathology was positive for squamous cell carcinoma. The subject died 107 days after study completion. Further details are not available.

Narratives for these subjects were read and reviewed. Of the 10 deaths reported, 8 were in subjects who received arformoterol, 3 who received 15 µg BID, 1 who received 25 µg BID, and 4 who received 50 µg QD. Of these deaths, 4 were related to the cardiovascular system, Subject 0706-S010-0317 (arformoterol 15 µg BID) had a history of coronary artery disease and died of complications from an abdominal aortic aneurysm, Subject 0749- S017-5283 (arformoterol 50 µg QD) died post-operatively from an aortic dissection. This subject had no evidence of blood pressure or heart rate elevations over baseline levels during the study. Subject 0197-S503 (arformoterol 50 µg QD) died of a myocardial infarction. Review the subject's 12-lead ECG and Holter monitor recordings taken during Study 091-050 did not show evidence of myocardial ischemia during that period. Subject 0844-S909 (arformoterol 50 µg QD), who had a history of hypertension, died as a result of cardiac damage due to ischemia. It is notable that 3 of the 4 deaths in arformoterol treated subjects that were related to the cardiovascular system were in

subjects who received the highest dose of 50 µg/day delivered as a single dose. This could be due to the more pronounced Beta adrenergic effects that the high dose of arformoterol delivered over a short period. However, the analysis is confounded by the much greater number of subjects who received 50 µg QD in arformoterol clinical trials (over 800) compared to those who received lesser doses (mostly 15 µg and 25 µg BID, approximately 300 subjects each).

### 7.1.2 Other Serious Adverse Events

There were a total of 5 SAEs reported for 562 subjects who participated in arformoterol single-dose studies [Table 6.7.2.1-1, *clinstat\copd\iss. Pdf*] and a total of 10 SAEs reported for subjects participating in the 091-026 dose-ranging study. [Tables 6.7.2.2.1-1 and 6.7.2.2-2, *clinstat\copd\iss. Pdf*] The events are few and do not contribute to the analysis of adverse events other than to note that there was a higher rate of SAEs in the Part B arformoterol 50 µg QD group (6.4%, 3 SAEs from 47 subjects) Than in the placebo groups for either Part A (5.6%, 3/54) or Part B (0%, 0/49).

### Serious Adverse Events Post-Randomization for Studies 091-050 and 051 (ITT) Population [Table 6.7.2.2.2-1, *clinstat\copd\iss. Pdf*]

BODY SYSTEM Preferred Term	Placebo (n=293)		Arformoterol 15 µg BID (n=288)		Arformoterol 25 µg BID (n=292)		Arformoterol 50 µg QD (n=293)		Salmeterol 42 µg BID (n=290)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
ANY ADVERSE EVENT	19 (6.5)	22	14 (4.9)	19	18 (6.2)	20	16 (5.5)	20	11 (3.8)	15
BODY AS A WHOLE	4 (1.4)	5	5 (1.7)	5	2 (0.7)	2	3 (1.0)	3	3 (1.0)	3
Abdominal Pain	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Accidental Injury	0 (0.0)	0	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Carcinoma	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	1 (0.3)	1
Cellulitis	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Chest Pain	1 (0.3)	1	3 (1.0)	3	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Cyst	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Infection Bacterial	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Multi Organ Failure	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Pain	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Sepsis	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Suicide Attempt	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
CARDIOVASCULAR	4 (1.4)	4	4 (1.4)	5	3 (1.0)	4	2 (0.7)	2	2 (0.7)	3
Arterial Anomaly	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Cardiovascular Disorder	0 (0.0)	0	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Congestive Heart Failure	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Coronary Artery Disorder	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	1 (0.3)	1	1 (0.3)	1
Deep Thrombophlebitis	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Hypertension	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

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Serious Adverse Events Post-Randomization for Studies 091-050 and 051 continued [Table 6.7.2.2.2-1, clinstat/copd/iss. Pdf]

BODY SYSTEM Preferred Term	Placebo (n=293)		Arformoterol 15 µg BID (n=288)		Arformoterol 25 µg BID (n=292)		Arformoterol 50 µg QD (n=293)		Salmeterol 42 µg BID (n=290)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Myocardial Infarction	0 (0.0)	0	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Peripheral Vascular Disorder	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Pulmonary Embolus	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Tachycardia	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Thrombosis	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Ventricular Tachycardia	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
DIGESTIVE	3 (1.0)	4	1 (0.3)	1	0 (0.0)	0	1 (0.3)	2	1 (0.3)	1
Cholecystitis	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Duodenal Ulcer	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Duodenal Ulcer Hemorrhage	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Gastrointestinal Carcinoma	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Gastrointestinal Disorder	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Intestinal Obstruction	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Rectal Hemorrhage	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
HEMIC & LYMPHATIC	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Anemia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
MUSCULOSKELETAL	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Joint Disorder	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0

BODY SYSTEM Preferred Term	Placebo (n=293)		Arformoterol 15 µg BID (n=288)		Arformoterol 25 µg BID (n=292)		Arformoterol 50 µg QD (n=293)		Salmeterol 42 µg BID (n=290)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
NERVOUS	2 (0.7)	2	1 (0.3)	1	1 (0.3)	1	4 (1.4)	5	0 (0.0)	0
Cerebral Infarction	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Cerebrovascular Accident	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Depression	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Drug Dependence	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Neuropathy	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Paresthesia	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Personality Disorder	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Subdural Hematoma	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Thinking Abnormal	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
RESPIRATORY	6 (2.0)	6	5 (1.7)	7	11 (3.8)	11	6 (2.0)	6	4 (1.4)	7
Apnea	0 (0.0)	0	0 (0.0)	0	3 (1.0)	3	0 (0.0)	0	0 (0.0)	0
Asthma	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Bronchitis	0 (0.0)	0	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Carcinoma of Lung	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
COPD	6 (2.0)	6	3 (1.0)	3	5 (1.7)	5	6 (2.0)	6	5 (1.7)	6
Pneumonia	0 (0.0)	0	1 (0.3)	1	2 (0.7)	2	0 (0.0)	0	0 (0.0)	0
Respiratory Disorder	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
SKIN & APPENDAGES	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Herpes Zoster	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0

BODY SYSTEM Preferred Term	Placebo (n=293)		Arformoterol 15 µg BID (n=288)		Arformoterol 25 µg BID (n=292)		Arformoterol 50 µg QD (n=293)		Salmeterol 42 µg BID (n=290)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
UROGENITAL	1 (0.3)	1	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	1 (0.3)	1
Fibrocystic Breast	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Prostatic Carcinoma	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Urogenital Disorder	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

In the placebo-controlled pivotal studies, 091-050 and 051, fewer subjects in the 15 µg BID and 50 µg QD arformoterol dosing groups reported SAEs, as compared with placebo while the 25 µg dosing group was comparable to placebo. As indicated in the table above, the difference was most notable in the 15 µg group in which 4.9% of subjects reported any adverse event compared to 6.5% in the placebo group. By comparison, 3.8% of subjects reported SAEs in the salmeterol active comparator group.

The most commonly reported SAEs occurred in the body as a whole, cardiovascular, and respiratory systems. The incidences of SAEs in each system was evenly distributed across all arformoterol treatment groups except the 25 µg BID dosing group which had a small increase in respiratory system SAEs (3.8% vs 1.4-2.0%) that was a result of 3 instances of “apnea” classified as SAEs. This is not likely specifically related to arformoterol as there were 0 instances of apnea in any other dose group, including the higher 50 µg group. The most common SAE was COPD (1.0%-2.0% in each group), with the highest rates in the placebo and arformoterol 50 µg QD groups and lowest rates in the arformoterol 15 µg BID and salmeterol groups. Individual cardiovascular SAEs were reported in no more than one subject per group. The incidence of nervous system SAEs was highest in the arformoterol 50 µg QD group (1.4%) compared with the other groups (0.0% to 0.7%) but the very low incidences and reasons (depression, neuropathy) make it difficult to ascribe the increase to a dose-response. There were no nervous system SAEs reported for subjects in the salmeterol group, however.

Serious adverse events reported for the open-label, long-term safety study, 091-060, in which subjects received either 50 µg of arformoterol QD or salmeterol, were very similar to those reported in the placebo-controlled pivotal studies except that the overall incidences of SAEs was higher (about 12 vs 6%) [Table 6.7.2.2.3-1, clinstat\copd\iss. pdf]. As in the placebo-controlled studies, the highest incidence of SAEs was in the respiratory (5.5% and 5.7%), cardiovascular (2.7% and 2.6%), and body as a whole systems (1.9% and 2.6%) in the arformoterol and salmeterol groups, respectively. Rates for individual SAEs were low. The most common SAE was COPD exacerbation (arformoterol 50 µg QD, 2.7%; salmeterol 1.9%). There were more nervous system SAEs reported for the arformoterol than salmeterol group (0.9 vs 0.4%), however, the incidences were quite low and the difference seemed to be 3 instances classified as “depression” in the arformoterol group.

### 7.1.3 Dropouts and Other Significant Adverse Events

The number and percentage of subjects who discontinued due to AEs in the placebo-controlled pivotal studies 091-050 and 091-051 are summarized in the table below.

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**Adverse Events Leading to Discontinuation During the Treatment Period of Pivotal Studies 091-050 and 051** [Table 6.7.3.2-1, *clinstatiss.pdf*]

BODY SYSTEM Preferred Term	Placebo (N=293)		Arformoterol 15 µg BID (N=288)		Arformoterol 25 µg BID (N=292)		Arformoterol 50 µg QD (N=293)		Salmeterol 42 µg BID (N=290)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
ANY ADVERSE EVENT	27 (9.2)	33	22 (7.6)	32	34 (11.6)	42	25 (8.5)	35	23 (7.9)	27
BODY AS A WHOLE	3 (1.0)	4	4 (1.4)	5	5 (1.7)	5	3 (1.0)	3	2 (0.7)	4
Accidental Injury	0 (0.0)	0	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Carcinoma	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Cellulitis	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Chest Pain	3 (1.0)	4	1 (0.3)	2	1 (0.3)	1	0 (0.0)	0	2 (0.7)	3
Fever	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Headache	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Multi Organ Failure	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Neoplasm	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Pain	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	1 (0.3)	1
Sepsis	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
CARDIOVASCULAR	5 (1.7)	6	11 (3.8)	12	16 (5.5)	20	8 (2.7)	10	9 (3.1)	10
Arrhythmias	1 (0.3)	1	1 (0.3)	1	2 (0.7)	2	0 (0.0)	0	0 (0.0)	0
Arterial Anomaly	0 (0.0)	0	1 (0.3)	1	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0
Atrial Fibrillation	0 (0.0)	0	0 (0.0)	0	2 (0.7)	2	1 (0.3)	1	1 (0.3)	1
AV Block	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Bundle Branch Block	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Cardiovascular Disorder	0 (0.0)	0	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Congestive Heart Failure	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Coronary Artery Disorder	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	1 (0.3)	1
Electrocardiogram Abnormal	1 (0.3)	1	2 (0.7)	2	2 (0.7)	2	1 (0.3)	1	2 (0.7)	2
Hypertension	0 (0.0)	0	1 (0.3)	1	2 (0.7)	2	2 (0.7)	3	1 (0.3)	1
Myocardial Infarction	0 (0.0)	0	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0

BODY SYSTEM Preferred Term	Placebo (N=293)		Arformoterol 15 µg BID (N=288)		Arformoterol 25 µg BID (N=292)		Arformoterol 50 µg QD (N=293)		Salmeterol 42 µg BID (N=290)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Peripheral Vascular Disorder	0 (0.0)	0	0 (0.0)	0	1 (0.3)	2	0 (0.0)	0	0 (0.0)	0
T Inverted	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Tachycardia	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Ventricular Extrasystoles	2 (0.7)	2	1 (0.3)	1	3 (1.0)	3	2 (0.7)	2	3 (1.0)	3
Ventricular Tachycardia	2 (0.7)	2	0 (0.0)	0	3 (1.0)	3	2 (0.7)	2	1 (0.3)	1
DIGESTIVE	3 (1.0)	3	3 (1.0)	3	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0
Duodenal Ulcer	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Duodenal Ulcer Hemorrhage	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Gastritis	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Gastrointestinal Carcinoma	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Liver Function Tests Abnormal	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Meleus	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Rectal Hemorrhage	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Vomiting	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
HEMIC & LYMPHATIC	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Iron Deficiency Anemia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
METABOLIC & NUTRITIONAL DISORDERS	2 (0.7)	3	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Diabetes Mellitus	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Hypokalemia	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Hypomagnesemia	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

**Adverse Events Leading to Discontinuation During the Treatment Period of Pivotal Studies 091-050 and 051 continued** [Table 6.7.3.2-1, *clinstat/iss.pdf*]

BODY SYSTEM Preferred Term	Placebo (N=293)		Arformoterol 15 µg BID (N=288)		Arformoterol 25 µg BID (N=292)		Arformoterol 50 µg QD (N=293)		Salmeterol 42 µg BID (N=290)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
<b>MUSCULOSKELETAL</b>	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	1 (0.3)	1
Joint Disorder	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Myopathy	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
<b>NERVOUS</b>	2 (0.7)	2	1 (0.3)	2	3 (1.0)	4	6 (2.0)	9	0 (0.0)	0
Cerebrovascular Accident	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Confusion	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Depression	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Drug Dependence	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Insomnia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Nervousness	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Neuropathy	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Paralysis	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Paresthesia	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Personality Disorder	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Subdural Hematoma	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
Thinking Abnormal	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
Tremor	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	3 (1.0)	3	0 (0.0)	0
<b>RESPIRATORY</b>	14 (4.8)	14	7 (2.4)	8	12 (4.1)	12	9 (3.1)	10	10 (3.4)	11
Apnea	0 (0.0)	0	0 (0.0)	0	2 (0.7)	2	0 (0.0)	0	0 (0.0)	0
Bronchitis	2 (0.7)	2	0 (0.0)	0	1 (0.3)	1	3 (1.0)	3	0 (0.0)	0
Carcinoma Of Lung	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
COPD	9 (3.1)	9	4 (1.4)	4	7 (2.4)	7	7 (2.4)	7	8 (2.8)	9
Cough Increased	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Dyspnea	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Infection	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Pneumonia	1 (0.3)	1	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0

BODY SYSTEM Preferred Term	Placebo (N=293)		Arformoterol 15 µg BID (N=288)		Arformoterol 25 µg BID (N=292)		Arformoterol 50 µg QD (N=293)		Salmeterol 42 µg BID (N=290)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Sinusitis	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0
<b>SKIN &amp; APPENDAGES</b>	1 (0.3)	1	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Angioedema	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Sweating	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
<b>SPECIAL SENSES</b>	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Abnormal Vision	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

The overall rate of discontinuations due to AEs was low across treatment groups. There were more cardiovascular discontinuations in the arformoterol treated groups but these rates were similar to that seen in the salmeterol active control group. All active treatment groups had fewer respiratory system related discontinuations than the placebo group. As a way to provide an inclusive representation of discontinuations due to AEs, the Applicant reviewed the study 091-050 and 051 databases to determine if an AE may have been a factor in study discontinuation in those subjects who discontinued for another reason. There were 17 additional subjects who discontinued the study for reasons other than AEs who also experienced AEs around the time of their discontinuation. The discontinuations were spread evenly across all study groups and did not add to any further understanding of the overall safety of arformoterol.

The overall rate of discontinuations in one year, open-label long-term safety study, 091-060, was slightly higher in the arformoterol 50 µg QD group than in the salmeterol 42 µg BID group, 22.2% vs 17.0%, respectively [Table 6.7.3.3-1, *clinstat/iss.pdf*]. This was most pronounced in the nervous system where the rate of discontinuations was rate 6.3% in the arformoterol 50 µg QD

group and 1.5% in the salmeterol group. The nervous system disorder that was most prevalent was tremor which is indicative of the increased Beta-2 agonist effects in the arformoterol group. Discontinuations due to cardiovascular AEs was also higher in the arformoterol 50 µg QD group, 6.1% vs 4.2% for salmeterol, although the effect was not as dramatic as for the nervous system discontinuations. The majority of cardiovascular and nervous system AEs leading to discontinuation occurred within the first 3 months of the study, with no increase in the rate of discontinuations over the 12-month period. Discontinuations due to respiratory AEs were comparable between the arformoterol and salmeterol groups.

### 7.1.3.1 Overall profile of dropouts

An overall profile of drop-outs in Phase 2 and 3 multiple-dose studies is shown in the table below.

**Subject Disposition for Pooled Multi-Dose Studies, 091-026, 050, 051, and 060** [Table 6.2.2.4-1, *clinstat/iss. Pdf*]

	Placebo (N=383)	ARF 5 µg BID (N=54)	ARF 15 µg QD (N=48)	ARF 25 µg QD (N=47)	ARF 15 µg BID (N=342)	ARF 25 µg BID (N=345)	ARF 50 µg QD* (N=368)	SAL 42 µg BID* (N=555)
	n (%)	N (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed	308 (80.4)	46 (85.2)	47 (97.9)	45 (97.9)	282 (82.5)	270 (78.3)	596 (68.7)	407 (73.3)
Withdrawn	75 (19.6)	8 (14.8)	1 (2.1)	1 (2.1)	60 (17.5)	75 (21.7)	272 (31.3)	148 (26.7)
Adverse Event	34 (8.9)	4 (7.4)	1 (2.1)	1 (2.1)	24 (7.0)	40 (11.6)	146 (16.8)	67 (12.1)
Protocol Violation	6 (1.6)	1 (1.9)	0 (0.0)	0 (0.0)	9 (2.6)	9 (2.6)	25 (2.9)	11 (2.0)
Subject Voluntary Withdraw	28 (7.3)	1 (1.9)	0 (0.0)	0 (0.0)	16 (4.7)	16 (4.6)	68 (7.8)	34 (6.1)
Lost To Follow-up	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	2 (0.6)	15 (1.7)	9 (1.6)
Did Not Meet Entry Criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	2 (0.6)	2 (0.2)	5 (0.9)
Other	5 (1.3)	2 (3.7)	0 (0.0)	0 (0.0)	5 (1.5)	6 (1.7)	16 (1.8)	22 (4.0)

\* Includes data primarily from long-term (12 month) study (Study 091-060)

The overall completion rates were lower for the arformoterol 50 µg QD and salmeterol 42 µg BID groups. This was mainly due to the lower completion rates in the long-term (12-month) safety study, 091-060 compared to the 12 week pivotal studies. Subjects in the proposed clinical dose group (15 µg BID) had an overall withdrawal rate and withdrawal rate due to AEs that was slightly lower (by about 2%) than placebo. The most common reasons for early termination were adverse events and voluntary withdrawal across all treatment groups.

### 7.1.3.2 Adverse events associated with dropouts

There were 2 types of adverse events that appeared to be associated with dropouts during clinical trials of arformoterol, those that were nervous system related and those from the cardiovascular system (refer to the table in Section 7.1.1 above and Table 6.7.3.3-1, *clinstat/iss.pdf*). These were likely related to excessive Beta-agonist effects and were seen at the higher arformoterol dosing groups of 25 µg BID and 50 µg QD. The nervous system effects were most pronounced for insomnia, nervousness, and tremor. There were more cardiovascular and nervous system discontinuations also in the arformoterol 25 µg BID and 50 µg QD groups. While no specific cardiovascular AE stands out, the increased AEs related to the cardiovascular system in the higher arformoterol dosing groups are those that would be consistent with increased Beta agonist effects in a population with a large number of cardiovascular co-morbidities.

### 7.1.3.3 Other significant adverse events

The nervous system adverse events related excessive Beta-2 agonist stimulation including tremor, insomnia, and nervousness seen in the higher 25 µg BID and 50 µg QD arformoterol dosing groups, while rarely meeting the criteria for an SAE, nevertheless, were significant and resulted in a relatively high number of study discontinuations, especially in the open-label long-term safety study, 091-060 [Table 6.7.3.3-1, *clinstat\liss.pdf*].

### 7.1.4 Other Search Strategies

The safety and toxicologic profile of Beta-2 agonists as a class has been extensively characterized. Therefore, no other search strategies involving combinations of clinical findings as markers for toxicities were utilized in the safety review.

### 7.1.5 Common Adverse Events

#### 7.1.5.1 Eliciting adverse events data in the development program

For the pivotal and supportive multi-dose studies, subjects were instructed to record adverse events in medical event calendars throughout the study period. COPD symptom questionnaires were also filled out daily. At each clinic visit, the questionnaires and event calendars were reviewed by study personnel and recorded on the CRF. Subjects were evaluated at clinic visits every three weeks in the pivotal studies, 091-050 and 091-051 with weekly telephone calls made between visits weeks to inquire about any adverse events, use of any concomitant medications, remind subjects to complete the medical event calendar, study drug/rescue medication logs, peak expiratory flow rate log, and COPD questionnaires. Similar safety evaluations were conducted for the long-term safety study, 091-060 except that subjects were evaluated at clinic visits at intervals ranging from 3-12 weeks (10 visits over the course of one year) with telephone contact made approximately half way between visits.

#### 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

The incidence of common adverse events is estimated from the pooled AEs reported for the two, 12 week, placebo-controlled pivotal studies, 091-050 and 051. These studies contained reports from approximately 1450 subjects in 5 dosing groups, 3 for arformoterol, an active comparator, salmeterol, and placebo. The open-label long-term safety study, 091-060, is of limited use in

looking at common AEs as it did not contain a 15 µg BID dosing group, the indicated dose proposed by the Applicant in this NDA.

The table below summarizes adverse events that were reported by ≥ 2% of patients in any treatment group.

**Treatment-Emergent Adverse Events Occurring in ≥ 2% of Subjects in Any Treatment Group in Pooled Pivotal Studies, 091-050 and 051 [Table 6.7.4.2.2-1, clinstatliss.pdf]**

BODY SYSTEM Preferred Term	Placebo (N=293)		Arformoterol 15 µg BID (N=288)		Arformoterol 25 µg BID (N=292)		Arformoterol 50 µg QD (N=293)		Salmeterol 42 µg BID (N=290)	
	Subjects n (%)	Events N	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
ANY ADVERSE EVENT	219 (74.7)	668	202 (70.1)	639	211 (72.3)	671	227 (77.5)	755	216 (74.5)	653
<b>BODY AS A WHOLE</b>										
Abdominal Pain	6 (2.0)	8	4 (1.4)	6	8 (2.7)	9	2 (0.7)	2	1 (0.3)	1
Accidental Injury	11 (3.8)	11	9 (3.1)	11	11 (3.8)	11	12 (4.1)	12	13 (4.5)	14
Asthenia	7 (2.4)	9	4 (1.4)	4	9 (3.1)	10	10 (3.4)	14	6 (2.1)	6
Back Pain	6 (2.0)	7	16 (5.6)	18	8 (2.7)	8	12 (4.1)	18	6 (2.1)	7
Cellulitis	6 (2.0)	7	1 (0.3)	1	1 (0.3)	1	2 (0.7)	4	2 (0.7)	3
Chest Pain	19 (6.5)	21	19 (6.6)	27	10 (3.4)	11	15 (5.1)	18	10 (3.4)	14
Fever	2 (0.7)	3	4 (1.4)	4	7 (2.4)	7	7 (2.4)	7	8 (2.8)	8
Flu Syndrome	4 (1.4)	4	10 (3.5)	10	7 (2.4)	7	8 (2.7)	9	3 (1.0)	3
Headache	24 (8.2)	29	24 (8.3)	42	26 (8.9)	31	30 (10.2)	46	35 (12.1)	40
Pain	16 (5.5)	23	23 (8.0)	25	23 (7.9)	25	26 (8.9)	35	18 (6.2)	19
Viral Infection	6 (2.0)	7	1 (0.3)	1	7 (2.4)	8	6 (2.0)	7	9 (3.1)	9
<b>CARDIOVASCULAR</b>										
Hypertension	5 (1.7)	6	3 (1.0)	3	5 (1.7)	5	7 (2.4)	8	2 (0.7)	2
Palpitation	3 (1.0)	3	0 (0.0)	0	5 (1.7)	5	4 (1.4)	4	7 (2.4)	8
<b>DIGESTIVE</b>										
Diarrhea	13 (4.4)	15	16 (5.6)	18	16 (5.5)	17	10 (3.4)	12	11 (3.8)	13
Dyspepsia	8 (2.7)	9	5 (1.7)	5	10 (3.4)	11	7 (2.4)	8	8 (2.8)	12
Nausea	18 (6.1)	23	13 (4.5)	15	15 (5.1)	16	10 (3.4)	14	5 (1.7)	5
Vomiting	9 (3.1)	10	5 (1.7)	5	10 (3.4)	10	10 (3.4)	10	5 (1.7)	5
<b>HEMIC &amp; LYMPHATIC</b>										
Leukocytosis	1 (0.3)	1	0 (0.0)	0	4 (1.4)	5	6 (2.0)	6	2 (0.7)	3

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**Treatment-Emergent Adverse Events Occurring in ≥ 2% of Subjects in Any Treatment Group in Pooled Pivotal Studies, 091-050 and 051 continued** [Table 6.7.4.2.2-1, clinstat/viss.pdf]

BODY SYSTEM Preferred Term	Placebo (N=293)		Arformoterol 15 µg BID (N=288)		Arformoterol 25 µg BID (N=292)		Arformoterol 50 µg QD (N=293)		Salmeterol 42 µg BID (N=290)	
	Subjects n (%)	Events N	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
<b>METABOLIC &amp; NUTRITIONAL</b>										
Hyperglycemia	3 (1.0)	3	4 (1.4)	4	6 (2.1)	6	5 (1.7)	5	10 (3.4)	12
Hyperkalemia	3 (1.0)	3	2 (0.7)	2	4 (1.4)	5	6 (2.0)	6	7 (2.4)	8
Hypokalemia	3 (1.0)	3	5 (1.7)	5	7 (2.4)	7	5 (1.7)	5	1 (0.3)	1
Peripheral Edema	7 (2.4)	7	8 (2.8)	8	6 (2.1)	7	5 (1.7)	7	6 (2.1)	8
<b>MUSCULOSKELETAL</b>										
Leg Cramps	6 (2.0)	6	12 (4.2)	13	10 (3.4)	13	8 (2.7)	12	12 (4.1)	15
<b>NERVOUS</b>										
Anxiety	6 (2.0)	6	3 (1.0)	3	4 (1.4)	4	5 (1.7)	5	3 (1.0)	3
Dizziness	8 (2.7)	9	7 (2.4)	8	8 (2.7)	8	8 (2.7)	9	11 (3.8)	14
Insomnia	6 (2.0)	7	6 (2.1)	6	12 (4.1)	12	9 (3.1)	9	4 (1.4)	4
Nervousness	2 (0.7)	2	2 (0.7)	2	4 (1.4)	4	10 (3.4)	15	1 (0.3)	1
Tremor	1 (0.3)	1	4 (1.4)	5	7 (2.4)	7	27 (9.2)	33	2 (0.7)	2
<b>RESPIRATORY</b>										
Asthma	6 (2.0)	7	3 (1.0)	3	2 (0.7)	2	3 (1.0)	7	4 (1.4)	4
Bronchitis	17 (5.8)	19	17 (5.9)	20	18 (6.2)	23	19 (6.5)	22	13 (4.5)	13
COPD	24 (8.2)	28	21 (7.3)	22	26 (8.9)	29	29 (9.9)	35	27 (9.3)	37
Cough Increased	15 (5.1)	18	15 (5.2)	19	10 (3.4)	12	10 (3.4)	13	17 (5.9)	19
Dyspnea	7 (2.4)	8	11 (3.8)	16	14 (4.8)	21	8 (2.7)	15	11 (3.8)	13
Epistaxis	7 (2.4)	9	3 (1.0)	4	4 (1.4)	11	4 (1.4)	4	3 (1.0)	3
Infection	43 (14.7)	49	37 (12.8)	40	32 (11.0)	34	38 (13.0)	40	42 (14.5)	49
Lung Disorder	2 (0.7)	2	7 (2.4)	7	6 (2.1)	8	2 (0.7)	2	5 (1.7)	6
Pharyngitis	21 (7.2)	23	10 (3.5)	12	13 (4.5)	14	18 (6.1)	20	20 (6.9)	20
Rhinitis	18 (6.1)	24	16 (5.6)	23	13 (4.5)	16	15 (5.1)	19	16 (5.5)	17
Sinusitis	11 (3.8)	13	13 (4.5)	14	17 (5.8)	18	10 (3.4)	11	17 (5.9)	18
<b>SKIN &amp; APPENDAGES</b>										
Rash	5 (1.7)	5	11 (3.8)	11	7 (2.4)	9	2 (0.7)	2	4 (1.4)	5
<b>SPECIAL SENSES</b>										
Conjunctivitis	6 (2.0)	6	0 (0.0)	0	2 (0.7)	2	3 (1.0)	3	2 (0.7)	2
<b>UROGENITAL</b>										
Urinary Tract Infection	14 (4.8)	16	11 (3.8)	14	10 (3.4)	10	15 (5.1)	18	13 (4.5)	14

The overall incidence of treatment emergent AEs in pooled Studies 091-050 and 091-051 (Weeks 0 to 12) was similar across all treatment groups (70.1% to 77.5%). The AEs reported in the arformoterol groups that appeared to have a dose response included asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor with nervousness and tremor showing the strongest dose-response relationship. Rates of these AEs in the arformoterol proposed 15 µg BID dose did not differ significantly from rates in the placebo group except for tremor (1.4% vs 0.3%). Respiratory infection was the most frequently reported AE (11.0% to 14.7%) and did not differ significantly between treatment groups. Rates of COPD were slightly lower in the arformoterol 15 µg BID group compared with placebo and increased at the higher arformoterol doses but the difference is not meaningful.

The incidence of overall cardiovascular events reported did not differ appreciably across treatment groups. There was an increased incidence of adverse events in the musculo-skeletal system (leg cramps) in all active treatment groups, including salmeterol. This is likely a Beta-agonist mediated effect. A dose-response for the arformoterol groups was not apparent. Although

there was no dose-related increase, this difference was driven by an increase in leg cramps among the active treatment groups (2.7% to 4.2%) compared with the placebo group (2.0%). A review of possible hypersensitivity reactions in pooled studies, including such terms as allergic reaction, face edema, rash, urticaria, and anaphylaxis revealed very low rates in the arformoterol groups similar to placebo [Table 7.1.2, *clinstat\iss\iss.pdf*].

#### 7.1.5.4 Common adverse event tables

The table below lists the common AEs occurring in the arformoterol 15 µg BID dosing group that were also greater than placebo for the placebo-controlled pivotal trials. The 15 µg BID dose is the indicated dose the Applicant has proposed. At higher arformoterol doses used in other studies, AEs associated with increased Beta-2 agonist effects become apparent, especially insomnia, nervousness, and tremor.

**Adverse Events Occurring in ≥ 2% of Subjects in the Arformoterol 15 µg BID Treatment Group and Greater than Placebo in Pooled Pivotal Studies 091-050 and 091-051** [Table 6.7.8-1, *clinstat\iss.pdf*]

BODY SYSTEM Preferred Term	Placebo (N=293)		Arformoterol 15 µg BID (N=288)		Salmeterol 42 µg BID (N=290)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
<b>BODY AS A WHOLE</b>						
Back Pain	6 (2)	7	16 (6)	18	6 (2)	7
Chest Pain	19 (6)	21	19 (7)	27	10 (3)	14
Flu Syndrome	4 (1)	4	10 (3)	10	3 (1)	3
Pain	16 (5)	23	23 (8)	25	18 (6)	19
<b>DIGESTIVE</b>						
Diarrhea	13 (4)	15	16 (6)	18	11 (4)	13
<b>METABOLIC &amp; NUTRITIONAL</b>						
Peripheral Edema	7 (2)	7	8 (3)	8	6 (2)	8
<b>MUSCULOSKELETAL</b>						
Leg Cramps	6 (2)	6	12 (4)	13	12 (4)	15
<b>RESPIRATORY</b>						
Dyspnea	7 (2)	8	11 (4)	16	11 (4)	13
Lung Disorder*	2 (1)	2	7 (2)	7	5 (2)	6
Sinusitis	11 (4)	13	13 (5)	14	17 (6)	18
<b>SKIN &amp; APPENDAGES</b>						
Rash	5 (2)	5	11 (4)	11	4 (1)	5

The only potential Beta-mediated AE reported in ≥2% of arformoterol subjects and at a rate greater than placebo was leg cramps. Chest pain could be related to the cardiovascular system and the incidence of chest pain was about equal to that in the placebo group. There were no AEs with an incidence of at least 2% in the arformoterol 15 µg BID group and greater than placebo listed in the cardiovascular system.

#### 7.1.5.5 Identifying common and drug-related adverse events

The physiologic effects of excessive Beta-2 agonist stimulation are well characterized and apparent at the higher dose levels of arformoterol used in clinical trials. The most common

events considered related to arformoterol were nervous system related; tremor, insomnia, and nervousness. There was a dose-response with effects noted more frequently in the 25 µg BID and 50 µg QD dosing groups compared to the 15 µg BID group. Insomnia appeared more frequently in the 25 µg BID dosing group compared to the 50 µg QD group. Presumably, this was because the subjects administered the second dose of arformoterol in the evening. A meaningful difference in cardiovascular system related AEs between arformoterol treatment groups and placebo cannot be elicited from AEs reported for the clinical trials.

#### 7.1.5.6 Additional analyses and explorations

As reported above, there is a dose-response evident for arformoterol in the frequency of nervous system related side effects. There were no significant gender, age, or racial differences that were apparent at the 15 µg BID dose, however, the very low number of non-Caucasians in the clinical trials greatly hinders the racial analysis.

#### 7.1.6 Less Common Adverse Events

Of the 1,456 patients in the two 12-week, placebo-controlled trials, 288 were treated with arformoterol 15 µg BID and 293 with placebo. Adverse events occurring in patients treated with arformoterol 15 µg BID with a frequency of <2%, but greater than placebo are listed below:

- Body as a Whole: abscess, allergic reaction, digitalis intoxication, fever, hernia, injection site pain, neck rigidity, neoplasm, pelvic pain, retroperitoneal hemorrhage
- Cardiovascular: arteriosclerosis, atrial flutter, AV block, congestive heart failure, heart block, myocardial infarct, QT interval prolonged, supraventricular tachycardia, inverted T-wave
- Digestive: constipation, gastritis, melena, oral moniliasis, periodontal abscess, rectal hemorrhage
- Metabolic and Nutritional Disorders: dehydration, edema, glucose tolerance decreased, gout, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia
- Musculoskeletal: arthralgia, arthritis, bone disorder, rheumatoid arthritis, tendinous contracture
- Nervous: agitation, cerebral infarct, circumoral paresthesia, hypokinesia, paralysis, somnolence, tremor
- Respiratory: carcinoma of the lung, respiratory disorder, voice alteration
- Skin and Appendages: dry skin, herpes simplex, herpes zoster, skin discoloration, skin hypertrophy
- Special Senses: abnormal vision, glaucoma
- Urogenital: breast neoplasm, calcium crystalluria, cystitis, glycosuria, hematuria, kidney calculus, nocturia, PSA increase, pyuria, urinary tract disorder, urine abnormality.

## 7.1.7 Laboratory Findings

### 7.1.7.1 Overview of laboratory testing in the development program

Laboratory findings will focus mainly on those obtained from the large, Phase 3 trials. Results from single-dose and Phase 2 studies have been reviewed and do not add anything to the analysis [Sections 6.8.1-6.8.3, *clinstat\liss.pdf*]. In the pivotal studies 091-050 and 051, laboratory evaluations were performed at baseline and at each of the 8 subsequent study visits over the 12 week period. Because of the known effects of Beta-2 agonists on potassium and glucose levels, these parameters were measured pre-dose and at 2 and 6 hours post-dose during study visits 0, 3, 5, and 7 during the 12 week period. Those time points were chosen because they represented the time interval when the greatest changes in serum potassium and glucose levels were observed to occur in earlier studies. For the one-year long-term safety study, 091-060, laboratory evaluations were performed at baseline and at 5 other time points equally spaced over the course of the year. For all studies, laboratory tests performed included hematology, clinical chemistry, and urinalysis.

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

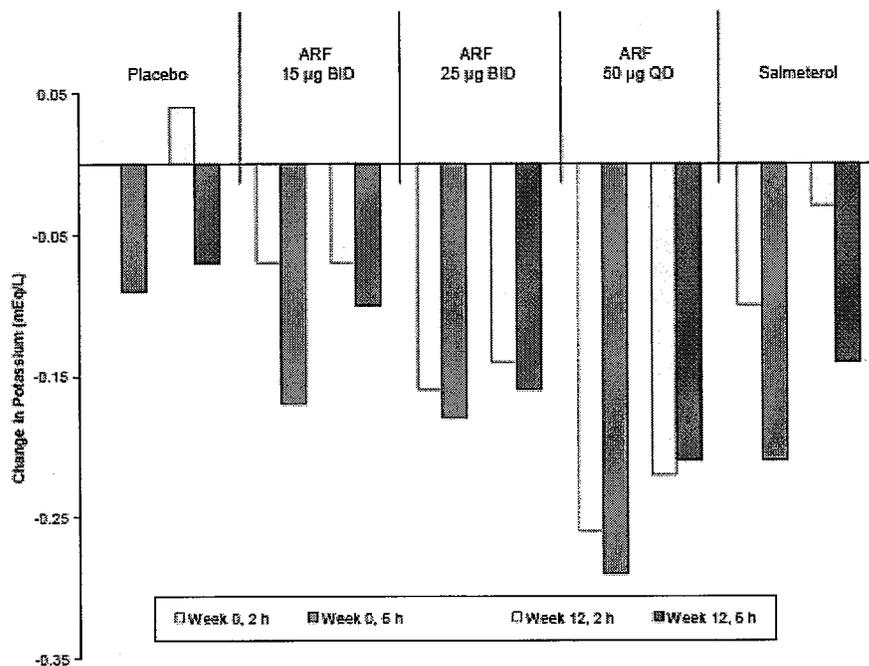
The laboratory data from the two, 12 week pivotal studies was pooled because the studies incorporated a placebo comparison, they were of identical design incorporating 3 different doses of arformoterol and an active comparator, and extensive laboratory data was collected. Data from the long-term safety study were reviewed separately as it was an open-label study utilizing a single dose of arformoterol. Since the dose of arformoterol used in the safety study was greater than the proposed indicated dose (50 µg QD vs 15 µg BID), it provides a safety assessment for a greater level of Beta stimulation, especially within the first several hours after administration, than the lower, proposed indicated dose.

### 7.1.7.3 Standard analyses and explorations of laboratory data

Hypokalemia and hyperglycemia are two recognized, potentially harmful consequences of Beta receptor stimulation that the Applicant paid special attention to during the conduct of clinical trials. The review of laboratory data will initially focus on alterations in serum potassium and glucose during the placebo-controlled pivotal studies and the year long-term safety study and then upon other laboratory tests performed. It should be noted that in the safety study a dose of 50 µg QD of arformoterol was used which is significantly higher, and thus resulting in greater Beta stimulation, than the indicated dose being proposed by the Applicant of 15 µg BID.

The figure below graphically displays mean changes in serum potassium from pre-dose level for the pivotal Phase 3 studies.

**Mean Change in Serum Potassium from Visit Pre-Dose (Pooled Studies 091-050 and 091-051, ITT Population)** [Figure 6.8.1.2.2-1, *clinstat\iss.pdf*]



There was a small but clear dose-related decrease in serum potassium levels with increasing doses of arformoterol both at the beginning and end of the treatment period. The effect was greatest at the 2 hour post-doses time point [Figure above and Table 6.8.1.2.2-1, *clinstat\iss.pdf*].

The number of subjects with potassium levels  $<3.5$  mEq/L and  $<3.0$  mEq/L 2 hours after arformoterol treatment, as well as the number of subjects with decreases in potassium of 0.25 mEq/L to  $>1.0$  mEq/L measured at 2-hours post treatment were also assessed [Table 6.8.1.2.2-2, *clinstat\iss.pdf*]. There was a dose-related increase in the frequency of potassium values  $<3.5$  mEq/L among subjects receiving arformoterol at both 2 and 6 hours post-dose. The arformoterol 15 µg BID dose group had decreases similar to or less than that for the salmeterol active comparator group. Decreases in potassium of 0.75 mEq/L or greater were more frequently observed in the active treatment groups than placebo. More subjects (9.3 and 10.7%) experienced decreases in potassium of  $>1.0$  mEq/L when receiving the 50 µg QD dose at both 2 and 6 hours post-dose, compared with subjects in the 25 µg BID (4.5 and 5.6%) or 15 µg BID (4.9 and 5.7%) groups. The post-dose changes seen were transient as evidenced by pre-dose values in the active treatment groups compared with placebo and the effects on serum potassium did not increase over time.

An analysis of serum potassium levels by baseline non-potassium sparing diuretic medication use revealed that of the 83 subjects with serum potassium  $<3.5$  mEq/L in the arformoterol treatment groups, only 1 (in the arformoterol 15 µg BID group) was receiving concomitant treatment with a non-potassium sparing diuretic.

Review of potassium levels from the long-term safety study 091-060, confirmed the more pronounced effects the 50 µg QD dose of arformoterol had on potassium levels seen in the 12 week pivotal studies.

Changes in serum glucose from visit pre-dose in pooled Studies 091-050 and 091-051 are summarized in the following Table.

**Serum Glucose (mg/dL) for Pooled Studies 091-050 and 091-051: Change from Visit Pre-Dose (ITT Population)** [Table 6.8.2.2.2-1, *clinstat/liss.pdf*]

Visit	Time Point	Statistic	Placebo BID (N=293)	Arformoterol 15 µg BID (N=288)	Arformoterol 25 µg BID (N=292)	Arformoterol 50 µg QD (N=293)	Salmeterol 42 µg BID (N=290)
Visit 3 (Week 0)	2 Hours Post- First Dose	n	285	277	283	287	282
		Mean (SD)	9.8 (34.1)	11.7 (33.3)	20.5 (35.9)	27.5 (39.4)	15.5 (38.2)
		Median	6.0	6.0	13.0	22.0	9.0
	6 Hours Post- First Dose	Min, Max	-91, 155	-147, 127	-117, 130	-122, 150	-107, 212
		n	286	279	283	286	281
		Mean (SD)	6.7 (32.3)	15.6 (35.0)	17.2 (31.6)	26.7 (40.5)	14.1 (34.8)
Visit 5 (Week 6)	2 Hours Post- Morning Dose	Median	6.0	13.0	13.0	22.0	10.0
		Min, Max	-94, 256	-138, 218	-89, 168	-86, 186	-105, 169
		n	242	242	251	264	259
	6 Hours Post- Morning Dose	Mean (SD)	9.2 (30.2)	11.3 (32.0)	11.3 (33.1)	25.8 (35.6)	14.9 (36.9)
		Median	7.0	6.0	7.0	20.0	8.0
		Min, Max	-95, 160	-119, 147	-115, 161	-75, 165	-81, 185
Visit 7 (Week 12)	2 Hours Post- Morning Dose	n	245	243	247	262	259
		Mean (SD)	8.5 (31.6)	11.8 (30.3)	14.7 (36.6)	18.3 (33.9)	11.9 (29.6)
		Median	7.0	8.0	10.0	15.5	8.0
	6 Hours Post- Morning Dose	Min, Max	-105, 137	-124, 158	-76, 333	-154, 178	-79, 108
		n	217	227	212	232	239
		Mean (SD)	5.1 (30.7)	8.5 (31.9)	15.5 (30.8)	27.1 (36.4)	14.8 (36.5)
6 Hours Post- Morning Dose	Median	3.0	7.0	9.0	21.0	7.0	
	Min, Max	-143, 183	-103, 129	-66, 157	-50, 200	-106, 159	
	n	216	225	214	235	235	
	Mean (SD)	5.5 (32.1)	8.8 (26.4)	12.2 (27.9)	18.2 (35.3)	11.4 (30.3)	
6 Hours Post- Morning Dose	Median	3.5	7.0	11.0	12.0	10.0	
	Min, Max	-128, 174	-74, 81	-62, 112	-73, 183	-97, 102	

Dose-related increases in serum glucose were evident at two hours post-dose and persisted at six hours post-dose at Week 0. Increases in serum glucose were similar or slightly lower in the arformoterol 15 µg BID treatment group than in the active control salmeterol group with both mildly elevated compared to placebo. There was no change over time. Again the dose-relationship was confirmed in study 091-060 in which the only dose of arformoterol tested was 50 µg QD.

Regarding other laboratory values, no trends were observed in mean clinical laboratory values over time, or in shifts from normal at screening to abnormal following treatment, across the Phase 3 multiple-dose studies [Tables 11.3.1.1, 11.3.2.1, 11.4.1, and 11.4.2, *clinstat/liss.pdf*].

The Applicant also analyzed the laboratory data according to what were felt to be clinically significant changes as previously defined [Table 5.2.10.1, *clinstat.pdf*]. These included a serum potassium < 3.0 mg/dL, AST and ALT > 3X ULN, and serum glucose > 175 mg/dL. The data for the pivotal Phase 3 studies are depicted in the following Table.

**Number and Percent of Subjects with Potentially Clinically Significant Laboratory Values During the Double-blind Period of Pooled Studies 091-050 and 091-051 (ITT Population)**

*[Table 6.8.3.2.2-1, clinstat/liss.pdf]*

Parameter	Placebo (N=293)		ARF 15 µg BID (N=288)		ARF 25 µg BID (N=292)		ARF 50 µg QD (N=293)		SAL 42 µg BID (N=290)	
	Low n (%)	High n (%)	Low n (%)	High n (%)	Low n (%)	High n (%)	Low n (%)	High n (%)	Low n (%)	High n (%)
Albumin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Alkaline phosphatase	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
AST	0 (0.0)	3 (1.0)	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.7)
Bicarbonate	3 (1.0)	1 (0.3)	4 (1.4)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.7)	0 (0.0)
Calcium	4 (1.4)	0 (0.0)	1 (0.3)	0 (0.0)	5 (1.7)	0 (0.0)	5 (1.7)	0 (0.0)	3 (1.0)	0 (0.0)
Chloride	5 (1.7)	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.3)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine	0 (0.0)	3 (1.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)
Glucose	1 (0.3)	47 (16.0)	1 (0.3)	46 (16.0)	2 (0.7)	58 (19.9)	2 (0.7)	90 (30.7)	2 (0.7)	72 (24.8)
Magnesium	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.7)	0 (0.0)	4 (1.4)	0 (0.0)
Phosphate	1 (0.3)	6 (2.0)	0 (0.0)	6 (2.1)	1 (0.3)	3 (1.0)	0 (0.0)	5 (1.7)	1 (0.3)	6 (2.1)
Potassium	2 (0.7)	6 (2.0)	3 (1.0)	6 (2.1)	3 (1.0)	5 (1.7)	5 (1.7)	8 (2.7)	1 (0.3)	5 (1.7)
Sodium	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total Bilirubin	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urea (BUN)	0 (0.0)	20 (6.8)	0 (0.0)	12 (4.2)	0 (0.0)	12 (4.1)	0 (0.0)	16 (5.5)	0 (0.0)	15 (5.2)
Uric Acid	0 (0.0)	12 (4.1)	0 (0.0)	13 (4.5)	0 (0.0)	9 (3.1)	0 (0.0)	9 (3.1)	0 (0.0)	4 (1.4)
Eosinophils	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.3)	0 (0.0)	3 (1.0)	0 (0.0)	6 (2.1)
Hematocrit	3 (1.0)	4 (1.4)	4 (1.4)	2 (0.7)	3 (1.0)	4 (1.4)	6 (2.0)	2 (0.7)	4 (1.4)	2 (0.7)
Hemoglobin	4 (1.4)	2 (0.7)	3 (1.0)	1 (0.3)	4 (1.4)	0 (0.0)	3 (1.0)	0 (0.0)	3 (1.0)	1 (0.3)
Monocytes	0 (0.0)	4 (1.4)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	3 (1.0)	0 (0.0)	1 (0.3)
Neutrophils	0 (0.0)	3 (1.0)	0 (0.0)	5 (1.7)	0 (0.0)	8 (2.7)	0 (0.0)	5 (1.7)	0 (0.0)	2 (0.7)
Platelets	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
RBCs	2 (0.7)	4 (1.4)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)
WBCs	1 (0.3)	4 (1.4)	0 (0.0)	6 (2.1)	0 (0.0)	6 (2.1)	0 (0.0)	7 (2.4)	0 (0.0)	6 (2.1)
Urine Protein	0 (0.0)	7 (2.4)	0 (0.0)	6 (2.1)	0 (0.0)	8 (2.7)	0 (0.0)	4 (1.4)	0 (0.0)	5 (1.7)

With the exception of glucose and potassium values discussed above, there was no consistent incidence of potentially significant laboratory values, including AST and ALT. There was a dose-related increase in potentially clinically significant high glucose levels in the arformoterol treatment groups, occurring in 16.0%, 19.9%, and 30.7% of the subjects treated with arformoterol 15 µg BID, 25 µg BID and 50 µg QD, respectively, compared with 16.0% of placebo subjects, and 24.8% of salmeterol-treated subjects. The incidence of potentially clinically significant low potassium was slightly higher in the arformoterol groups (1.0%, 1.0%, and 1.7% in the 15 µg BID, 25 µg BID and 50 µg QD groups, respectively) compared with the placebo group (0.7%). There were no other patterns of clinically significant laboratory results in any of the multiple-dose studies, including the one year safety study 091-060.

7.1.7.4 Additional analyses and explorations

Because of the known effects of Beta-2 agonists on potassium and glucose levels, additional analyses were performed to assess the effects of several dose levels of arformoterol on serum potassium and glucose during the clinical trials. These results are presented above.

7.1.7.5 Special assessments

No other special assessments of laboratory parameters were conducted other than those described above.

## 7.1.8 Vital Signs

### 7.1.8.1 Overview of vital signs testing in the development program

Vital sign, like laboratory assessments will focus mainly on those obtained from the large, Phase 3 trials. Results from single-dose and Phase 2 studies have been reviewed and do not add anything to the analysis [Sections 6.10.1-6.10.2.1.1-1, *clinstatliss.pdf*]. In the pivotal studies 091-050 and 051, vital signs were performed at baseline and at each of the 8 subsequent study visits over the 12 week period. Because of the possible effects of Beta-2 agonists on vital signs, especially heart rate and blood pressure, these parameters were measured pre-dose and at up to 4 hours post-dose during study visits 0, 3, 5, and 7 during the 12 week period. For the one-year long-term safety study, 091-060, laboratory evaluations were performed at baseline and at 5 other time points equally spaced over the course of the year.

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

The vital sign data from the two, 12 week pivotal studies was pooled because the studies incorporated a placebo comparison, they were of identical design incorporating 3 different doses of arformoterol and an active comparator, and extensive vital sign data were collected. Data from the long-term safety study were reviewed separately as it was an open-label study utilizing a single dose of arformoterol. Since the dose of arformoterol used in the safety study was greater than the proposed indicated dose (50 µg QD vs 15 µg BID), it provides a safety assessment for a greater level of Beta stimulation, especially within the first several hours after administration, than the lower, proposed indicated dose.

### 7.1.8.3 Standard analyses and explorations of vital signs data

As shown in the Table below, there were no meaningful differences in mean heart rate 2 hours post-dose among any of the treatment groups (differences < 3 beats/min).

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**Heart Rate (beats/min) at Week 0, 6, and 12 for Pooled Studies 091-050 and 091-051** [Table 6.10.2.1.2-1, *clinstat\liss.pdf*]

	Placebo (N=293)	Arformoterol 15 µg BID (N=288)	Arformoterol 25 µg BID (N=292)	Arformoterol 50 µg QD (N=293)	Salmeterol 42 µg BID (N=290)
<b>Week 0</b>					
<b>Pre-dose</b>					
n	293	287	292	291	289
Mean (SD)	76.9 (11.1)	76.6 (10.4)	76.4 (10.2)	77.3 (10.8)	77.1 (11.3)
Median	76.0	76.0	76.0	76.0	78.0
<b>2 hours Post-dose</b>					
n	293	286	292	292	289
Mean (SD)	76.4 (10.9)	75.4 (10.1)	76.3 (10.0)	78.3 (11.3)	76.3 (11.5)
Median	76.0	75.0	76.0	79.5	76.0
<b>Week 6</b>					
<b>Pre-dose</b>					
n	250	245	255	265	262
Mean (SD)	77.0 (11.1)	75.4 (10.8)	76.0 (10.2)	77.0 (11.2)	76.1 (10.6)
Median	76.0	76.0	76.0	76.0	76.0
<b>2 hours Post-dose</b>					
n	249	246	255	266	262
Mean (SD)	77.0 (10.5)	76.0 (10.8)	76.6 (10.4)	77.7 (10.5)	77.2 (10.5)
Median	76.0	76.0	76.0	78.0	76.0
<b>Week 12</b>					
<b>Pre-dose</b>					
n	226	232	221	241	242
Mean (SD)	77.2 (11.0)	76.3 (10.5)	76.4 (10.0)	76.0 (10.9)	76.8 (10.7)
Median	78.0	76.0	76.0	76.0	76.0
<b>2 hours Post-dose</b>					
n	221	229	215	239	238
Mean (SD)	76.3 (10.2)	75.2 (10.5)	77.0 (10.7)	78.9 (10.6)	77.6 (11.4)
Median	76.0	75.0	76.0	80.0	78.0

The maximum change from visit pre-dose in heart rate over the 4-hour post-dose period, and time to mean maximum change at Weeks 0, 6, and 12 were also summarized and again there were no meaningful differences among groups with the range of maximal increases from 8.5-10.3 beats/min [Table 6.10.2.1.2-2, *clinstat\liss.pdf*].

Mean systolic and diastolic blood pressure at predose and 2 hours post dose for Weeks 0, 6, and 12 were summarized and did not differ between treatment groups. There was a general fall in the systolic and diastolic pressures of from 1-3 mm/Hg post-dose [Tables 6.10.2.1.2-3 and 6.10.2.1.2-4, *clinstat\liss.pdf*].

The Applicant also evaluated for potentially clinically significant changes in vital signs as defined in Table 5.2.13-1 [*clinstat\liss\liss.pdf*]. These included increases or decreases of 15 or 20 mm/Hg in diastolic or systolic pressures, respectively or an increase > 25 or heart rate > 120 beats/min. The table below summarizes the percentage of subjects with potentially clinically significant values for vital signs for the pooled pivotal studies 091-050 and 091-051.

**Potentially Clinically Significant Vital Signs for the Pooled Studies 091-050 and 091-051**

*[Table 6.10.2.2.2-1, clinstat\liss.pdf]*

Parameter	Placebo (N=293)		ARF 15 µg BID (N=288)		ARF 25 µg BID (N=292)		ARF 50 µg QD (N=293)		Salmeterol 42 µg BID (N=290)	
	Low	High	Low	High	Low	High	Low	High	Low	High
Heart Rate (beats/min)	6 (2.0)	2 (0.7)	3 (1.0)	1 (0.3)	1 (0.3)	2 (0.7)	2 (0.7)	4 (1.4)	0 (0.0)	2 (0.7)
Systolic Blood Pressure (mmHg)	5 (1.7)	12 (4.1)	13 (4.5)	12 (4.2)	10 (3.4)	5 (1.7)	11 (3.8)	11 (3.8)	10 (3.4)	11 (3.8)
Diastolic Blood Pressure (mmHg)	4 (1.4)	7 (2.4)	8 (2.8)	2 (0.7)	9 (3.1)	5 (1.7)	18 (6.1)	9 (3.1)	15 (5.2)	4 (1.4)
Respiration Rate (breaths/min)	0 (0.0)	15 (5.1)	1 (0.3)	13 (4.5)	0 (0.0)	13 (4.5)	2 (0.7)	14 (4.8)	0 (0.0)	4 (1.4)
Temperature (degrees F)	13 (4.4)	1 (0.3)	13 (4.5)	0 (0.0)	13 (4.5)	1 (0.3)	13 (4.4)	0 (0.0)	14 (4.8)	1 (0.3)

There were few clinically significant vital signs in any treatment group. The only difference may be a dose-related decrease in low diastolic blood pressure in the arformoterol groups. However, the rate in the arformoterol 50 µg QD group (6.1%) was about the same as that seen in the salmeterol 42 µg BID active comparator group (5.2%). There were no differences in respiratory rate or temperature vital signs in the pivotal studies. In addition, review of data for the long-term safety study, 091-060, revealed no meaningful differences in heart rate, systolic blood pressure, diastolic blood pressure, respiration rate, or body temperature among the arformoterol 50 µg QD group compared to the salmeterol active comparator group.

7.1.8.4 Additional analyses and explorations

No other assessments of vital signs were conducted other than those described above

7.1.9 Electrocardiograms (ECGs)

The data from the clinical studies demonstrated no consistent mean change in ECG measures. Study 091-026, in which an extensive assessment of potential cardiac repolarization effects of arformoterol was conducted, demonstrated no meaningful impact of arformoterol on QT<sub>c</sub>, regardless of heart rate correction formula or analysis method. This study included a dose (50 µg QD) which is significantly higher than the proposed dose of 15 µg BID, especially because it was given as a single dose, than the proposed clinical dose.

In the pivotal studies, there is a hint of a dose-response after the first dose of study drug at Week 0 when QT<sub>C-F</sub> increased from 2.38 to 3.15 to 4.71ms compared to 0.60ms in the placebo group, in the arformoterol 15 µg BID, 25 µg BID, and 50 µg QD groups, respectively. The effect is not clinically significant. This effect was not maintained at later time points (Weeks 6 or 12).

Analyses of data from study 091-060 showed that, over the course of the one year study, at a dose of 50 µg QD, arformoterol resulted in an approximately 3.0ms increase in QT<sub>C-F</sub> compared to the active comparator salmeterol.

The Applicant has included language in the “Warnings” section of the proposed arformoterol that Beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. With minor changes, the warning is appropriate.

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

Electrocardiograms were evaluated at baseline and on-treatment to assess the effect of arformoterol on ECG parameters. In Study 091-026, a multiple-dose, placebo-controlled, dose-ranging study, intensive ECG monitoring was performed both post-first dose and at steady-state levels. Assessments included three ECGs about one minute apart obtained at each of 17 time points for subjects in Part A and 13 time points for Part B at baseline and when at steady-state. Additional ECGs were collected at screening as well as pre-dose and 30 minutes post-dose for each of the clinic visits (Visits 2-6). In Studies 091-050, 091-051, and 091-060, ECG assessments were collected at screening, during the single-blind run-in period (pivotal trials only), at each on-treatment clinic visit, and at the end of study visit.

ECG evaluations included summaries of standard ECG parameters (ventricular heart rate, PR, QRS, and QT), as well as QT interval corrected for heart rate by Fridericia's [QT<sub>C-F</sub>] and Bazett's [QT<sub>C-B</sub>] correction formula, QTC outlier analyses, ECG alerts, and ECG abnormalities. In Study 091-026, an additional QT interval correction formula was employed, an individual subject-specific baseline linear regression model (QT<sub>C-M</sub>). This correction formula, considered the most accurate approach by the Applicant, was possible given the extensive number of ECGs obtained at baseline.

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<sub>C-F</sub>, and QT<sub>C-B</sub>. Changes from pre-dose in heart rate, QT<sub>C-F</sub> and QT<sub>C-B</sub> were calculated for each visit.

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

The extensive ECG data from the placebo-controlled multiple dose, dose-ranging study, 091-026, were reviewed separately from the pooled placebo-controlled pivotal studies (091-050 and 051). Both sets of studies evaluated several doses of arformoterol which allowed the assessment of a dose-response relationship. The comparison of ECG data from the one year safety study, 091-060, while reviewed, was not very useful as the study was not placebo-controlled and the dose of arformoterol used was higher (50 µg QD vs 15 µg BID) than the proposed indicated dose.

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 Fridericia's formula as the Bazett formula may overcorrect at elevated heart rates, which may be present with Beta agonist use. In Study 091-026, an additional QT interval correction formula was employed, an individual subject-specific baseline linear regression model

(QTC-M). This correction formula, which the Applicant stated was considered the most accurate approach, was possible given the extensive number of ECGs obtained at baseline in the 091-026 study.

### 7.1.9.3 Standard analyses and explorations of ECG data

Analyses of the ECG data for Study 091-026 showed no consistent mean changes in ECG measures. The largest mean increases in QT<sub>C-M</sub> and QT<sub>C-F</sub> in Part A were -0.2 and 0.2ms, respectively, in the arformoterol 15 µg BID treatment group compared to -2.9 and -2.5ms, in the placebo group. For Part B, the largest mean increases were 0.9 and 2.3ms in the arformoterol 50 µg QD and 15 µg QD dosing groups, compared to 1.4 and 3.0ms in the placebo group for QT<sub>C-M</sub> and QT<sub>C-F</sub>, respectively [Tables 6.9.1.1.1-1 and 6.9.1.1.1-2, *clinstat\iss\iss.pdf*]. A categorical summary QT measures for study 091-026 is displayed in the following table.

**Categorical Analysis of QTc-M at Steady-State, Study 091-026** [Table 6.9.1.1.1-6, *clinstat\iss\iss.pdf*]

PART A				
Category	Placebo N=54 n (%)	ARF 5 µg BID N=54 n (%)	ARF 15 µg BID N=54 n (%)	ARF 25 µg BID N=53 n (%)
QT <sub>C-M</sub> >450 ms at any post-dose time point and <450 ms at baseline	1 (1.9)	5 (9.3)	4 (7.4)	5 (9.4)
QT <sub>C-M</sub> >500 ms at any post-dose time point and <500 ms at baseline	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)
Change in QT <sub>C-M</sub> ≥60 ms for any post-dose measurement	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Change in QT <sub>C-M</sub> ≥30 ms for any post-dose measurement but <60 ms at all time points	4 (7.4)	9 (16.7)	4 (7.4)	5 (9.4)
PART B				
Category	Placebo N=49 n (%)	ARF 15 µg QD N=48 n (%)	ARF 25 µg QD N=47 n (%)	ARF 50 µg QD N=47 n (%)
QT <sub>C-M</sub> >450 ms at any post-dose time point and <450 ms at baseline	5 (10.2)	2 (4.2)	3 (6.4)	4 (8.5)
QT <sub>C-M</sub> >500 ms at any post-dose time point and <500 ms at baseline	0 (0.0)	1 (2.1)	0 (0.0)	1 (2.1)
Change in QT <sub>C-M</sub> ≥60 ms for any post-dose measurement	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Change in QT <sub>C-M</sub> ≥30 ms for any post-dose measurement but <60 ms at all time points	2 (4.1)	5 (10.4)	4 (8.5)	2 (4.3)

Findings of QT<sub>C-F</sub> correction analyses were no different than that for QT<sub>C-M</sub>.

To assess a possible PK/PD relationship, time-matched individual QT<sub>C-M</sub> interval change from baseline by t<sub>max</sub> plasma concentration for Parts A and B was also analyzed for Study 091-026.

The analyses demonstrated no correlation between change in QT<sub>C-M</sub> values at t<sub>max</sub> and peak arformoterol plasma concentrations [Tables 6.9.1.1.1-1 and 6.9.1.1.1-2, *clinstat\iss\iss.pdf*].

For the pivotal studies 091-050 and 051, again no meaningful increase in QT<sub>C-F</sub> in any treatment group at any post-dose time point was observed. There is a hint of a dose-response after the first dose of study drug at Week 0 when QT<sub>C-F</sub> increased from 2.38 to 3.15 to 4.71ms compared to 0.60ms in the placebo group, in the arformoterol 15 µg BID, 25 µg BID, and 50 µg QD groups, respectively. This effect was not seen at steady-state drug concentrations when analyzed at Weeks 6 or 12 [Table 6.9.1.1.1-8, *clinstat\iss\iss.pdf*]. A categorical summary QT measures for study 091-026 is displayed in the following table.

**QT<sub>C-F</sub> Categorical Summary for Pooled Studies 091-050 and 091-051** [Table 6.9.1.1.1-9, *clinstat\iss\iss.pdf*]

Category	Placebo (N=293) n (%)	ARF 15 µg BID (N=288) n (%)	ARF 25 µg BID (N=292) n (%)	ARF 50 µg QD (N=293) n (%)	SAL 42 µg BID (N=290) n (%)
QT <sub>C-F</sub> >450 ms at any post-dose time point and <450 ms at baseline	4 (1.1)	7 (2.4)	2 (0.7)	3 (1.0)	6 (2.1)
QT <sub>C-F</sub> >500 ms at any post-dose time point and <500 ms at baseline	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.3)	0 (0.0)
Change ≥60 ms for at least one post-dose measurement	3 (1.0)	5 (1.8)	2 (0.7)	3 (1.0)	4 (1.4)
Change ≥30 ms for at least one post-dose measurement but <60 ms for all post-dose measurements	55 (19.2)	61 (21.8)	63 (21.9)	74 (25.5)	64 (23.0)

Analyses of data from study 091-060 over the course of the one year study showed that at a dose of 50 µg QD, arformoterol resulted in an approximately 3.0ms increase in QT<sub>C-F</sub> compared to the active comparator salmeterol [Table 6.9.1.1.1-10, *clinstat\iss\iss.pdf*].

#### 7.1.9.4 Additional analyses and explorations

##### *Holter Monitoring*

Holter monitoring data were presented for studies 091-026, 050, 051, and 060. Monitoring was performed at baseline, following a single dose and at steady-state after 2 weeks of dosing for both Parts A and B in study 091-026, the multiple-dose, dose-ranging study in which extensive cardiac testing was performed.

In study 091-026, there were more ventricular ectopic beats in a 24 hour period in the 25 µg BID dosing group in Part A than in other groups, however, this difference did not translate into an increased number of subjects with nonsustained (3-9 beat run) or sustained (≥ beat run) ventricular tachycardia. For Part B, the 50 µg QD dosing group had more ventricular ectopic beats, but again, this finding did not translate to an increase in nonsustained or sustained

ventricular tachycardia [Tables 6.9.2.1-1 and 6.9.2.1-2, *clinstat/liss/liss.pdf*]. There were no new treatment emergent Holter arrhythmias noted in either Parts A or B.

For the pivotal studies Holter monitoring was performed at the screening visit and at Weeks 0 (1<sup>st</sup> dose), 6 and 12. The data collected show an absence of consistent effects on heart rate, supraventricular, ventricular ectopic beats, or monitoring alerts with onset during the double-blinded treatment period [Tables 6.9.2.2-1 and 6.9.2.2-3 *clinstat/liss/liss.pdf*]. When analyzed as to the rates of arrhythmia events not present at baseline over the double-blind period, there were slightly higher rates in the higher dose arformoterol 25 µg BID and 50 µg QD groups and in the salmeterol group, (37.6, 40.1, and 39.6%, respectively). The rates in subjects in the placebo and arformoterol 15 µg groups with new, treatment emergent arrhythmias was the same (approximately 33-34%) [Table 6.9.2.2-4, *clinstat/liss/liss.pdf*].

Analysis of Holter monitoring data for study 091-060 did not reveal significant differences between the arformoterol 50 µg QD and salmeterol 42 µg BID groups.

In addition, several other analyses of cardiovascular safety were performed by the Applicant including the effects on heart rate, serum potassium, blood pressure, and analysis of COSTART coded terms for cardiovascular events. These analyses are reviewed in other safety sections of this review and did not reveal any previously unknown information regarding cardiovascular safety.

#### *COPD Exacerbations*

Respiratory safety was evaluated in both the pivotal studies (091-050 and 091-051) and safety study (091-060) by examining the frequency of COPD exacerbations. COPD exacerbations were defined in three ways; any spontaneous report of an AE of "COPD exacerbation", a protocol defined, symptom based definition of an increase in symptoms that requires any change in baseline medication other than bronchodilators or causes the subject to require additional medical attention, and a more general definition that included any respiratory event reported as asthma, bronchitis, pneumonia, COPD, cough, cough increased, dyspnea, sputum increased, apnea or hypoxia. While analyses of data collected for all three definitions is similar, this review will focus on the analysis of the protocol-defined definition as it required an intervention to treat the exacerbation and, as such, would be a specific, medically important event.

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**Post-Randomization COPD Events in Pooled Pivotal Studies 091-050 and 091-051** [Table 6.13.1.1-1, *clinstat/liss/liss.pdf*]

n (%)	Placebo (N=293)	ARF 15 µg BID (N=288)	ARF 25 µg BID (N=292)	ARF 50 µg QD (N=293)	Salmeterol 42 µg BID (N=290)
Overall COPD AEs*	24 (8.2)	21 (7.3)	26 (8.9)	29 (9.9)	27 (9.3)
COPD AEs during double-blind period	24 (8.2)	19 (6.6)	21 (7.2)	26 (8.9)	26 (9.0)
COPD AEs during follow-up	0	2 (0.7)	5 (1.7)	3 (1.0)	1 (0.3)
COPD AEs leading to Discontinuation	9 (3.1)	4 (1.4)	7 (2.4)	7 (2.4)	8 (2.8)
Serious COPD AEs	6 (2.0)	3 (1.0)	5 (1.7)	6 (2.0)	3 (1.0)
Severe COPD AEs	5 (1.7)	1 (0.3)	6 (2.1)	6 (2.0)	4 (1.4)
<b>Protocol-defined COPD exacerbations</b>					
Any Exacerbations	44 (15.1)	35 (12.2)	39 (13.5)	38 (13.0)	41 (14.2)
1	33 (11.3)	29 (10.1)	29 (10.0)	32 (11.0)	32 (11.8)
≥2	11 (3.8)	6 (2.1)	10 (3.5)	6 (2.1)	7 (2.4)
<b>Expanded Definition COPD exacerbations</b>					
Any Exacerbations	66 (22.6)	61 (21.3)	63 (21.8)	60 (20.5)	67 (23.2)
1	47 (16.1)	46 (16.0)	45 (15.6)	43 (14.7)	48 (16.6)
≥2	19 (6.5)	15 (5.2)	18 (6.2)	17 (5.8)	19 (6.6)

\*Overall COPD AEs include any COPD AE occurring post-randomization, including 30 days after completion of study medication.

The number of any protocol defined COPD exacerbations was highest in the placebo group [44(15.1%)]. The arformoterol 15 µg BID treatment group had the lowest number of exacerbations [35 (12.2%)] with the other treatment groups reporting similar numbers. The arformoterol 15 µg group also had the fewest overall COPD AEs [21 (7%)]. The number of COPD exacerbations using the expanded definition was about the same in all groups probably due to the less sensitive nature of the reporting method.

More COPD related AEs were reported during the follow-up period for the active treatment groups compared to placebo but the numbers overall were very small.

In study 091-060, protocol defined exacerbation rates were higher than in the pivotal studies for both active treatment groups with 32% and 27.5% for the arformoterol 50 µg QD and salmeterol 42µg BID groups, respectively [Table 6.13.1.2-1, *clinstat/liss/liss.pdf*]. This is likely the result of the longer reporting period in this one year study.

Subgroup analyses of protocol defined and expanded definition COPD exacerbations were performed by age, race, gender, current smoking status, baseline corticosteroid use, and percent predicted FEV1 focusing on a >5% difference between the treatment groups. Regarding age, in the pooled pivotal studies, the highest rates of protocol defined COPD exacerbations were observed in the placebo group in subjects 65 to <75 years, and in the arformoterol 50 µg QD group in subjects ≥75 years. As would be expected, there was a clear trend for more protocol defined COPD exacerbations across treatment groups in subjects with more severe disease (lower % predicted FEV1). There were no clear differences in the occurrence of protocol-defined COPD exacerbations in the pivotal studies with respect to baseline steroid use, current smoking

status, or race, although the representation of non-Caucasian races was low [*Section 6.13.2, clinstat/liss/liss.pdf*].

#### 7.1.10 Immunogenicity

Immunogenicity is not applicable to the safety or pharmacokinetics of arformoterol.

#### 7.1.11 Human Carcinogenicity

This section is not applicable as human carcinogenicity studies have not been performed with arformoterol and cancers reported during relatively short clinical trials (pivotal trials 12 weeks, safety study 1 year) were few and likely related to co-morbid conditions/risk factors such as cigarette smoking. Carcinogenicity studies with arformoterol tartrate in rats showed no increase in treatment related tumors in animals who received 40 µg/kg/day, which is approximately 35.9-55.5 times the systemic exposure for the proposed clinical dose of 15 µg BID. At higher doses (100-200 µg/kg/day), increased incidences of thyroid C-cell adenoma and carcinoma in female rat treatment groups was seen [*Pharm/Tox Review/ Carcinogenicity Study Review/Timothy Robison*].

#### 7.1.12 Special Safety Studies

The safety and adverse event profile of Beta-2 agonists, including LABAs such as arformoterol, have been well described and include cardiovascular effects such as tachycardia and QT prolongation, nervous system effects such as anxiety, nervousness, and tremor, and metabolic effects including hypokalemia and hyperglycemia. As such, these Beta-2 agonist class effect safety parameters were incorporated into the clinical studies performed to support the NDA. The review of these potential safety concerns is, therefore, incorporated into the appropriate section of the NDA safety section, e.g., Adverse Events, Vital Signs, Laboratory, etc.

One specific study deserves mention; study 091-026, a multiple-dose, dose-ranging study in which the Applicant designed to characterize the effect of arformoterol on cardiovascular safety outcomes in COPD patients. Many study design components of a study specifically designed to assess for QT prolongation were incorporated into this study including: 1) inclusion of multiple arformoterol doses (with doses higher than those proposed for marketing), 2) timing of ECG assessments to match the arformoterol PK profile, including C<sub>max</sub>, 3) sufficient number of ECG assessments at baseline such that individual QT correction formulae could be determined, 4) sufficient number of ECG assessments postdose such that characterization of the effects of arformoterol on cardiac repolarization throughout the dosing interval could be performed, and 5) utilization of a placebo-controlled, double-blind study design. The results of study 091-026 pertaining to cardiovascular safety are incorporated into Section 7.1.9 (ECGs).

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is little to no abuse potential for arformoterol. Pulmonary function testing conducted after discontinuing therapy in clinical trials failed to demonstrate withdrawal phenomena which would be manifest as worsening pulmonary function (FEV<sub>1</sub>) or adverse events.

#### 7.1.14 Human Reproduction and Pregnancy Data

There were no pregnancies in the arformoterol inhalation solution clinical program.

#### 7.1.15 Assessment of Effect on Growth

All clinical trials were conducted in adults. There were no growth assessments made.

#### 7.1.16 Overdose Experience

There were no overdoses reported during the clinical development of arformoterol. However, in Phase 1 studies, single doses of up to 96 µg of arformoterol were administered to subjects with COPD. Side effects were dose-related and consistent with excessive Beta-receptor stimulation. Notable nervous system effects were tremor and nervousness which occurred more often in subjects who received  $\geq 50$  µg of arformoterol as a single dose. Cardiovascular effects were relatively few and limited to palpitations and atrial fibrillation in 3 out of 251 subjects who received  $\geq 50$  µg of arformoterol as a single dose. [Table 6.7.4.1-1, *clinstat\copd\liss.Pdf*] One subject, a 65 year old male with comorbid conditions of hypertension, diabetes, coronary artery disease, hypercholesterolemia, and status post abdominal aortic aneurism repair experienced angina pectoris and ECG changes two hours after treatment with arformoterol 96 µg. He continued to have tachycardia and increased blood pressure in the subsequent 3 days and required treatment with a Beta-blocker.

#### 7.1.17 Postmarketing Experience

To date, arformoterol has not been approved for treatment of any medical condition. There is no postmarketing experience.

### 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

The tables of all clinical studies provided in Section 4.2 provides a summary of the pivotal, supportive, and other clinical studies in this application including descriptive information on study type, treatment groups, design, patient population, subject numbers, dosing schedule, and indication.

### 7.2.1.2 Demographics

Demographic information for single-dose and Phase 2-3 multiple-dose studies are shown in the tables below.

#### Subject Demographics and Baseline Characteristics for Single-Dose Exposure Studies (091-001, 091-007, 091-012, 091-013, and 091-021) [Table 6.3.1-1, *clinstatississ.pdf*]

n (%)	Placebo (N=80)	Arformoterol ≤15 µg (N=86)	Arformoterol 24 µg (N=77)	Arformoterol 48-50 µg (N=173)	Arformoterol ≥72 µg (N=78)	Salmeterol 42 µg (N=68)
<b>Age (years)</b>						
N	80	86	77	173	78	68
Mean (SD)	58.7 (14.9)	58.2 (16.3)	60.5 (13.2)	49.7 (19.6)	60.3 (13.6)	63.4 (7.8)
Median	62.0	62.0	62.0	54.0	62.0	63.0
Min, Max	20, 77	18, 79	18, 77	18, 80	18, 79	46, 77
<b>Sex</b>						
Male	50 (62.5)	55 (64.0)	50 (64.9)	118 (68.2)	49 (62.8)	44 (64.7)
Female	30 (37.5)	31 (36.0)	27 (35.1)	55 (31.8)	29 (37.2)	24 (35.3)
<b>Race</b>						
Black	0 (0.0)	0 (0.0)	0 (0.0)	23 (13.3)	0 (0.0)	0 (0.0)
Caucasian	79 (98.8)	85 (98.8)	76 (98.7)	141 (81.5)	77 (98.7)	67 (98.5)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.7)	0 (0.0)	0 (0.0)
Hispanic	1 (1.3)	1 (1.2)	1 (1.3)	4 (2.3)	1 (1.3)	1 (1.5)
Other	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
<b>Height (cm)</b>						
N	80	86	77	173	78	68
Mean (SD)	171.1 (10.4)	171.1 (10.1)	170.7 (10.5)	171.9 (11.1)	170.6 (10.3)	170.5 (10.3)
Median	172.4	172.7	172.0	173.0	171.6	171.6
Min, Max	134.6, 198.1	134.6, 198.1	134.6, 198.1	134.6, 198.1	134.6, 198.1	134.6, 198.1
<b>Weight (kg)</b>						
N	80	86	77	173	78	68
Mean (SD)	77.5 (17.7)	77.8 (17.6)	78.4 (17.9)	79.8 (16.7)	78.9 (18.6)	78.5 (18.0)
Median	74.6	74.8	75.7	77.5	75.3	74.8
Min, Max	39.5, 126.1	39.5, 126.1	39.5, 126.1	39.5, 126.1	39.5, 126.1	39.5, 126.1
<b>Visit 1 Pre-Dose FEV<sub>1</sub> (liters)</b>						
N	70	74	71	71	72	68
Mean (SD)	1.24 (0.48)	1.24 (0.48)	1.24 (0.48)	1.24 (0.48)	1.24 (0.48)	1.25 (0.49)
Median	1.14	1.14	1.12	1.12	1.14	1.14
Min, Max	0.55, 2.82	0.55, 2.82	0.55, 2.82	0.55, 2.82	0.55, 2.82	0.55, 2.82
<b>Visit 1 Pre-Dose Percent of Predicted</b>						
N	70	74	71	71	72	68
Mean (SD)	41.09 (14.88)	41.20 (14.83)	40.99 (14.79)	40.87 (14.88)	41.09 (14.69)	41.16 (14.88)
Median	38.15	38.15	38.00	38.00	38.15	38.15
Min, Max	16.9, 80.5	16.9, 80.5	16.9, 80.5	16.9, 80.5	16.9, 80.5	16.9, 80.5
<b>Visit 1 Pre-Dose FEV<sub>1</sub> Percent Reversibility</b>						
N	69	73	70	70	71	67
Mean (SD)	18.71 (12.12)	18.94 (12.01)	18.72 (12.03)	18.99 (12.26)	18.81 (12.00)	18.53 (12.08)
Median	16.90	17.00	16.95	16.95	17.00	16.90
Min, Max	-7.7, 54.3	-7.7, 54.3	-7.7, 54.3	-7.7, 54.3	-7.7, 54.3	-7.7, 54.3

The arformoterol 48-50 µg group was younger (49.7 years) compared with the other treatment groups (58.2 to 63.4 years). Approximately two thirds of all subjects were male, and the large majority Caucasian (81.5% to 98.8%). Subjects had a significant degree of airflow obstruction with baseline characteristics of moderated to severe COPD, with mean FEV<sub>1</sub> levels of 1.24 to 1.25 L, and 41.0 to 41.2 percent predicted FEV<sub>1</sub>.

**Subject Demographics and Baseline Characteristics for Pooled Phase 2-3 Multi-Dose Studies (091-026, 091-050, 091-051 and 091-060) [Table 6.3.2.4-1, clinstatississ.pdf]**

	Placebo BID (N=383)	ARF 5 µg BID (N=54)	ARF 15 µg QD (N=48)	ARF 25 µg QD (N=47)	ARF 15 µg BID (N=342)	ARF 25 µg BID (N=345)	ARF 50 µg QD (N=868)	SAL 42 µg BID (N=555)
<b>Age (years)</b>								
N	383	54	48	47	342	345	868	555
Mean (SD)	63.2 (8.8)	64.5 (8.3)	61.2 (9.8)	63.1 (8.0)	62.3 (8.9)	63.5 (9.4)	63.1 (9.2)	63.7 (8.8)
Median	63.0	65.0	60.5	62.0	62.5	64.0	63.0	64.0
Min, Max	40, 89	46, 84	41, 87	48, 79	34, 80	40, 84	35, 91	37, 89
<b>Sex (n, %)</b>								
Male	228 (59.5)	30 (55.6)	25 (52.1)	29 (61.7)	198 (57.9)	207 (60.0)	501 (57.7)	333 (60.0)
Female	155 (40.5)	24 (44.4)	23 (47.9)	18 (38.3)	144 (42.1)	138 (40.0)	367 (42.3)	222 (40.0)
<b>Race (n, %)</b>								
Black	10 (2.6)	4 (7.4)	6 (12.5)	2 (4.3)	17 (5.0)	15 (4.3)	33 (3.8)	15 (2.7)
Caucasian	366 (95.6)	50 (92.6)	42 (87.5)	45 (95.7)	319 (93.3)	327 (94.8)	821 (94.6)	532 (95.9)
Asian	3 (0.8)	0 (0)	0 (0)	0 (0)	2 (0.6)	2 (0.6)	5 (0.6)	3 (0.5)
Hispanic	3 (0.8)	0 (0)	0 (0)	0 (0)	4 (1.2)	0 (0)	4 (0.5)	4 (0.7)
Other	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	5 (0.6)	1 (0.2)
<b>Height (cm)</b>								
N	383	54	48	47	342	345	862	555
Mean (SD)	170.3 (9.8)	171.2 (10.5)	169.9 (10.6)	171.4 (10.2)	170.9 (9.9)	170.2 (9.7)	170.1 (9.7)	170.8 (9.8)
Median	171.0	170.75	171.0	172.0	171.0	170.9	170.18	172.0
Min, Max	136.0, 195.6	152.0, 194.0	149.1, 188.0	149.0, 188.0	132.0, 197.0	141.0, 193.0	140.0, 198.0	132.0, 196.0
<b>Weight (kg)</b>								
N	383	54	48	47	342	345	868	551
Mean (SD)	80.0 (18.0)	79.0 (18.3)	80.8 (22.0)	79.7 (19.4)	81.4 (18.2)	80.9 (20.4)	81.2 (19.3)	80.1 (19.2)
Median	78.2	74.0	76.9	75.3	80.1	78.0	78.9	78.0
Min, Max	40.5, 157.0	55.4, 150.0	47.6, 151.8	48.2, 137.7	40.5, 156.4	39.5, 155.0	42.0, 194.0	29.7, 150.6
<b>Visit 1 Pre-Dose FEV<sub>1</sub> (liters)</b>								
N	383	54	48	47	341	344	866	549
Mean (SD)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.2 (0.5)	1.2 (0.4)	1.3 (0.5)
Median	1.2	1.1	1.2	1.3	1.2	1.1	1.2	1.2
Min, Max	0.6, 2.8	0.5, 2.2	0.5, 2.3	0.6, 2.3	0.5, 3.0	0.5, 2.8	0.3, 2.8	0.5, 2.9
<b>Visit 1 Pre-Dose FEV<sub>1</sub> Percent of Predicted</b>								
N	383	54	48	47	341	344	866	549
Mean (SD)	42.1 (12.4)	42.8 (12.2)	42.2 (11.9)	41.3 (12.4)	41.9 (13.5)	41.1 (13.0)	41.9 (12.4)	41.6 (13.0)
Median	41.2	42.3	42.9	38.6	40.6	40.2	41.6	40.4
Min, Max	17.2, 69.9	17.2, 65.5	17.2, 62.7	19.2, 65.4	14.5, 78.2	14.7, 73.7	13.4, 82.0	15.1, 91.0
<b>Visit 1 Pre-Dose FEV<sub>1</sub> Percent Reversibility</b>								
N	379	51	45	47	334	341	857	543
Mean (SD)	15.9 (14.3)	19.2 (12.9)	16.4 (12.2)	19.7 (10.8)	16.8 (13.7)	18.4 (15.6)	17.5 (23.8)	17.0 (15.4)
Median	13.7	17.2	12.8	17.3	14.5	16.9	14.9	15.0
Min, Max	-54.0, 89.0	3.7, 89.0	-10.4, 58.9	-1.5, 46.7	-19.7, 69.9	-40.7, 95.8	-40.7, 420.6	-54.0, 107.4
<b>COPD Duration (n, %)</b>								
≥0 to <5 Years	184 (48.0)	27 (50.0)	20 (41.7)	23 (48.9)	167 (48.8)	183 (53.0)	441 (50.8)	291 (52.4)
≥5 to <10 Years	111 (29.0)	15 (27.8)	10 (20.8)	15 (31.9)	79 (23.1)	87 (25.2)	211 (24.3)	137 (24.7)
≥10 to <15 Years	48 (12.5)	6 (11.1)	8 (16.7)	3 (6.4)	41 (12.0)	34 (9.9)	99 (11.4)	57 (10.3)
≥15 Years	39 (10.2)	6 (11.1)	10 (20.8)	6 (12.8)	54 (15.8)	41 (11.9)	117 (13.5)	70 (12.6)
Missing	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)
<b>Pack-years Smoked (n, %)</b>								
≥15 to <25 Years	26 (6.8)	6 (11.1)	2 (4.2)	4 (8.5)	31 (9.1)	29 (8.4)	68 (7.8)	30 (5.4)
≥25 to <30 Years	22 (5.7)	2 (3.7)	5 (10.4)	5 (10.6)	13 (3.8)	20 (5.8)	44 (5.1)	36 (6.5)
≥30 Years	335 (87.5)	46 (85.2)	41 (85.4)	38 (80.9)	298 (87.1)	296 (85.8)	756 (87.1)	489 (88.1)

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	Placebo BID (N=383)	ARF 5 µg BID (N=54)	ARF 15 µg QD (N=48)	ARF 25 µg QD (N=47)	ARF 15 µg BID (N=342)	ARF 25 µg BID (N=345)	ARF 50 µg QD (N=868)	SAL 42 µg BID (N=555)
<b>Packs Per Day Smoked (n, %)</b> <sup>1,2</sup>								
Does not currently smoke	189 (49.3)	34 (63.0)	17 (35.4)	23 (48.9)	177 (51.8)	189 (54.8)	466 (53.7)	322 (58.0)
≥0 to 1 Pack	92 (24.0)	10 (18.5)	18 (37.5)	10 (21.3)	69 (20.2)	81 (23.5)	200 (23.0)	116 (20.9)
≥2 to <3 Packs	71 (18.3)	7 (13.0)	10 (20.8)	13 (27.7)	72 (21.1)	54 (15.7)	138 (15.9)	77 (13.9)
≥3 to <4 Packs	30 (7.8)	3 (5.6)	3 (6.3)	1 (2.1)	24 (7.0)	20 (5.8)	63 (7.3)	39 (7.0)
≥4 Packs	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.1)	1 (0.2)
<b>Family COPD History (n, %)</b>								
Father	84 (21.9)	10 (18.5)	13 (27.1)	10 (21.3)	77 (22.5)	80 (23.2)	203 (23.4)	111 (20.0)
Mother	51 (13.3)	2 (3.7)	6 (12.5)	3 (6.4)	51 (14.9)	54 (15.7)	146 (16.8)	74 (13.3)
Siblings	87 (22.7)	11 (20.4)	6 (12.5)	13 (27.7)	77 (22.5)	86 (24.9)	191 (22.0)	109 (19.6)
Maternal Grandparent	29 (7.6)	2 (3.7)	2 (4.2)	3 (6.4)	25 (7.3)	21 (6.1)	43 (5.0)	23 (4.1)
Paternal Grandparent	10 (2.6)	3 (5.6)	1 (2.1)	3 (6.4)	15 (4.4)	18 (5.2)	26 (3.0)	19 (3.4)
<b>COPD Exacerbations</b>								
N	383	54	48	47	342	345	868	555
Mean (SD)	0.0 (0.1)	0.0 (0.2)	0.1 (0.3)	0.1 (0.2)	0.0 (0.2)	0.0 (0.3)	0.0 (0.2)	0.0 (0.1)
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min, Max	0.0, 1.0	0.0, 1.0	0.0, 2.0	0.0, 1.0	0.0, 1.0	0.0, 5.0	0.0, 5.0	0.0, 1.0
Baseline Corticosteroid Use	108 (28.2)	25 (46.3)	17 (35.4)	20 (42.6)	93 (27.2)	100 (29.0)	300 (34.6)	167 (30.1)

Age, gender, and pulmonary characteristics were balanced across treatment groups with baseline pulmonary characteristics consistent with the general population characteristics of COPD patients. Mean ages ranged from 61-64 years across groups with approximately 60% of subjects male. Subjects had a significant degree of airflow obstruction with baseline characteristics of moderate to severe COPD, with mean FEV1 levels of 1.2 to 1.3 L, and 41.1 to 42.8 percent predicted FEV1. Smoking history was similar across treatment groups. Approximately 95% of subjects were Caucasian.

### 7.2.1.3 Extent of exposure (dose/duration)

The overall extent of exposure to arformoterol across all studies is shown in the table below.

### Extent of Exposure for Unique Subjects Across All Studies Receiving Arformoterol (by Total Daily Dose) [Table 6.1.4-1, clinstatississ.pdf]

Duration of Exposure (weeks)	Arformoterol ≤15 µg (N=69)	Arformoterol 24-25 µg (N=110)	Arformoterol 30 µg (15 µg BID) (N=254)	Arformoterol 48-50 µg (24-25 µg BID) (N=273)	Arformoterol 48-50 µg QD (N=1094)	Arformoterol >50 µg (N=177)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Single Dose	6 (10.0)	6 (5.5)	0 (0)	0 (0)	209 (19.1)	93 (52.5)
≤1	2 (3.3)	4 (3.6)	14 (5.5)	12 (4.4)	42 (3.8)	5 (2.8)
>1 to ≤4	52 (86.7)	99 (90.0)	50 (19.7)	50 (18.3)	170 (15.5)	79 (44.6)
>4 to ≤13	0 (0)	1 (0.9)	180 (70.9)	204 (74.7)	231 (21.1)	0 (0)
>13 to ≤26	0 (0)	0 (0)	10 (3.9)	7 (2.6)	60 (5.5)	0 (0)
>26 to <52	0 (0)	0 (0)	0 (0)	0 (0)	156 (14.3)	0 (0)
≥52	0 (0)	0 (0)	0 (0)	0 (0)	226 (20.7)	0 (0)
<b>Total Daily Dose (µg)</b>						
N	69	110	254	273	1094	177
Mean (SD)	12.1 (2.7)	24.2 (6.0)	28.6 (3.9)	48.5 (3.7)	48.7 (3.9)	78.2 (11.7)

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Secondary data sources referenced by the Applicant pertained to the Beta-2 agonist class of drugs and, specifically, to the LABA class of Beta-2 agonists, including the marketed products salmeterol and racemic formoterol. The Salmeterol Multicenter Asthma Research Trial

(SMART) in patients with asthma and Phase 3 program for racemic formoterol for an asthma indication were discussed with the focus on the possibility of the use of these LABAs being associated with an increase in severity of asthma exacerbations and/or increase in asthma-related death.

#### 7.2.2.1 Other studies

All pertinent studies performed for arformoterol are provided in this NDA application.

#### 7.2.2.2 Postmarketing experience

As it has not been approved for treatment of any medical condition, there is no postmarketing experience with arformoterol.

#### 7.2.2.3 Literature

No independent literature review was performed by the reviewer. The review submitted by the Applicant evaluated the clinical literature that referenced arformoterol, pertinent racemic formoterol (Foradil Aerolizer) articles, and selected articles for salmeterol in an attempt to provide a detailed review of key safety issues. The review was complete and included a discussion of the known class effects of Beta agonists. The safety concerns about the use of LABAs resulting in more severe asthma exacerbations and/or death in patients with asthma was also discussed in the context of the Salmeterol Multicenter Asthma Research Trial (SMART) and Phase 3 safety data for Foradil Aerolizer.

### 7.2.3 Adequacy of Overall Clinical Experience

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. The extent of exposure to arformoterol during the clinical development program exceeded the ICH minimum requirements. There were a total of 595.7 person-years of exposure data to arformoterol in the clinical program. Specifically, there were a total of 342 COPD subjects exposed to arformoterol 15 µg BID for up to 12 weeks, and 345 COPD subjects exposed to arformoterol 25 µg BID for up to 12 weeks. In addition, 383 COPD subjects received arformoterol 50 µg QD for at least six months, and 308 subjects received arformoterol 50 µg QD for one year (defined as  $\geq 49$  weeks). The clinical database consists of a total of 2722 subjects (approximately 596 person-years of exposure), representing 1968 unique subjects, including subjects with COPD, subjects with asthma, as well as healthy volunteers [Section 6.1, *clinstatliss/liss.pdf*].

There was a lack of racial representation in the clinical trials with  $\leq 5\%$  of study subjects representing racial minorities. The lack of minority representation is significant, especially in light of findings from the large salmeterol post-marketing safety study in subjects with asthma (SMART) which found that African-American individuals who were treated with the LABA,

salmeterol, had a higher incidence of asthma related death than Caucasians receiving it. The Applicant is aware of this deficiency and another arformoterol safety study (091-061) is in progress with the goal of enrolling more minority populations.

The doses and extent of exposure were appropriate for studies of bronchodilators in COPD patients. Safety analyses were appropriate as well with adequate attention paid to assessing LABA class effects of respiratory, nervous system and cardiovascular systems including extensive ECG and Holter monitoring throughout the program and a thorough QTc evaluation in study 091-026. Specific studies (091-014 and 015) were performed in subjects with renal and hepatic insufficiency. Finally, all subjects with COPD in clinical studies had sufficient co-morbid conditions (hypertension, coronary artery disease, etc.) that safety assessments and conclusions made throughout the trials would be relevant to clinical use.

#### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The preclinical animal and in vitro testing program was adequate to address the potential for adverse events that would be predictable for a member of the Beta-2 adrenergic agonist class of drugs. Extensive evaluations included in vitro and in vivo studies demonstrating that the Beta-2 adrenergic agonist activity of racemic formoterol is attributable to arformoterol, studies investigating potential effects of arformoterol on other receptors, ion channels and enzyme activities, potential proinflammatory properties of arformoterol, assessment of the pharmacological activity of (S,S) formoterol, and studies evaluating the inhibitory effects of arformoterol on human CYP450, sulfotransferase, and glucuronosyltransferase enzyme activities.

#### 7.2.5 Adequacy of Routine Clinical Testing

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 for a LABA indicated for use in patients with COPD who typically have co-morbid conditions.

#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Drug metabolism studies were adequate and confirmed that CYP2D6 is not an important component of the metabolism of arformoterol and that a drug-drug interaction with any CYP2D6 inhibitor would be unlikely. Drug clearance was also shown to be delayed in subjects with hepatic, but not renal, insufficiency. Analysis of concomitant drug use during clinical trials demonstrated that there were no significant drug interactions with the bronchodilator theophylline resulting in increased cardiovascular effects or changes in vital signs. For a more complete discussion of drug metabolism see Sections 5 and 8.2 of this review and the Clinical Pharmacology review by Dr. Shinja Kim.

### 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 the LABA arformoterol is the active enantiomer of racemic formoterol, which is an approved drug (Foradil®) indicated for treatment of bronchospasm in both asthma and COPD, the side effect profile of arformoterol can be predicted. The Applicant's effort to detect potential adverse events included an assessment of Beta agonist effects, such as those associated with ECG, QTc, vital sign, cardiovascular and nervous system changes, and hypokalemia, and hyperglycemia. The Applicant's evaluation for potential adverse events in the clinical studies is adequate.

### 7.2.8 Assessment of Quality and Completeness of Data

The overall quality and completeness of the data available to conduct the safety review is acceptable. The intentional unblinding of safety data for 24 subjects in the pivotal trials (discussed in Section 4.4 of this review), would not have an impact on the quality of the safety analyses.

### 7.2.9 Additional Submissions, Including Safety Update

A 120-day safety update was submitted by the Applicant that contained new safety data from the time of the cut-off date for the original NDA submission (08/17/05) through 02/15/06. The clinical data are reviewed herein and were derived from 2 sources:

- 1) The final study report for study 091-019, a Phase 2, open-label, randomized, multiple-dose, 3-way crossover, multicenter study that compared the PK profile of arformoterol inhalation solution at the proposed clinically indicated dose of 15 µg BID) to Foradil DPI (12 µg and 24 µg BID) in 39 male and female subjects with COPD. This study was conducted essentially to further support the proposed clinically dose of 15 µg BID by demonstrating comparable (R,R) formoterol pharmacokinetics between the 15µg dose of arformoterol delivered by **nebulization** and the 12 µg dose of racemic formoterol contained in the approved LABA Foradil that is delivered by **dry powder inhaler**.
- 2) Blinded safety data from the ongoing study 091-061. This study, which was initiated on 11/10/05, is a Phase 3, double-blind, double-dummy, multicenter, randomized, active-controlled, parallel group, safety study to evaluate the long-term safety of arformoterol (15 µg and 25 µg BID) compared with racemic formoterol dry powder inhaler (DPI) (Foradil®) 12 µg BID in the treatment of subjects with COPD. Study participation consists of a total of 6 visits over approximately 6 months. It is this study in which the Applicant is trying to ensure that at least 10% of randomized subjects have a racial classification of "Black." This is in response to comments from DPAP pointing to the lack of racial diversity in their clinical trials (≥ 95% Caucasian).

An updated literature review and additional analyses of Phase 3 studies have also been submitted.

As shown in the table below, results of study 091-019 support the comparability of the steady-state pharmacokinetics between arformoterol 15 µg BID and Foradil (racemic formoterol) 12 µg BID.

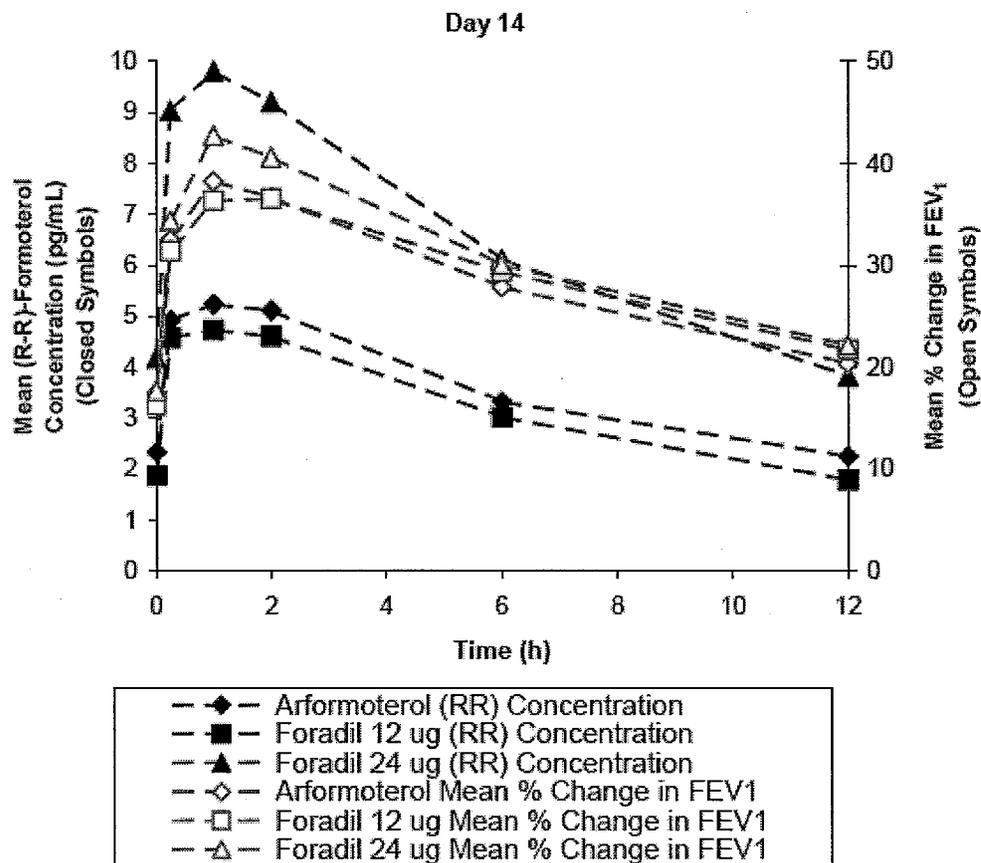
**Study 091-019: Analysis of the Effect of Treatment on Steady State Primary (R,R)-Formoterol PK Parameters** [Table 4.2.2-1, update\updatsum.pdf]

Parameter	Treatment Group	Geometric LS Mean	Treatment Comparison	Ratio	90% CI
AUC <sub>(0-∞)</sub> (pg*hr/mL)	Racemic Formoterol 12 µg DPI BID	33.93	Arformoterol 15 µg / Foradil 12 µg	1.16	1.00, 1.35
	Arformoterol 15 µg BID	39.33	NA	NA	NA
	Racemic Formoterol 24 µg DPI BID	67.69	Arformoterol 15 µg / Foradil 24 µg	0.58	0.50, 0.67
C <sub>max</sub> (pg/mL)	Racemic Formoterol 12 µg DPI BID	4.75	Arformoterol 15 µg / Foradil 12 µg	0.91	0.76, 1.09
	Arformoterol 15 µg BID	4.30	NA	NA	NA
	Racemic Formoterol 24 µg DPI BID	9.14	Arformoterol 15 µg / Foradil 24 µg	0.47	0.39, 0.56

The pharmacodynamic relationship between mean time-matched plasma concentrations of (R,R)-formoterol and percent change in FEV1 from study baseline (%ΔFEV1) was also assessed. As shown in the figure below, the %ΔFEV1 from study baseline increased with plasma (R,R)-formoterol concentrations in all three treatments after 14 days. In addition, there appears to be a correlation between systemic exposure to (R,R)-formoterol and FEV1 in subjects with COPD.

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**Study 091-019: Mean %Change in FEV1 from Study Baseline and Mean (R,R)-Formoterol Plasma Concentrations Versus Time Following Arformoterol or Racemic Formoterol in COPD Subjects** [Table 4.2.2-1, update\updatsum.pdf]



There were no deaths during the study, one SAE in a patient receiving 12 µg racemic formoterol and relatively few AEs for the COPD population. Twenty-eight per cent of subjects receiving arformoterol 15 µg BID had adverse events vs 37 and 36 %, respectively, for those receiving Foradil 12 and 24 µg BID [Table 4.2.3-1, update\updatsum.pdf].

In the ongoing safety study, 091-061, subjects receive one of three double-blind, double-dummy treatments: arformoterol 15 µg BID by nebulization with a placebo DPI capsule, or arformoterol 25 µg BID by nebulization with a placebo DPI capsule, or formoterol fumarate (Foradil®) 12 µg BID by DPI with a placebo UDV. Randomization is stratified by race (Caucasian, Black or Other), and occurs in a 1:1:1 ratio. To date a total of 45 subjects have been randomized of which 8 (17%) are Black. Five subjects (11.1%) have reported a total of 10 adverse events, the most common being sinus congestion [Table 5.3.3-1, update\clinstat\clinsum.pdf]. The small numbers of

subjects enrolled and the blinded nature of the groups makes this update not useful for safety analyses.

The updated literature review and additional analyses from Phase 3 studies that re-summarized arformoterol exposure by treatment, COPD exacerbation, and race did not add any meaningful information to the NDA application. Specifically, due to the low number of African-Americans in the studies (1-8/group) it was not able to give additional information concerning possible safety differences in any non-Caucasian race.

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

#### **Beta Adrenergic Agonist Mediated Events**

Beta adrenergic agonists have been studied extensively and have the potential to produce certain Beta-mediated AEs, such as tachycardia, palpitations, dizziness, nervousness, tremors, insomnia, nausea, chest pain, arrhythmia, and worsening hypertension. Beta mediated AEs were noted in all the clinical studies, the incidences were generally low, but for many, a dose-relationship could be seen, especially for nervousness and tremor. Overall, for the proposed dose of 15 µg BID, AEs were not appreciably different than for placebo except for a higher incidence of tremor and leg cramps.

Below common Beta adrenergic mediated effects are listed and discussed:

#### *Hypokalemia*

There was a dose-related decrease in serum potassium levels with increasing doses of arformoterol [Section 7.1.7.3]. The arformoterol 15 µg BID dose group had minimal decreases ranging from 0.05-0.15 meq/L, which were similar or less than that for the salmeterol active comparator group. The Applicant has appropriately included language in the proposed product label regarding the potential of arformoterol to produce hypokalemia.

#### *Hyperglycemia*

Small, dose-related increases in serum glucose were also evident with increasing arformoterol doses. Increases in serum glucose were small in the arformoterol 15 µg BID treatment group with mean increases ranging from 8-11 mg/dL, which were similar or slightly lower than in the active control salmeterol group. The Applicant has appropriately included language in the proposed product label regarding the potential of arformoterol to aggravate diabetes mellitus and ketoacidosis.

#### *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 these potential cardiovascular effects will be discussed briefly.

Significant changes in mean heart rate and blood pressure were not noted in the clinical studies with arformoterol. Additional details regarding changes in vital signs are located in Section 7.1.8.

The data from the multiple dose clinical studies demonstrated no consistent mean change in ECG measures, including QT prolongation. Study 091-026, in which an extensive assessment of potential cardiac repolarization effects of arformoterol was conducted, demonstrated no meaningful impact of arformoterol on QT<sub>c</sub>, regardless of heart rate correction formula or analysis method. In the pivotal studies, there is a slight, clinically insignificant QT dose-response after the first dose of study drug at Week 0 when QT<sub>C-F</sub> increased from 2.38 to 3.15 to 4.71ms compared to 0.60ms in the placebo group, in the arformoterol 15 µg BID, 25 µg BID, and 50 µg QD groups, respectively. The effect was not maintained at later time points (Weeks 6 or 12). Holter monitoring data show an absence of consistent effects on heart rate, supraventricular or ventricular ectopic beats, or monitoring alerts. The rates of arrhythmia events in subjects in the placebo and arformoterol 15 µg groups with new, treatment emergent arrhythmias was the same (approximately 33-34%) [Section 7.1.9.4]. The Applicant has included language in the “Warnings” section of the proposed arformoterol label that Beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT<sub>c</sub> interval, and ST segment depression.

Despite the older age and the presence of cardiovascular co-morbidities in many subjects, cardiovascular AEs in the clinical studies were uncommon in any treatment group. However, there were more cardiovascular discontinuations in the arformoterol treated groups but these rates were similar to that seen in the salmeterol active control group [Section 7.1.1].

## 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

To determine appropriateness of pooling data, the study populations, study designs, dosing levels, dosing durations, and administration times for each study were considered. In addition, within the studies, safety measures were reviewed for the appropriateness of pooling. Studies in asthmatic and COPD populations were not pooled which is appropriate due to differences in the disease populations. Also, multiple dose studies were analyzed separately from single dose studies.

It was appropriate to pool the safety data from the two, 12 week, pivotal studies (091-050 and 091-051) as they had identical study populations and designs. These data represent the primary source for safety data obtained for the dose selected for the COPD indication, since the long-term safety study, 091-060, actually used a higher total daily dose (50 µg QD) than that selected as the indicated dose (15 µg BID). Safety data from the two-week dose ranging study (091-026) and

12-month long-term safety study (091-060) were pooled with the 12-week pivotal studies for selected analyses only (i.e., summaries of adverse events adjusted for observation time) due to the differences in study durations. Single dose pharmacokinetic studies in special subject populations (renal and hepatic deficiency) and the multiple-dose drug-drug interaction study (091-018) in normal volunteers were not pooled with the COPD studies.

#### 7.4.1.2 Combining data

In general, data for the selected studies were simply combined without the use of any formal weighing method.

### 7.4.2 Explorations for Predictive Factors

#### 7.4.2.1 Explorations for dose dependency for adverse findings

The assessment of possible dose dependency for adverse findings was inherent in the pivotal trials as 3 different dose groups of arformoterol were employed as was an active comparator group (salmeterol). While several adverse findings listed below demonstrated dose dependency, the adverse finding profile of the proposed indicated dose group of 15 µg BID was generally similar to that of the placebo group except for tremor.

AEs reported in the arformoterol groups that appeared to have a dose response included asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor with nervousness and tremor showing the strongest dose-response relationship. Rates of these AEs in the arformoterol proposed 15 µg BID dose did not differ significantly from rates in the placebo group except for tremor (1.4% vs 0.3%).

Cardiovascular monitoring findings demonstrated that Holter monitoring from study 091-026 showed more ventricular ectopic beats in a 24 hour period in the higher dose arformoterol groups (25 µg BID in Part A and 50 µg QD in Part B) than in lower dose groups, however, this difference did not translate into an increased number of subjects with nonsustained (3-9 beat run) or sustained ( $\geq$  beat run) ventricular tachycardia. [Tables 6.9.2.1-1 and 6.9.2.1-2, *clinstat\liss\liss.pdf*]. In the pivotal studies the rates of arrhythmia events not present at baseline over the double-blind period were slightly higher in the higher dose arformoterol 25 µg BID and 50 µg QD groups and salmeterol group, (37.6, 40.1, and 39.6%, respectively). The rates in subjects in the placebo and arformoterol 15 µg groups with new, treatment emergent arrhythmias was the same (approximately 33-34%) [Table 6.9.2.2-4, *clinstat\liss\liss.pdf*].

#### 7.4.2.2 Explorations for time dependency for adverse findings

The Applicant analyzed the time to onset for AEs that had a frequency of at least 10% in any group in the 2 pivotal trials (091-050 and 091-051) and in the Phase 3 safety trial (091-060) and did not find any significant differences between treatment groups [Section 6.7.7, *clinstat\liss\liss.pdf*].

#### 7.4.2.3 Explorations for drug-demographic interactions

Drug-demographic interaction analyses for age, race, gender, current smoking status, and percent predicted FEV1 were performed for pooled pivotal studies 091-050 and 091-051 and for the one year long-term safety study 091-060.

The only likely age by treatment effects seen were a higher rate of ventricular ectopy by ECG in the arformoterol 50 µg QD group in the 65 to <75 age bracket and an age-related increase in ventricular ectopy in arformoterol 50 µg QD subjects by Holter monitoring [Section 11.1, *clinstat\iss.pdf*].

No race by treatment interactions were observed, however, there were very few African-American and other races who participated in the clinical trials ( $\leq 5\%$ ) [Section 11.2, *clinstat\iss.pdf*].

Females who received 50 µg QD of arformoterol demonstrated a greater number of AEs classified as tremor and nervousness than males [Section 11.3, *clinstat\iss.pdf*].

There was no clear treatment by baseline FEV1 status or subjects who were current smoker interactions noted [Sections 11.4 and 11.5, *clinstat\iss.pdf*].

#### 7.4.2.4 Explorations for drug-disease interactions

In the pivotal studies 091-050 and 091-051, overall arrhythmic cardiovascular events occurred in 4.4% of subjects in the placebo group, 3.1% to 5.5% of subjects in the arformoterol treatment groups, and 5.5% of subjects in the salmeterol 42 µg BID group. When subjects were stratified based on a history of cardiac arrhythmias at baseline, more subjects with a history of cardiac arrhythmias experienced arrhythmic cardiovascular events across treatment groups, except for the arformoterol 50 µg QD group, in which no subjects with an arrhythmia history experienced an arrhythmic event [Table 7.12.1.1, *clinstat\iss\iss.pdf*]. Because of the small number of subjects reporting arrhythmic cardiovascular events and the absence of any events in the highest arformoterol dose group, these data should be interpreted with caution. However, the Applicant's proposed product label appropriately includes information regarding the potential cardiovascular effects of arformoterol and to use with caution in patients with cardiovascular disorders. In addition, the proposed product label appropriately states that arformoterol should also be used with caution in patients with hypertension, convulsive disorders,  $\square$   $\square$  and in patients who are unusually responsive to sympathomimetic amines.

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#### 7.4.2.5 Explorations for drug-drug interactions

The Applicant conducted animal studies and studies in subjects who were extensive, normal or poor metabolizers of common metabolic enzymes. The results suggest that arformoterol does not inhibit common CYP enzymes, that CYP2D6 is not an important component of the metabolic pathway of arformoterol, and that a drug-drug interaction with any CYP2D6 inhibitor would not be likely. In addition, in data collected from Phase 3 trials, concomitant use of arformoterol with

theophylline appears to be safe, with minimal increases in heart rate and systolic blood pressure observed.

#### 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, dyspepsia, chest pain, arrhythmia, worsening hypertension, hypokalemia, increased glucose, and ECG changes. The findings of any of the above listed AEs were assumed to be due to a systemic effect of arformoterol.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The proposed dosing regimen for arformoterol tartrate inhalation solution is 15 µg supplied in 2 mL single-dose vials twice daily. The Applicant's clinical studies demonstrated the efficacy of 15 µg of nebulized arformoterol as a bronchodilator in the proposed COPD population when delivered via a PARI LC PLUS nebulizer and a PARI Dura-neb 3000 compressor. Dose-ranging studies demonstrated that doses of 5 µg BID and 9.6 µg QD were not efficacious over the entire 12 and 24 hour dosing intervals, respectively, and, that doses greater than 50 µg/day failed to demonstrate further efficacy while Beta-2 agonist-related side effects were noted more frequently. While a dose of 25 µg twice daily demonstrated a slightly greater efficacy as determined from pulmonary function test data, the increase in side effects seen as a result of excessive Beta-2 adrenergic receptor stimulation, especially as they related to nervousness, tremor, anxiety, and insomnia was greater than those seen in the 15 µg twice daily dose. This difference is indicative of a relatively narrow therapeutic index for this particular LABA and highlights the need to bring attention to fact that if arformoterol is administered with nebulizers that are more efficient than the PARI LC PLUS, increased Beta agonist mediated side effects may occur. The 15 µg dose was well-tolerated in older adults with COPD and had an AE profile, other than an increase in tremor that differed little from placebo. The recommended dosing regimen is supported by the duration of effect.

In terms of dosing in special populations, dosing modification is not recommended for subjects with cardiac, renal, hepatic, or respiratory disease. However, because of the potential Beta receptor mediated AEs and the increased systemic exposure to arformoterol observed in persons with hepatic insufficiency, the proposed product label recommends cautious use in patients with cardiovascular disorders, hepatic  $\subset$  convulsive disorder,  $\subset$   $\supset$ . A more detailed review of drug effects in special populations is contained in Section 8.3.

*Reviewer's Comment: It is notable that, to my knowledge, albuterol and racemic formoterol have never been studied in subjects with hepatic insufficiency; there is no mention of caution in using the drug in those patients in the product labels.*

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## 8.2 Drug-Drug Interactions

Arformoterol is primarily metabolized in man and animals by direct conjugation (glucuronidation), and secondarily by O-demethylation. These investigations suggest that arformoterol at therapeutic concentrations does not inhibit common CYP enzymes [Section 5, *pharmtox/pharmsum.pdf*]. To confirm these findings, the Phase 1 studies 091-007 and 091-018 were performed in healthy subjects to evaluate the pharmacokinetics of arformoterol tartrate inhalation solution in subjects classified as poor versus extensive CYP2D6 metabolizers, or with reduced uridine diphosphate glycosyl transferase 1 polypeptide A1 (UGT1A1) activity and to evaluate the effects of paroxetine, a potent inhibitor of CYP2D6, on the pharmacokinetic profile of arformoterol at steady state in healthy subjects. Results confirmed that CYP2D6 is not an important component of the metabolism of arformoterol and that a drug-drug interaction with any CYP2D6 inhibitor would not be likely [Study 091-007 and 018 Clinical Study Reports].

Since patients with COPD may also receive theophylline preparations as bronchodilators, the safety profile of subjects taking theophylline at baseline was analyzed in the 12-week pivotal studies (pooled Studies 091-050 and 091-051) and the 12-month long-term study (Study 091-060). Although the numbers of subjects taking theophylline was small 12-23/group in the pivotal studies and 21-30/group in the safety study, there was no real difference in the rates of AEs in subjects taking theophylline vs those not receiving it [Section 10.2.1, *clinstat/iss.pdf*]. Subjects receiving theophylline had minimal elevations in heart rate and systolic blood pressure after receiving arformoterol but to no greater extent than those who received salmeterol, the active comparator [Table 13.2.1.2.6, *clinstat/iss/iss.pdf*].

## 8.3 Special Populations

Drug-demographic interaction analyses for age, race, gender, current smoking status, and percent predicted FEV1 were performed for pooled pivotal studies 091-050 and 091-051 and for the one year long-term safety study 091-060. Separate studies were also conducted in the elderly and subjects with renal and hepatic insufficiency, studies 091-013, 014, and 015, respectively. Safety parameters (AEs, SAEs, serum potassium and glucose, potentially clinically significant laboratory results and vital signs, ECG alerts and Holter monitors) were analyzed for pooled pivotal studies 091-050 and 091-051, and for the one year long-term safety study 091-060.

### *Age*

In the pooled pivotal studies (Studies 091-050 and 091-051) and the long-term safety study (091-060), there was no clear age by treatment group interaction with respect to adverse events, serious adverse events, serum potassium, or serum glucose. The only likely age by treatment effects seen were a higher rate of ventricular ectopy by ECG in the arformoterol 50 µg QD group in the 65 to <75 age bracket and an age-related increase in ventricular ectopy in arformoterol 50 µg QD subjects by Holter monitoring [Section 11.1, *clinstat/iss.pdf*].

Safety and PK parameters of a single inhaled dose of 50 µg of arformoterol in the elderly were also evaluated in study 091-013. Compared to subjects aged 18-45 years, there was a 15%

increase in  $C_{max}$  and no differences in  $AUC_{(0-last)}$ ,  $AUC_{0-\infty}$ , half-life, or safety assessments in those aged  $\geq 65$  years [*hpbio\hupharm\091-013.pdf*].

#### *Race*

No race by treatment interactions were observed for AEs, SAEs, vital signs, ECG abnormalities or Holter monitor abnormalities. There were no laboratory values with meaningful treatment by race interactions. However, this analysis is made meaningless by the very few African-American and other races who participated in the clinical trials ( $\leq 5\%$ ). This lack of data for other races was conveyed to the Applicant at the pre-NDA meeting on March 07, 2005 and reiterated in the filing review. Acquiring more safety data in racial subgroups will be a potential Phase 4 commitment [*Section 11.2, clinstat\iss.pdf*].

#### *Gender*

Females comprised approximately 40% of the Phase 3 study population. Those who received 50  $\mu\text{g}$  QD of arformoterol demonstrated a greater number of AEs classified as tremor and nervousness than males. No treatment by gender interaction was observed for SAEs, vital signs, ECG abnormalities or Holter monitor abnormalities [*Section 11.3, clinstat\iss.pdf*].

#### *Smoking Status*

Although current smokers tended to have lower baseline FEV1 values, there were no clear treatment by smoking status interactions for any safety parameter analyzed [*Section 11.4, clinstat\iss.pdf*].

#### *Per Cent Predicted FEV1*

For this analysis, subjects were stratified into groups of  $<30\%$ ,  $\geq 30$  to  $<50\%$ , and  $\geq 50\%$  percent predicted FEV1. The placebo group had the highest rate of overall adverse events in subjects with the poorest lung function ( $<30\%$  predicted FEV1) while the salmeterol group had the highest rate of COPD adverse events. There was no clear treatment by baseline FEV1 status interaction for any of the safety parameters analyzed. Specifically, there was no difference in the rates of AEs in the cardiovascular or nervous systems [*Section 11.5, clinstat\iss.pdf*].

#### *Renal Insufficiency*

Study 091-014 was an open-label, single-dose efficacy and safety study of 40 subjects in three groups of 8 subjects each with renal insufficiency (i.e., mild, moderate, severe) and 1 group of 16 healthy subjects with normal renal function. Each subject received a single 50  $\mu\text{g}$  dose of arformoterol by nebulization followed by extensive pharmacokinetic measurements in serum and urine samples over 3 days. The degree of renal function was categorized by creatinine clearance in mL/min with normal function  $\geq 80$ , mild impairment  $\geq 50 < 80$ , moderate impairment  $\geq 30 < 50$ , and severe impairment defined as  $< 30$ . Safety assessments included serial 12-lead ECGs, physical examination; vital signs; clinical laboratory evaluations Holter monitoring; and adverse clinical events. Overall, the extent of exposure appeared to be similar across renal function groups based on  $AUC_{(0-12)}$ ,  $AUC_{(0-24)}$ , and  $C_{max}$ , but may be slightly higher in the renal dysfunction subjects compared to normal subjects based on  $AUC_{(0-last)}$ . Renal clearance of unchanged arformoterol decreased with the degree of renal impairment, however this finding was not clinically relevant since only 1% of the arformoterol dose was recovered in urine as

unchanged drug in normal subjects in this study. There were no meaningful differences in the safety profile of arformoterol in subjects with renal impairment. Based on the pharmacokinetic and safety results of this study, no dosing adjustment is necessary in patients with renal impairment [hpbio\hupharm\091-014.pdf].

*Hepatic Insufficiency*

Study 091-015 was an open-label, single-dose study of 40 subjects in three groups of 8 subjects each with hepatic impairment (i.e., mild, moderate-to-severe, severe) and 1 group of 16 healthy subjects with normal hepatic function. Arformoterol plasma and urine pharmacokinetics were determined following a single dose of 50 µg of arformoterol administered by nebulization. The subject's degree of hepatic impairment was assessed based on the Child-Pugh classification system shown in the table below.

**Child-Pugh Classification of Hepatic Dysfunction** [Table 9.4.3-1, hpbio\hupharm\091-015.pdf]

Risk Factor	Score		
	1	2	3
Ascites	Absent	Slight	Moderate
Neurological symptoms	Absent	Transient or mild	Hepatic coma
Prothrombin time prolonged from control (sec)	<4	4 to 6	>6
Serum bilirubin (mg/dL)	<2	2 to 3	>3
Serum bilirubin (mg/dL) for subjects with primary biliary cirrhosis	<4	4 to 10	>10
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8

Hepatic dysfunction was considered mild if the Child-Pugh Score was 5 or 6, moderate-to-severe for a score of 7 to 9, and severe for a score of 10 to 12.

Safety assessments included serial 12-lead ECGs, physical examination; vital signs; clinical laboratory evaluations Holter monitoring; and adverse clinical events. A comparison of plasma PK parameters between subjects with hepatic impairment compared to normal subjects is shown in the table below.

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**Study 091-015: Statistical Treatment Comparison of Plasma Pharmacokinetic Parameters Between Subjects with Normal Hepatic Function and Subjects with Hepatic Impairment After a Single Inhaled 50-µg Dose of Arformoterol** [Table 11.4.1.2-2, hpbio\hupharm\091-015.pdf]

Parameter	Hepatic Function Group	n	Geometric LS Mean	Comparison	Ratio	90% CI
AUC <sub>(0-12h)</sub> (pg*hr/mL)	Mild	8	57.74	Mild/Normal	2.35	1.39, 3.98
	Moderate	7	48.85	Moderate/Normal	1.99	1.15, 3.45
	Severe	8	53.73	Severe/Normal	2.19	1.29, 3.70
	Normal	15	24.57			
C <sub>max</sub> (pg/mL)	Mild	8	8.92	Mild/Normal	1.39	0.80, 2.41
	Moderate	7	9.35	Moderate/Normal	1.46	0.82, 2.59
	Severe	8	8.03	Severe/Normal	1.25	0.72, 2.17
	Normal	15	6.42			
AUC <sub>(0-12)</sub> (pg*hr/mL)	Mild	8	39.74	Mild/Normal	1.72	1.22, 2.41
	Moderate	6	30.11	Moderate/Normal	1.30	0.90, 1.89
	Severe	7	46.00	Severe/Normal	1.99	1.39, 2.83
	Normal	13	23.16			
AUC <sub>(0-24)</sub> (pg*hr/mL)	Mild	5	78.42	Mild/Normal	2.04	1.39, 2.98
	Moderate	6	41.64	Moderate/Normal	1.08	0.75, 1.56
	Severe	6	71.97	Severe/Normal	1.87	1.30, 2.69
	Normal	6	38.51			
AUC <sub>(0-∞)</sub> (pg*hr/mL)	Mild	6	71.35	Mild/Normal	1.55	1.00, 2.41
	Moderate	6	92.46	Moderate/Normal	2.01	1.17, 3.44
	Severe	3	89.69	Severe/Normal	1.95	1.25, 3.03
	Normal	6	46.03			
t <sub>1/2</sub> (hr)	Mild	6	10.43	Mild/Normal	0.98	0.67, 1.42
	Moderate	4	15.02	Moderate/Normal	1.41	0.92, 2.16
	Severe	7	15.30	Severe/Normal	1.43	1.00, 2.06
	Normal	8	10.68			
t <sub>max</sub> (hr)			Median	Comparison	p-value	
	Mild	8	0.25	Mild/Normal	0.088	
	Moderate	7	0.17	Moderate/Normal	0.321	
	Severe	8	0.23	Severe/Normal	0.67	
	Normal	15	0.22			

Note: The normal hepatic function group was used as the reference group.

The results demonstrated significant increases in exposure to arformoterol in subjects with mild, moderate-to-severe, or severe hepatic impairment when compared with subjects with normal hepatic function. Similarly, C<sub>max</sub> values in subjects with any level of hepatic impairment were higher than those of subjects with normal hepatic as well as a longer half-life in subjects with moderate-to-severe and severe hepatic impairment. Although exposures were higher in the hepatic-impaired treatment groups, there was no difference in the safety profile between groups in this single dose study including QT prolongation or changes in serum potassium levels. These findings must be tempered by the fact that there were a total of only 2-4 subjects who had any AE in each treatment group with no SAEs reported in this brief study. Also, as this was only a single dose study, there is no assessment of whether drug could accumulate in patients with hepatic impairment which could result in an increase of treatment related AEs or ECG/laboratory abnormalities. Of note is that other marketed Beta-2 agonists including albuterol (Ventolin HFA) and racemic formoterol (Foradil<sup>®</sup> Aerolizer) have never been studied in patients with hepatic impairment and there is no mention of using these drugs cautiously in persons with hepatic

dysfunction. Given the higher exposure, however, arformoterol should be used cautiously in subjects with hepatic impairment [Section 12.2, *hpbio\hupharm\091-015.pdf*].

#### *Pregnancy/Lactation*

The majority of females with COPD, the disease for which arformoterol is indicated as treatment for, will be post-menopausal, however, off-label use may occur in younger women with asthma. There are no adequate and well-controlled studies in pregnant women; therefore arformoterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Similarly, it is not known if arformoterol is excreted in human milk and, therefore, a decision should be made whether to discontinue nursing or to discontinue the drug during while nursing.

#### **8.4 Pediatrics**

The indication for arformoterol in this NDA is for treatment of [redacted] associated with COPD. As COPD is a disease specific to older adults, a Pediatric Waiver was granted to the Applicant for this NDA.

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#### **8.5 Advisory Committee Meeting**

The arformoterol NDA was not presented to the Pulmonary and Allergy Drug Advisory Committee.

#### **8.6 Literature Review**

As discussed in Section 7.2.2.3, the literature review submitted by the Applicant evaluated the clinical literature that referenced arformoterol, pertinent racemic formoterol (Foradil Aerolizer) articles, and selected articles for salmeterol in an attempt to provide a detailed review of key safety issues including those associated with excessive Beta receptor stimulation and the possibility of causing more severe asthma exacerbations and/or asthma related deaths.

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The DPAP and Office of Surveillance and Epidemiology (OSE); Division of Drug Risk Evaluation (DDRE) responded to the proposed [redacted] during a face-to-face meeting with the Applicant held June 27, 2006 [see Meeting Minutes dated July 11, 2006]. While all agreed that the concerns outlined were appropriate, DPAP and OSE agreed [redacted] [redacted] would not be able to address the safety issues concerning LABAs in patients with COPD or be helpful in monitoring safety in the off-label use of arformoterol. DPAP preferred that the Applicant conduct randomized safety studies in patients with COPD and asthma, including children to help address their safety concerns in these populations.

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Subsequent correspondence from the Applicant on July 13, 2006 communicated that they are considering to the conduct of post-marketing studies to assess both the long term safety of

arformoterol in patients with COPD and to evaluate the safety of arformoterol use in patients in which a nebulized LABA would be attractive, including children with asthma.

On August 25, 2006, a Regulatory Briefing was held in order to provide guidance to DPAP regarding the above-mentioned safety concerns of arformoterol. The Panel concurred with DPAP's concerns and felt that both the collection of additional long-term safety data of arformoterol in the COPD population, including the possibility of a randomized, large simple trial, and establishing the safety profile of arformoterol in patients, especially children, with asthma should be components of arformoterol [REDACTED] b(4)

## 8.8 Other Relevant Materials

A product quality microbiology review conducted by John W. Metcalfe, Ph.D. concluded that NDA 21-912 is recommended for approval on the basis of microbiological product quality.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The data submitted in this Application provide support, from a clinical perspective, for approval. The two Phase 3, placebo and active-controlled studies establish the efficacy of arformoterol 15 µg BID for the relief of bronchoconstriction associated with COPD. Efficacy was established by the demonstration of a statistically significant improvement over placebo in trough FEV1 over the course of a 12-week treatment period as compared to placebo. In addition, arformoterol achieved comparable bronchodilation to that of the active comparator, salmeterol. Secondary analyses of pulmonary function test data, including area under the FEV1 curve analyses from 0-12 hours post dose and peak FEV1 supported the primary endpoint analysis. Finally, other than the 6-minute walk test and SGRQ, most other non-spirometry based secondary efficacy variables, such as morning and evening home peak flow measurements and "rescue" albuterol and ipratropium bromide use also generally supported the efficacy of arformoterol in COPD patients.

The dose finding for this application was adequate. Throughout the clinical program, arformoterol solution was delivered via a PARI LC PLUS nebulizer and a PARI Dura-neb 3000 compressor. Dose-ranging studies demonstrated that doses of 5 µg BID and 9.6 µg QD were not efficacious over the entire 12 and 24 hour dosing intervals, respectively, and doses greater than 50 µg/day failed to demonstrate further efficacy while Beta-2 agonist-related side effects were noted more frequently. While a dose of 25 µg twice daily demonstrated a slightly greater efficacy as determined from pulmonary function test data, the increase in side effects seen as a result of excessive Beta-2 adrenergic receptor stimulation, especially as they related to nervousness, tremor, anxiety, and insomnia was greater than those seen in the 15 µg twice daily dose. This difference is indicative of a relatively narrow therapeutic index for this particular LABA and highlights the need to bring attention to fact that if arformoterol is administered with nebulizers that are more efficient than the PARI LC PLUS, increased Beta agonist mediated side

effects may occur. The 15 µg dose was well-tolerated in older adults with COPD and had an AE profile, other than an increase in tremor that differed little from placebo. The recommended dosing regimen is supported by the duration of effect.

In the pivotal Phase 3 studies the Applicant also included an active control group treated with the approved LABA, salmeterol 42 µg BID. As expected, salmeterol was also superior to placebo for the spirometry-based endpoints. In general, arformoterol treatment groups produced results similar to that of salmeterol. Occasionally arformoterol was statistically superior to salmeterol such as in time to peak FEV1 response, but those differences were generally the result of known pharmacodynamic differences between the two drugs. It is unclear if any differences noted would be clinically significant.

In terms of dosing in special populations, dosing modification is not recommended for subjects with cardiac, renal, hepatic, or respiratory disease. However, because of the potential Beta receptor mediated AEs and the increased systemic exposure to arformoterol observed in persons with hepatic insufficiency, the proposed product label recommends cautious use in patients with cardiovascular disorders, hepatic  convulsive disorder,

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The extent of patient exposure to arformoterol inhalation solution during the development program is adequate. In the clinical studies, adverse events attributable to arformoterol were relatively few and related to systemic Beta adrenergic agonist effects. The incidence of COPD exacerbations in the arformoterol 15 µg BID treatment group was less than that for placebo while the exacerbation rates for the higher dose arformoterol groups and for the approved LABA, salmeterol were similar to placebo. Thus, the safety profile of arformoterol at a dose of 15 µg twice daily via the PARI LC PLUS nebulizer is acceptable.

## 9.2 Recommendation on Regulatory Action

From a clinical perspective, the data submitted in this NDA provide support for Approval. The clinical studies demonstrate that the proposed dose of 15 µg of arformoterol tartrate by nebulization twice daily delivered via a PARI LC PLUS nebulizer and a PARI Dura-neb 3000 compressor is statistically superior to placebo in relief of bronchospasm associated with COPD. Efficacy was established by the demonstration of an improvement in trough FEV1 over the course of a 12-week treatment period as compared to placebo. Secondary analyses, including area under the FEV1 curve from 0-12 hours post dose and peak FEV1 as well as non-spirometry based secondary efficacy variables including morning and evening home peak flow measurements and "rescue" albuterol and ipratropium bromide use, also generally supported the efficacy of arformoterol in COPD patients. The proposed dose of 15 µg of arformoterol tartrate by nebulization BID also had an acceptable safety profile and demonstrated fewer Beta-2 adrenergic-mediated side effects than other doses tested.