9.3 Recommendation on Postmarketing Actions

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DPAP and Office of Surveillance and Epidemiology (OSE); Division of Drug Risk Evaluation (DDRE) responded to the proposed[ ] 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 use of [ ] DPAP and OSE did not agree [ ] would 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. Subsequent correspondence from the Applicant on July 13, 2006 communicated that they are considering the two post-marketing studies outlined below.

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9.3.2 Required Phase 4 Commitments

Discussions relating to [ ] and possible Phase 4 commitments with the Applicant have taken place in the context of knowledge of the safety issues listed above and discussed in detail in this review [Sections 2.4, 8.7, and 9.3.1]. In response to comments from DPAP at a face-to-face meeting held on June 27, 2006 to discuss [ ] for arformoterol, the Applicant 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

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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 safety concerns of arformoterol. The Panel agreed 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 required Phase 4 commitments.

An additional concern of DPAP regarding this NDA is 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 at least 10% African-American representation. No further commitments for the conduct of studies in minority populations will be sought from the Applicant.

9.3.3 Other Phase 4 Requests

As of the time of this review, there are no other recommended Phase 4 requests for this application.

9.4 Labeling Review

The proposed product label was reviewed in detail. The following are general comments regarding the proposed product label.

In the Clinical Pharmacology Section:

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- The Animal Pharmacology section is too long. [

]

[

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- The Absorption, Pharmacodynamic, and Tolerance Sections can be shortened.

In the Clinical Trials Section:

[

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In the Warnings Section:

- A strongly worded warning, similar to that in the Foradil label about the increased risk of death in patients with asthma should be added, with the caveat that the risks to persons with COPD are not yet known.
- A Medication Guide modified for a COPD-only indication should be required.

In the Precautions Section:

- Pediatric and Geriatric subsections should be added for completeness.

In the Adverse Reaction Section:

- In order to get a better sense of Beta agonist mediated adverse events, consideration should be given to including examples of the types of cardiovascular adverse events observed in the clinical trials.

At the time of the finalization of this review, detailed labeling negotiations have not been initiated with the Applicant. The preliminary opinion of DPAP is that a Boxed Warning and, possibly, a Medication Guide, modified from those in place for the LABAs salmeterol and formoterol to indicate that the increased risk of LABAs seen when used for asthma is not known for COPD, is warranted. This issue was subsequently discussed at a Regulatory Briefing held on August 25, 2006. The general consensus was that the arformoterol label should contain both a Boxed Warning and Medication Guide.

Jeanine Best M.S.N., R.N., P.N.P., Drug Safety Officer reviewed the draft *Patient Instructions for Use* submitted with the NDA on June 1, 2006, and has made many suggestions that should improve risk communication to a broad audience of varying educational backgrounds. Suggested changes will not be communicated to the Applicant until the issue of including a Boxed Warning and Medication Guide in the labeling has been resolved.

DDMAC reviewed the proposed draft labeling and provided comments [Michelle Safarik, DDMAC Review, August 02, 2006]. DPAP reviewed the comments and incorporated many of the suggestions into the revised product label.

DMETS reviewed the container labels, carton, and package insert for arformoterol tartrate and had the following comments [Kristina Arnwine, DMETS Review, March 30, 2006].

General Comments

- Revise the established name to read "Arformoterol Tartrate Inhalation Solution" and ensure that the established name and finished dosage forms are presented in the same font type and size.
- Relocate the product strength so that it is presented immediately underneath the proprietary and established names. Furthermore, include [redacted] b(4)
  [redacted] followed by the [redacted]
- Revise the labels and labeling to the following format.
  Tradename
  [redacted] b(4)
  15 mcg/2 mL
  [redacted]
- Per 21CFR 201.10(g)(2), increase the prominence of the established name so that it is at least ½ the size of the proprietary name. Additionally, increase the font weight of the text print used for the established name in order to increase the prominence.

[redacted]

Pouch Label

- See General Comments 1 through 5.

[redacted] b(4)

Container Label

[redacted] b(4)

[redacted]

Carton Labeling

- See General Comments 1 through 5.

[redacted] b(4)

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9.5 Comments to Applicant

There are no comments to convey to the Applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

A. **Pivotal 12 Week Studies**

Study 091-050
Title of Study: A Double-Blind, Double-Dummy, Randomized, Placebo- and Active-Controlled, Multicenter, Parallel-Group Study of Arformoterol in the Treatment of Subjects with Chronic Obstructive Pulmonary Disease

Design
This was a multi-center, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group study of arformoterol in the treatment of subjects with chronic obstructive pulmonary disease. Randomization was performed 1:1:1:1:1 between placebo, salmeterol MDI 42 μg bid, and arformoterol 15 μg bid, 25 μg bid, and 50 μg qd. The study was double-blinded through the use of both unit dose vial (UDV) and metered-dose inhaler (MDI) placebos, as appropriate.

Duration
The duration of active treatment was 12 weeks. The study was performed during the period of February 27, 2002, to June 18, 2003. The final study report is dated August 24, 2005.

Study Centers
The study was conducted at 60 US centers in the following states: AL, AR, CA, CO, FL, GA, IL, IN, KS, MO, MN, NC, NM, NJ, NV, NY, OH, OK, OR, PA, SC, TX, VA, WA.

Population
A total of 724 subjects with relatively stable, moderately severe COPD were randomized into the study with 717 analyzed (ITT). A total of 587 completed the study, 111 placebo, 124 arformoterol 15 μg BID; 110 arformoterol 25 μg BID; 124 arformoterol 50 μg QD, and 118 salmeterol 42 μg BID.

Treatments Administered
Arformoterol tartrate inhalation solution in unit dose vials (UDVs) at doses of 50 μg QD, 25 μg BID, and 15 μg BID, Serevent® (salmeterol) inhalation aerosol MDI at a dose of 42 μg BID, and placebo inhalation aerosol MDIs and UDVs were supplied in identically appearing blinded UDVs and MDIs, each of which delivered the amount of active ingredient as described below. Arformoterol and placebo solutions were delivered via a PARI LC PLUS nebulizer and a PARI Dura-neb 3000 compressor. Each randomized subject received one of the following five treatments:

- Arformoterol 50 µg QD and placebo MDI (AM dose)/placebo UDV and placebo MDI (PM dose)
- Arformoterol 25 µg BID and placebo MDI BID
- Arformoterol 15 µg BID and placebo MDI BID
- Salmeterol (Serevent®) MDI 42 µg BID and placebo UDVs via nebulization BID
- Placebo UDV BID and placebo MDI BID

Materials
The study treatments were:

- Arformoterol inhalation solutions of 15, 25, and 50 µg in 2 mL volume
- Placebo MDI or UVD as appropriate

Blinded study medications included active salmeterol MDI presented in blinded canisters and matching placebo MDI canisters. The salmeterol was provided as a 13-g canister containing 120 actuations. The placebo consisted of a pressurized metered-dose aerosol containing Freon 11, Freon 12, and lecithin in a non-anodized aluminum canister (14 mL) fitted with a metering valve (63 µL) and mouthpiece/actuator. Each canister contained a minimum of 120 actuations. Commercially available racemic albuterol MDI (Ventolin 6.8-g canister/80 inhalations) was provided to each study site for reversibility testing during screening and as rescue medication for use by the subject as needed throughout the study. Commercially available ipratropium MDI (Atrovent 14-g canister/200 inhalations) was provided to each study subject for use as supplemental medication for COPD as needed throughout the study.

Study 091-050: Drug Supply Lot Numbers

Arformoterol tartrate inhalation solution 50 µg QD	Lot No. 03501C
Arformoterol tartrate inhalation solution 25 µg QD	Lot No. 03501B
Arformoterol tartrate inhalation solution 15 µg QD	Lot No. 03501A
Serevent® (salmeterol) inhalation aerosol MDI 42 µg BID	Lot No. 1ZP1729W; 2ZP1391
Atrovent® (ipratropium bromide) MDI 14 g	Lot No. 010719W; 020077W
Ventolin® (racemic albuterol) MDI 17 g	Lot No. 1ZP0791; ZP1204
Ventolin 6.8 g	Lot No. 1ZP1408
Soya Lecithin placebo inhalation aerosol MDI CFC	Lot No. 1H947
Placebo for arformoterol 2 mL	Lot No. 02301A

Objectives
The primary objective was to investigate the effect on FEV1 over 12 weeks of treatment among the following treatment groups: Arformoterol 50 µg QD, Arformoterol 25 µg BID, Arformoterol 15 µg BID, salmeterol metered-dose inhaler (MDI) 42 µg BID, and placebo.

The key secondary objective was to compare Arformoterol with salmeterol in time-normalized area under the percent change from visit predose curve for FEV1.

Inclusion Criteria

- Male or female ≥35 years of age

- Diagnosis of COPD
- Baseline FEV1 ≤65% of predicted normal value and >0.70 L
- FEV1/forced vital capacity (FVC) ratio ≤70%
- Minimum smoking history of 15 pack-years
- Medical Research Council (MRC) Dyspnea Scale Score ≥2.
- Chest x-ray taken ≤3 months prior to Visit 1 that was consistent with the diagnosis of COPD
- Ability to complete all study questionnaires and logs reliably.

Notable Exclusion Criteria

- History of asthma or any chronic respiratory disease (including a current history of sleep apnea) other than COPD (chronic bronchitis and/or emphysema).
- Blood eosinophil count >5% of total white blood cell count.
- Clinically significant cardiac, hepatic, renal, gastrointestinal, endocrine, metabolic, neurologic, or psychiatric disorder
- History of cancer except non-melanomatous skin cancer.
- History of lung resection of more than one full lobe.
- Use of continuous supplemental oxygen therapy
- Use of any prescription drug for which concomitant Beta-agonist administration was contraindicated (e.g., Beta-blockers).
- Concurrent or intermittent use of once-a-day controlled release theophylline

Study 091-050: Disallowed Medications

Medication Disallowed for Study Duration	Required Withholding Interval Prior to Visit 1
Albuterol	≥6 hours and study duration*
Ipratropium	≥6 hours and study duration*
Levalbuterol	≥8 hours and study duration
Pirbuterol	≥8 hours and study duration
Salmeterol	≥24 hours and study duration
Combivent®	≥6 hours and study duration
Cromolyn sodium and nedocromil sodium	≥7 days and study duration
Foradil® (formoterol fumarate)	≥10 days and study duration
Methylphenidate HCl	≥30 days and study duration
Monoamine oxidase inhibitors	≥30 days and study duration
Tricyclic antidepressants	≥30 days and study duration

*With the exception of use as directed in the event of worsening COPD.

If the subject required one of the disallowed medications during the study, the subject was discontinued from the study and completed an Early Termination Visit.

Conduct

Each subject attended the study clinic for eight scheduled study visits over approximately four months. An additional visit was possible during the single-blind placebo run-in period (to meet the spirometry requirements). The visits included a screening visit (Visit 1/Week -3), initiation of

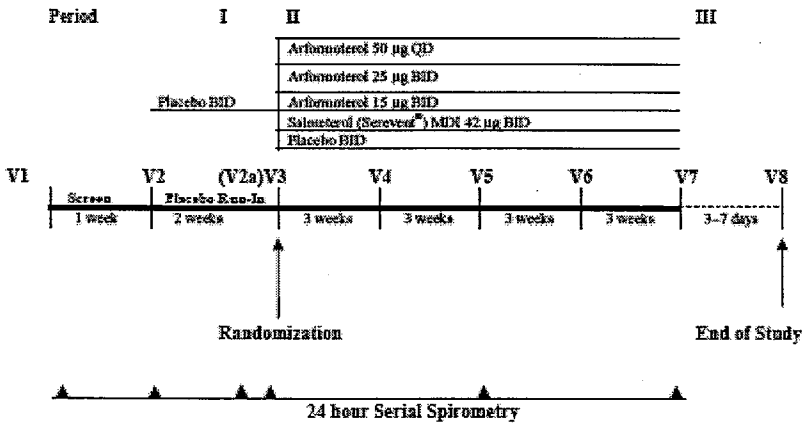
the single-blind placebo run-in period (Visit 2/Week -2), a possible additional visit during the placebo run-in period (between Visit 2 and Visit 3 [Visit 2a] to meet the spirometry requirements), a double-blind randomization visit (Visit 3/Week 0), interim visits during the double-blind period (Visits 4, 5, 6, and 7/Weeks 3, 6, 9, and 12, respectively), and final study visit (Visit 8/Week 13). After meeting all inclusion criteria and completion of the 2 week placebo run-in period, patients were randomized into the 12 week double-blind treatment portion of the study in which each subject received one of the following five treatments:

- Arformoterol 50 µg QD and placebo MDI (AM dose)/placebo UDV and placebo MDI (PM dose)
- Arformoterol 25 µg BID and placebo MDI BID
- Arformoterol 15 µg BID and placebo MDI BID
- Salmeterol (Serevent®) MDI 42 µg BID and placebo UDVs via nebulization BID
- Placebo UDV BID and placebo MDI BID

The randomization was stratified by site type. Sites that were to conduct additional spirometry assessments at the 13, 14, and 16 hour time points (the "24-hour sites") were designated as one site type, and sites that did not conduct these additional spirometry assessments (the "12-hour sites") were designated as the other site type. This stratification was to ensure that an equal distribution of the treatment groups occurred within each of the two site types. Study visits were scheduled every 3 weeks over the 12 week study period and a final study visit was scheduled for week 13. Commercially available racemic albuterol MDI (Ventolin 6.8-g canister/80 inhalations) was provided for use as rescue medication by the subjects as needed throughout the study. Commercially available ipratropium MDI (Atrovent 14-g canister/200 inhalations) was also provided to each study subject for use as supplemental medication for COPD as needed throughout the study.

A study schematic and schedule of evaluations are shown below.

Study 091-050: Study Schematic



Study 091-050: Schedule of Evaluations

		Screening	Period I Single-Blind		Period II Double-Blind												EOS/ ET
	Visit	V1	V2	V2a	V3[1]			V4			V5			V6			V7	V8
Assessments	Week	-3	-2		0	1	2	3	4	5	6	7	8	9	10	11	12	13
Informed consent[2]		X																
Inclusion/exclusion criteria (review)		X																
Medical/COPD history/COPD symptoms		X																
Prior/concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examinations (including height, weight[3])		X																X
Vital signs (HR, BP, RR, oral temperature)[4]		X	X		X			X			X			X			X	X
Chest x-ray[5]		X																
12-lead ECG[6]		X	X		X			X			X			X			X	X
Serum β-hCG (pregnancy test)[7]		X																X
FSH level[8]		X																
Urine drug screen[9]		X	X															X
Medical Research Council (MRC) Dyspnea Scale		X																
Clinical laboratory evaluations (blood/urine)[10]		X	X		X			X			X			X			X	X
Glucose and potassium levels[11]		X	X		X			X			X			X			X	X
Serum theophylline levels[12]		X			X						X							X

1 Randomization occurred at Visit 3.
2 Women of childbearing potential signed the Women of Childbearing Potential Addendum.
3 Height was assessed at Visit 1 only.
4 Vital signs were obtained once at Visits 1, 2, and 8; predose and 2 hours post-first dose at Visits 4 and 6; and predose and immediately post-first dose and at 15 and 40 minutes, 1, 2, 3, 4, 5, 6, 8, 10, 12, 23, and 24 hours post-first dose at Visits 3, 5, and 7 (Weeks 0, 6, and 12). For the subset of subjects who underwent pulmonary function tests (PFTs) at 13, 14, and 16 hours, vital signs were obtained at 13, 14, and 16 hours.
5 If not performed within 3 months of study entry.
6 ECG was performed once at Visits 1 and 8, predose and 2 hours post-first dose at Visits 2, 4, and 6, and predose and 2 and 6 hours post-first dose at Visits 3, 5, and 7 (Weeks 0, 6, and 12).
7 Serum β-hCG test for all women ≤65 years of age was done at Visits 1 and 8.
8 Serum FSH level for all applicable women, see Inclusion Criterion Section 9.3.1.
9 Done at Visit 2 if Visit 1 screen was positive.
10 Clinical laboratory evaluations were done once at Visits 1 and 8 and once (predose) at Visits 2 through 7.
11 Glucose and potassium levels were done once at Visits 1, 2, and 8 and predose and post-first dose at 2 and 6 hours at Visits 3 through 7. Glucose and potassium determinations at Visits 1, 2, and 8 and predose at Visits 3 through 7 are done as part of the serum chemistry panel.
12 Serum theophylline was obtained (if subject is taking theophylline) once at Visits 1 and 8 and predose at Visits 3 and 5.

Study 091-050: Schedule of Evaluations continued

		Screening	Period I Single-Blind		Period II Double-Blind												EOS/ ET
	Visit	V1	V2	V2a	V3[1]			V4			V5			V6			V7	V8
Assessments	Week	-3	-2		0	1	2	3	4	5	6	7	8	9	10	11	12	13
Pharmacokinetic samples[13]					X						X						X	
Genotyping[14]																		X
Reversibility testing (albuterol)		X	X	X														
Spirometry/serial spirometry		X[15]	X[15]	X[15]	X[16]			X[16]			X[16]			X[16]			X[16]	
Attach/remove Holter monitor[17]			X		X						X						X	
Baseline Dyspnea Index (BDI)			X															
Transitional Dyspnea Index (TDI)											X						X	
Six-minute walk[18]			X[19]	X[19]				X						X				
Administer study medication			X		X			X			X			X			X	
Dispense single-blind study medication			X															
Dispense double-blind study medication					X			X			X			X				
(Re)dispense supplemental/rescue medication as needed		X	X		X			X			X			X			X	
Dispense/collect COPD questionnaire[20]			X	X	X			X			X			X			X	
Dispense/collect Medical Event Calendar		X	X	X	X			X			X			X			X	X
Dispense/collect PEF/study drug/rescue med logs		X	X	X	X			X			X			X			X	X
Assess adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject/Investigator Global Evaluations[21]			X														X	X
St. George's Hospital Respiratory Questionnaire					X						X							X
Telephone contact[22]						X	X		X	X		X	X		X	X		

13 Pharmacokinetic samples were obtained predose and post-first dose at 10 minutes and 2 and 6 hours at Visits 3, 5, and 7 (Weeks 0, 6, and 12) only on a subset of subjects.
14 Genotyping for CYP2D6 enzyme was performed on the pharmacokinetic (PK) subset of subjects.
15 Subjects must have met spirometry requirements on two of three visits between screening and randomization.
16 PFTs were performed predose, immediately post-first dose, and at 15 and 40 minutes, 1, 2, 3, 4, 5, 6, 8, 10, 12, 23, and 24 hours post-first dose at Visits 3, 5, and 7 (Weeks 0, 6, and 12). Subjects returned the morning following these three visits to perform the 23- and 24-hour time points, and predose and 2 hours post-first dose at Visits 4 and 6. A subset of subjects underwent PFTs at 13, 14, and 16 hours post-first dose at Visits 3, 5, and 7 (Weeks 0, 6, and 12), and remained in the clinic overnight.
17 Subjects were requested to return the following day of the scheduled visit to remove the Holter at Visit 2 and at Visits 3, 5, and 7 (Weeks 0, 6, and 12), and to have the 23- and 24-hour PFTs performed, with the exception of the subset of subjects who have remained in the clinic overnight at Visits 3, 5, and 7 (Weeks 0, 6, and 12).
18 Six-minute walk was performed between 3 and 4 hours post-first dose after the 2-hour postdose ECG.
19 Six-minute walk was performed at either Visit 2 or Visit 2a.
20 COPD questionnaire was completed by the subject at home in the morning upon rising (prior to taking any medication) and in the evening (prior to taking their evening dose), from the evening of Visit 2 through the morning of Visit 7.
21 Subject and Investigator Global Evaluations were done at separate times and with no knowledge on the part of the Investigator of the subject's ratings. The subject completed his/her evaluation at the beginning of the study visit; the Investigator should complete his/her evaluation after review of medical history and concomitant medications, physical examination, and PFTs.
22 Telephone contact between visits was conducted with the subject.

Concomitant Therapies

Subjects could not take any of the medications listed in the Disallowed Medications Table above for the duration of the study, including washout. Oral and inhaled steroids and xanthines were allowed at study entry and for the study duration as long as the regimen was stable for at least 14 days prior to study entry and during study participation. Subjects on concurrent oral corticosteroids at study entry may have been taking ≤10 mg/day of prednisone or equivalent. One 14-day course of oral corticosteroids may have been administered at a maximum dose of 40 mg/day. The decision about initiation or continuation of a course of oral corticosteroids was at the Investigator's discretion. If possible, in the case of a COPD exacerbation, FEV1 was measured before initiation of corticosteroid therapy. Subjects who required oral steroids for more than 14 consecutive days and/or required >40 mg/day, or required any additional courses of oral steroids were discontinued from the study unless a special approval was granted and documented by the Contract Research Organization (CRO) medical monitor. Subjects who maintained a stable dose (at least 14 days prior to study start) of a short-acting theophylline (BID or TID regimen), or who used such drugs intermittently at a stable dose, were eligible for this study. However, subjects must have been able to avoid the use of a short-acting theophylline for at least 24 hours before Visits 1 through 7. Once-a-day controlled-release theophylline preparations were not allowed. Subjects who maintained a stable dose (at least 14 days prior to study entry) of leukotriene inhibitors were allowed to continue their regimen. However, the subjects must have been able to avoid the use of leukotriene inhibitors for at least 24 hours before Visits 3, 4, 5, 6, and 7. Other concurrent medications were permitted on a case-by-case basis and at stable doses for a minimum of 30 days prior to Visit 1.

Data Analysis

The sample size determination was arrived at from the assumption that with a standard deviation of 21%, a total of 575 subjects (115 per treatment arm) would be required to detect a 10% difference between any dose level of arformoterol and placebo with at least 90% power for the 50 μg QD dose of arformoterol compared with placebo and 85% power for the comparison of the two BID doses of arformoterol relative to placebo for the primary endpoint, percent change from study baseline FEV1 to the end of the dosing interval (12 hours post-second dose for the BID treatment arms and 24 hours postdose for the QD treatment arm).

A Bonferroni adjustment was made for the primary analysis of the primary efficacy endpoint. A pairwise test between the 50 μg QD dose of arformoterol and placebo for the percent change from study baseline at 24 hours postdose was performed at the 0.0250 level, while pairwise tests between the two BID doses of arformoterol and placebo for the percent change from study baseline at 12 hours post-second dose were performed at the 0.0125 level. No other adjustments were made for multiple comparisons. A secondary analysis of the primary efficacy endpoint was performed on the ITT population utilizing the same repeated measures linear model for the primary analysis (but without Bonferroni adjustment).

All other significance testing was two-tailed and conducted at an $\alpha = 0.05$ level of significance. All pairwise comparisons between treatment groups were performed using least squares means from the linear model.

For continuous variables, statistical summaries included numbers of subjects, means, standard deviations, medians, 25th percentiles, 75th percentiles, minima, and maxima. For categorical variables, statistical summaries included frequency counts and percentages. All change from visit predose calculations had the visit predose value subtracted from postdose values. All change from study baseline calculations had the study baseline values subtracted from the post-study baseline values.

There were three populations in this study: enrolled (ENR) population, all subjects randomized (RND) population, and the ITT population. The ENR population was defined as those subjects who entered the single-blind placebo period and had taken at least one dose of single-blind medication. All listings were performed using the ENR population. The RND population was defined to be those subjects who were randomized to double-blind treatment. This population was defined for use in data presentations for the DSMB. The ITT population was defined as those subjects who were randomized to double-blind treatment, and had taken at least one dose of double-blind study medication. All efficacy analyses (primary, key secondary, and secondary), and safety analyses were performed on the ITT population, according to treatment assigned. All tabular and graphical summaries were performed using the ITT population (by treatment group), and all data listings contain the ENR population. Subjects who failed to successfully pass the screening criteria, or those who passed the screening criteria but did not receive any single-blind medication, were termed Screen Failures. Subjects who participated in the single-blind placebo period (i.e., ENR subjects), but who were not randomized were termed Randomization Failures. Subjects who were randomized and had taken at least one dose of double-blind study medication (i.e., ITT subjects) but who failed to complete the full 12 weeks of the double-blind period were termed Discontinued Subjects.

The primary efficacy endpoint 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).

FEV1 was the primary efficacy variable. It was collected using serial spirometry at Visit 3 (Week 0), Visit 5 (Week 6), and Visit 7 (Week 12) over a 24-hour period at the following time points: predose, immediately postdose, 15 and 40 minutes postdose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 23, and 24 hours postdose. A subset of subjects (approximately 20%) also underwent additional PFTs at 13, 14, and 16 hours post-first dose. The maximum FEV1 value from two maneuvers was recorded at each collection time. For a given subject at any particular visit, the percent change from study baseline FEV1 at time t is defined as:

$$\%\Delta FEV1\{t\} = \frac{100 \times (\text{Postdose FEV1}\{t\} - \text{Study Baseline FEV1}),}{\text{Study Baseline FEV1}}$$

where study baseline is defined to be the predose FEV1 prior to the first dose at Visit 3.

A key secondary efficacy endpoint for the study was FEV1 time-normalized area under the percent change from visit predose curve over 12 hours ($nAUC_{0-12-P}$) or, for the q day dosing group over 24 hours ($nAUC_{0-24-P}$).

The following practices were employed in the calculation of AUC, utilizing 24 hours (1440 minutes) or 12 hours (720 minutes) as appropriate (references to "rescue" apply to both the use of rescue medication [racemic albuterol MDI] and supplemental medication [ipratropium bromide MDI]):

- If a subject used rescue medication at any time during the visit, then the last FEV1 measurement prior to rescue medication use was carried forward for the 6-hour period following each rescue. Observations beyond six hours following rescue were considered valid measurements for analysis. No observation was carried forward past 1440 minutes (24 hours) post-first dose (i.e., from the start time of nebulization).
- If a subject did not have an FEV1 measurement at 1440 minutes post-first dose, then the last available FEV1 measurement was carried forward to 1440 minutes after the start time of nebulization.
- If a subject's actual time of postdose spirometry testing was missing when the corresponding FEV1 value for that spirometry test was not missing, then the actual time of spirometry was set to the corresponding scheduled time interval added to the end of dosing time.
- If a subject had FEV1 measurements beyond the 24th hour, and no measurement at the 24th hour, then the FEV1 value for the 24th hour was interpolated between the next measurement beyond 24 hours and the last measurement prior to 24 hours. The time of this interpolated measurement was the start time of nebulization plus 1440 minutes (24 hours).
- If a subject's CRF start time of nebulization was missing, it was assigned a time 10 minutes prior to the CRF end time of nebulization, or else 12 minutes prior to the CRF end of dosing time if the CRF end time of nebulization was missing.

Reviewer's Comment: These conventions are reasonable.

Other spirometry bases secondary endpoints were:

- FEV1 Time-normalized Area Under the Percent Change from Study Baseline Curve Over 12 hours (nAUC0-12-B)
- FEV1 Time-normalized Area Under the Percent Change from Visit Predose Curve Over 24 hours (nAUC0-24-P)
- FEV1 Time-normalized Area Under the Percent Change from Study Baseline Curve Over 24 hours (nAUC0-24-B)
- Peak Percent of Predicted FEV1
- Peak Percent Change in FEV1
- FEV1-specific endpoints included the following:

- Percent change in visit predose FEV1 (i.e., trough FEV1 at Visits 4, 5, 6, and 7) from study baseline at Visit 3 (Week 0)
- Percent change in FEV1 at each time point from visit predose
- Percent change in FEV1 at each time point from study baseline
- FEV1 at each time point
- Percent predicted FEV1at each time point
- Time to Onset of Response (TOR)
- Time to Peak Change (TOPC) in FEV1

Non-Spirometry based secondary endpoints included:

- At-home and In-clinic Peak Expiratory Flow Rate (PEFR)
- Relationship Between Plasma Concentration of Arformoterol and Percent Change in FEV_1
- Supplemental Ipratropium Bromide MDI Use
- Rescue Racemic Albuterol MDI Use
- Exacerbations of COPD
- COPD Symptom Ratings (Over 12 Weeks of Treatment)
- St. George's Hospital Respiratory Questionnaire (Quality of Life)
- Subject/Investigator Global Evaluations
- Baseline/Transitional Dyspnea Index (BDI/TDI)
- Six-Minute Walk

Disposition of Subjects

A total of 917 subjects were enrolled at Visit 1 (screening) and entered the single-blind placebo run-in period. Of the 917 enrolled subjects, 193 subjects (21.0%) withdrew prior to randomization. Of the 193 subjects enrolled but not randomized, 83 (43.0%) did not meet the eligibility criteria; 40 (20.7%) experienced an adverse event; 35 (18.1%) voluntarily discontinued; and 35 (18.1%) terminated for other reasons, including protocol violation and lost to follow-up. Seven randomized subjects were excluded from the ITT population because they did not take study medication. The ITT population consisted of 717 subjects. Subject disposition for the ITT population is presented in following Table .

Study 091-050: Subject Disposition (ITT Population)

	Placebo	ARF 15 µg BID	ARF 25 µg BID	ARF 50 µg QD	Salmeterol 42 µg BID	All Treatment Groups
Subjects Randomized	143	141	143	146	144	717
Subjects Withdrawn (%) *	32 (22.4)	17 (12.1)	33 (23.1)	22 (15.1)	26 (18.1)	130 (18.1)
Adverse event	14 (9.8)	8 (5.7)	17 (11.9)	9 (6.2)	13 (9.0)	61† (8.5)
Protocol violation	3 (2.1)	4 (2.8)	6 (4.2)	3 (2.1)	3 (2.1)	19 (2.6)
Voluntary	14 (9.8)	4 (2.8)	8 (5.6)	10 (6.8)	4 (2.8)	40 (5.6)
Lost to follow-up	1 (0.7)	0	0	0	1 (0.7)	2 (0.3)
Other	0	1 (0.7)	2 (1.4)	0	5 (3.5)	8 (1.1)
Subjects Completed (%)	111 (77.6)	124 (87.9)	110 (76.9)	124 (84.9)	118 (81.9)	587 (81.9)

* After a review of the clinical database, Sepracor determined that 7 subjects who were discontinued from the study for reasons other than an adverse event had adverse events near the time of study discontinuation that may have contributed to the reason for discontinuation. Narratives for these 7 subjects are provided in Appendix 16.5.3.

† Narratives for subjects who discontinued the study due to an adverse event was derived from study termination records (Appendix 16.2.2.1).

Of the 717 subjects, 587 subjects (81.9%) completed the study and 130 subjects (18.1%) terminated early: 61 of 130 subjects (46.9%) experienced an adverse event, 40 (30.8%) voluntarily discontinued, 19 (14.6%) discontinued because of protocol violations, and 10 (7.7%) discontinued for other reasons or were lost to follow-up. Upon review of the clinical database, the Applicant determined that seven subjects who discontinued for reasons other than adverse events had an adverse event that may have contributed to study termination (1 subject each: placebo, arformoterol 25µg BID; 2 arformoterol 50 µg QD subjects; and 3 salmeterol subjects).

The definition of important protocol deviations and the process for their review was specified prior to end of study unblinding. The Table below lists and summarizes the defined categories of important protocol deviations by treatment group. Important protocol deviations were applicable only to the ITT population. The first three categories of important protocol deviations were determined programmatically. For the "disallowed medication" deviations, all potentially disallowed coded medications were clinically reviewed on a per-subject basis. For the "other" important deviations, all investigator comments were clinically reviewed on a per-subject basis.

Study 091-050: Important Protocol Deviations

Important Protocol Deviation*	Placebo (N=143)	ARF 15 µg BID (N=141)	ARF 25 µg BID (N=143)	ARF 50 µg QD (N=146)	Salmeterol 42 µg BID (N=144)
Any Important Deviation (%)	54 (38)	42 (30)	36 (25)	51 (35)	39 (27)
Did not meet inclusion/exclusion criteria (%)	20 (14)	17 (12)	17 (12)	18 (12)	16 (11)
Study medication compliance† (%)	11 (8)	6 (4)	5 (4)	6 (4)	6 (4)
Continuation criteria not met‡	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)
Used disallowed medication (%)	4 (3)	4 (3)	2 (1)	4 (3)	5 (4)
Other Important Deviations § (%)	27 (19)	25 (18)	23 (16)	34 (23)	21 (15)

* A subject may have had more than one Important Protocol Deviation.

† Noncompliant subjects had compliance rates <80%.

‡ At Visits 3, 5, or 7.

§ Important protocol deviations listed in the Investigator's comments log.

Important protocol deviations were reported for 222 of the 717 ITT subjects (31.0%) at least once during the double-blind treatment period and were fairly evenly distributed across treatment groups. The most common important protocol deviations were other important deviations (130/717, 18.1%), did not meet inclusion/exclusion criteria (88/717, 12.3%), and noncompliance with study medication schedule (34/717, 4.7%). Some of the 130 deviations in the "other" important protocol deviation categories identified by review of the Investigator comments may have been cited in other categories, such as inclusion/exclusion criteria or disallowed medications. The other important deviations not already discussed were primarily related to drug dispensing and study procedure errors. The majority of other deviations from inclusion criteria were for subjects who did not meet pre-randomization pulmonary function criteria, FEV1, and/or FEV1/FVC ratio (26/717, 3.6%). There were also a number of other deviations from inclusion criteria for subjects who did not meet the chest x-ray criteria (i.e., performed outside the protocol-specified time window; 24/717, 3.3%).
Reviewer's Comment: As these protocol deviations were either fairly equally distributed across study treatment groups and/or were very small in number, they would not be expected to influence the results or conclusions from the study.

Concurrent pulmonary medications used during the study were similar between treatment groups. Over 70% of subjects reported using at least one agent for COPD before Visit 1 which included albuterol (42 to 51%), salmeterol (24 to 38%), fluticasone (14 to 23%), ipratropium (18 to 21%), and Combivent® (18 to 29%).

Study Demographics

The following Table summarizes the demographic and baseline characteristics for the ITT population:

Study 091-050: Summary of Demographic and Other Baseline Characteristics (ITT Population)

Parameter	Placebo (N=143)	ARF 15 µg BID (N=141)	ARF 25 µg BID (N=143)	ARF 50 µg QD (N=146)	Salmeterol 42 µg BID (N=144)
Age (yrs)					
Mean (SD)	63.1 (8.4)	62.0 (9.1)	63.5 (9.2)	62.4 (9.4)	63.4 (8.8)
25th percentile	58.0	56.0	57.0	56.0	58.0
Median	64.0	63.0	63.0	63.5	63.5
75th percentile	69.0	70.0	71.0	70.0	70.0
Gender (n,%)					
Male	91 (63.6)	72 (51.1)	81 (56.6)	85 (58.2)	87 (60.4)
Female	52 (36.4)	69 (48.9)	62 (43.4)	61 (41.8)	57 (39.6)
Race (n,%)					
Caucasian	137 (95.8)	132 (93.6)	138 (96.5)	140 (95.9)	133 (92.4)
Black	4 (2.8)	6 (4.3)	5 (3.5)	3 (2.1)	7 (4.9)
Asian	1 (0.7)	1 (0.7)	0	1 (0.7)	0
Hispanic	1 (0.7)	2 (1.4)	0	2 (1.4)	4 (2.8)
Height (in)					
Mean (SD)	67.3 (3.8)	67.0 (4.0)	66.6 (3.8)	67.4 (3.7)	67.3 (3.8)
25th percentile	65.0	64.0	64.0	64.6	64.2
Median	67.7	66.9	66.1	67.0	67.9
75th percentile	70.0	70.0	69.7	70.1	70.1
Weight (lb.)					
Mean (SD)	184.2 (35.1)	179.1 (38.5)	179.3 (48.2)	179.7 (46.0)	178.8 (42.0)
25th percentile	159.4	150.0	146.4	150.0	148.7
Median	180.3	176.0	170.0	175.1	174.2
75th percentile	209.0	205.5	200.4	202.4	201.3
FEV_1 (L)					
Mean (SD)	1.31 (0.5)	1.24 (0.5)	1.22 (0.5)	1.27 (0.5)	1.32 (0.5)
25th percentile	0.94	0.88	0.84	0.90	0.94
Median	1.20	1.13	1.10	1.21	1.21
75th percentile	1.63	1.52	1.38	1.57	1.60
FEV_1 % predicted† (%)					
Mean (SD)	42.4 (12.7)	41.6 (13.1)	41.4 (13.5)	41.9 (13.8)	43.4 (13.5)
25th percentile	30.6	31.5	29.8	30.9	32.7
Median	42.1	40.2	39.4	40.7	43.1
75th percentile	53.8	51.6	51.4	52.8	53.8
FEV_1/FVC ratio					
Mean (SD)	51.5 (11.1)	50.2 (11.2)	51.0 (10.2)	50.4 (10.9)	52.1 (11.0)
25th percentile	42.6	42.3	42.7	43.2	44.4
Median	50.3	49.8	49.8	50.3	52.0
75th percentile	60.6	59.6	58.4	58.1	61.2
FEV_1 % reversibility† (%)					
Mean (SD)	13.7 (14.8)	16.0 (12.6)	17.3 (15.9)	21.3 (36.6)	19.4 (15.2)
25th percentile	5.7	7.0	7.2	9.1	9.7
Median	11.6	13.4	16.2	16.2	16.4
75th percentile	21.8	22.9	26.7	24.8	26.3
Nonreversible subjects* (%)	23 (16.1)	24 (17.0)	25 (17.5)	20 (13.7)	15 (10.4)

* Subjects were classified as reversible if their FEV_1 percent reversibility was ≥10% for at least one of two (or three) visits prior to randomization; otherwise subjects were defined to be nonreversible.

† Predose FEV_1 and percent reversibility values provided are from the Week 1 visit.

Almost all the subjects in the study were Caucasian (95%). There was about 5% more females in the arformoterol 15 µg group than in other groups. Otherwise, age, gender, and pulmonary characteristics, including reversibility, were fairly well balanced across treatment groups. *Reviewer's Comment: The Applicant knows that the lack of some diversity in the ethnic make-up of the studies is a review issue and will likely result in some type of post-market commitment on their part.*

Analysis of Efficacy

The primary efficacy endpoint 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 groups and 24 hours postdose for the QD treatment group) over 12 weeks of treatment. FEV1 trough data were also analyzed at individually for Visits 3, 5, and 7 (Weeks 0, 6, and 12). These data are summarized in the following Table.

Percent Change in FEV1 from Study Baseline to the End of the Dosing Interval Over the 12-Week Double-Blind Period and at Weeks 0, 6, and 12 (ITT Population)

	Placebo (N=143)	ARF 15 µg BID (N=141)	ARF 25 µg BID (N=143)	ARF 50 µg QD (N=146)	Salmeterol 42 µg BID (N=144)
Baseline FEV_1 (L)					
n	143	141	142	145	140
Mean (SD)	1.20 (0.5)	1.15 (0.5)	1.13 (0.5)	1.21 (0.4)	1.22 (0.5)
Overall (Weeks 0 to 12)					
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)
Mean (SD)	6.4 (17.2)	18.3 (20.0)	20.9 (20.6)	15.4 (19.6)	17.7 (17.5)
Median	3.1	14.6	18.4	12.9	16.6
25th, 75th pctiles	-3.1, 12.1	6.0, 27.2	7.3, 35.1	1.4, 23.2	6.5, 29.0
P-value†					
vs placebo	–	<0.001	<0.001	<0.001	<0.001
vs salmeterol		0.848	0.480	0.268	
Week 0 (post-first dose)					
n	126	128	134	135	127
LS Mean (SE)*	6.8 (1.7)	22.1 (1.7)	23.9 (1.7)	18.3 (1.7)	21.1 (1.7)
Mean (SD)	7.5 (15.8)	22.5 (20.5)	24.8 (21.7)	17.8 (19.0)	21.3 (20.8)
Median	6.2	20.7	20.5	14.8	20.1
25th, 75th pctiles	-4.8, 14.6	9.2, 33.2	10.3, 40.5	5.2, 26.7	8.7, 29.8
P-value					
vs placebo	–	<0.001	<0.001	<0.001	<0.001
vs salmeterol		0.648	0.229	0.234	
Week 6					
n	106	121	120	120	120
LS Mean (SE)*	6.2 (2.0)	14.8 (1.9)	17.6 (1.9)	13.2 (1.9)	15.9 (1.9)
Mean (SD)	5.6 (20.7)	16.0 (22.3)	20.0 (21.4)	13.0 (22.8)	16.5 (19.9)
Median	0.7	11.9	20.1	11.7	14.0
25th, 75th pctiles	-7.0, 15.3	0.0, 25.5	4.7, 33.0	0.0, 21.1	4.0, 27.5
P-value					
vs placebo	–	<0.001	<0.001	0.008	<0.001
vs salmeterol		0.683	0.505	0.306	
Week 12					
n	94	110	95	110	104
LS Mean (SE)*	5.0 (2.1)	13.8 (2.0)	15.3 (2.1)	13.2 (2.0)	15.1 (2.0)
Mean (SD)	4.7 (23.1)	15.2 (22.1)	17.8 (24.0)	14.2 (23.8)	15.3 (18.1)
Median	1.7	11.4	15.5	11.9	11.8
25th, 75th pctiles	-10.1, 13.7	3.13, 23.4	1.8, 29.1	0.7, 22.8	3.2, 28.0
P-value					
vs placebo	–	0.002	<0.001	0.003	<0.001
vs salmeterol		0.638	0.953	0.486	

Note: End of the dosing interval = 12 hours post-second dose for the BID treatment arms and 24 hours postdose for the QD treatment arm. Baseline FEV_1 value from Visit 3 predose.

* From Repeated Measures Model: with fixed effects for treatment, time (Weeks 0, 6, and 12), treatment-by-time interaction, and site type, with baseline FEV_1 as a covariate, and treatment-by-baseline-FEV_1 interaction. P-values for the treatment-by-time interaction and treatment-by-baseline FEV_1 interaction were 0.102 and 0.902, respectively.

† Bonferroni adjustment: comparison of 50 µg QD arformoterol dose versus placebo tested at the 0.0250 significance level, and two comparisons of each BID arformoterol dose versus placebo tested at the significance 0.0125 level. All other comparisons tested at the 0.05 significance level.

Arformoterol at all 3 doses was statistically superior to placebo on the primary endpoint: FEV1 at trough from study baseline versus placebo over the 12-week double-blind treatment period (all p-values <0.001). The LS mean percent change in FEV1 from study baseline was greater for all arformoterol treatment groups than placebo, with treatment differences of 10.9% for arformoterol 15 µg BID, 12.9% for arformoterol 25 µg BID, and 8.9% for arformoterol 50 µg QD. A dose-response relationship in FEV1 at trough from study baseline was observed for the arformoterol BID dose groups. The mean percent change from study baseline in FEV1 for the salmeterol group was 11.4% greater than the placebo group. The percent improvement in FEV1 the end of the dosing interval demonstrated no significant differences between any of the arformoterol dosages and salmeterol. As would be expected, among the approximately 15% of subjects whose FEV1 reversibility was <10% prior to randomization, the improvement in FEV1 at the end of the dosing interval compared to placebo was less than that observed for subjects with ≥10% reversibility. For nonreversible subjects, the overall mean improvement difference

relative to placebo was 2.3 to 8.7% for the arformoterol dose groups, and <1% for the salmeterol dose group *[Table 11.4.1.1-2, clinstat\copd\091-050.pdf].*

Secondary Analyses

The Applicant listed a key secondary efficacy endpoint for the study as FEV1 time-normalized area under the percent change from visit predose curve over 12 hours ($nAUC_{0\text{-}12\text{-}P}$). The overall LS mean FEV_1 $nAUC_{0\text{-}12\text{-}P}$ was significantly improved for all arformoterol doses compared with placebo, and ranged from approximately 10 to 16% greater across the arformoterol groups compared with placebo. In addition, the mean FEV_1 $nAUC_{0\text{-}12\text{-}P}$ was significantly improved for all arformoterol doses compared to placebo at each study time point. Improvements in lung function appeared to increase with higher doses of arformoterol. *Reviewer's Comment: The 15 and 25 µg bid groups were very similar while the 50 µg qd group was about 5% greater than the lower doses. The fact that the measurement was taken at trough (12 hr) for the lower doses but after only half the dosing period had elapsed for the higher qd dose favored the high dose.* Overall improvement in FEV_1 $nAUC_{0\text{-}12\text{-}P}$ was also approximately 3 to 9% greater for the arformoterol doses compared with salmeterol and was greater at each individual study time point as well.
Reviewer's Comment: These differences were statistically different at the $p < 0.05$ level for all 3 formoterol doses. The high qd day dose would not be comparable for reasons given in the comment above. The lower bid doses of formoterol showed a 3-4% difference from salmeterol which, while statistically significant, may not be clinically significant. This could be an issue for the label. Also, salmeterol may be at a disadvantage in this type of measurement because it takes several hours to reach peak effect compared to formoterol.

Subgroup analyses of subjects who demonstrated reversible (>10% response in FEV1 to albuterol) to those who were less reversible (< 10%) demonstrated greater responses in those who had demonstrated greater reversibility to albuterol. Again it appears that the arformoterol groups performed several percentage points higher than the salmeterol group.

Other Spirometric Secondary Analyses

- FEV_1 Time-normalized Area Under the Percent Change from Study Baseline Curve Over 12 Hours ($nAUC_{0\text{-}12\text{-}B}$)

All arformoterol doses had significantly (all p-values <0.001) greater increases in $nAUC_{0\text{-}12\text{-}B}$ compared with placebo, both averaged over the 12-week double-blind period and at Weeks 0, 6, and 12. Overall, improvement was slightly greater for the arformoterol 15 µg BID dose than for salmeterol, but the difference was not statistically significant.

- FEV_1 Time-normalized Area Under the Percent Change from Visit Predose Curve Over 24 hours ($nAUC_{0\text{-}24\text{-}P}$)

Approximately 20% of subjects remained in the clinic overnight and had at least one spirometry measurement taken at the 13, 14, or 16 hour time points. Subjects in all arformoterol treatment

groups demonstrated significantly ($p<0.001$) greater FEV_1 AUC responses over 24 hours from visit predose over the double-blind period ($nAUC_{0-24-P}$) relative to placebo. The extent of improvement in this small subset of subjects who remained at the clinic overnight, and had spirometry assessments scheduled at the 13-,14-, and 16-hour time points, was not dose-dependent.

- FEV_1 Time-normalized Area Under the Percent Change from Study Baseline Curve Over 24 Hours ($nAUC_{0-24-B}$)

For this outcome variable, percent improvement in FEV_1 over 24 hours after dosing is compared to the FEV_1 value at the Week 0 (Visit 3) baseline. Again, approximately 20% of subjects remained in the clinic overnight and had at least one spirometry measurement taken at the 13, 14, or 16 hour time points. Subjects in all the arformoterol treatment groups had significantly improved time-normalized area under the FEV_1 percent change from study baseline curve over 24 hours ($nAUC_{0-24-B}$) compared with placebo over the double-blind period (all p values <0.001) and at Weeks 0, 6, and 12 (all p-values ≤ 0.017).

- Peak Percent of Predicted FEV_1

Subjects in all arformoterol treatment groups demonstrated significant (all p-values <0.001) improvement in mean peak percent of predicted FEV_1 compared with placebo, both over the double-blind period and at Weeks 0, 6, and 12.
Reviewer's Comment: Although the Applicant states there was a dose-response effect for arformoterol, it is minimal (1-2%).

- Peak Percent Change in FEV_1

Subjects in all arformoterol treatment groups demonstrated significant improvement in mean FEV_1 peak percent change from visit predose when compared with placebo both over the double-blind period and at Weeks 0, 6, and 12 (all p-values ≤ 0.001). Again, a dose-response is stated but is minimal. All arformoterol treatments were significantly better than salmeterol (all p-values ≤ 0.003), except for arformoterol 15 µg BID at Week 0.

- Predose FEV_1 and Percent Predicted FEV_1

Mean predose FEV_1 values were between 1.13 and 1.22 L and mean predose FEV_1 percent predicted values were between 38.1 and 40.1% for all treatment groups at Week 0, with the arformoterol 50 µg QD and salmeterol groups having the highest for both values at Week 0. Mean predose FEV_1 and mean predose percent predicted FEV_1 increased between Weeks 0 and 6 for all treatment groups then either decreased slightly or remained stable between Weeks 6 and 12.

- Time Point Changes in FEV_1

Changes at specific FEV_1 time points were assessed for Weeks 0, 6, and 12. All subjects had spirometry assessments scheduled at all time points between predose and 12-hours postdose, as well as at 23 and 24 hours postdose while a subset of approximately 20% subjects had spirometry values scheduled at 13, 14, and 16 hours postdose. All endpoints show that both the arformoterol and salmeterol BID doses achieved a second increase in FEV_1 values following the second daily dose after 12 hours.

- Time to Onset of Response

A responder was defined *post hoc* as a subject who achieved at least a 10% increase in FEV_1 from predose values within 12 hours after dosing. At Week 0, a 10% response in FEV_1 was achieved with a median of less than three minutes of dosing for all the arformoterol groups, compared with a median of approximately 15 minutes for the salmeterol group. At Weeks 6 and 12, the median time to achieve a 10% increase in FEV_1 for all arformoterol groups ranged from four to 14 minutes, compared with two to three hours for salmeterol.

- Time to Peak Change in FEV_1

The median peak change in FEV_1 occurred at approximately three hours for all dose groups after the first dose at Week 0. At Weeks 6 and 12, the median time to peak change decreased for all arformoterol treatment groups, occurring between one to two hours.

- In-clinic and At-home Peak Expiratory Flow Rate (PEFR)

The in-clinic average PEFR values increased 0.37 to 0.52 L/sec in the active treatment groups and 0.33 L/sec in the placebo group by 15 minutes after dosing. The morning and evening at-home average PEFR values increased in the first three weeks of the double-blind treatment (Weeks 0 to 3) for all active treatment groups. These increases were maintained with little change throughout the 12-week double-blind treatment period.

- Ipratropium Bromide MDI Supplemental Use

Prior to randomization, ipratropium bromide use was similar across treatment groups. Over 80% of subjects across treatment groups used ipratropium bromide prior to randomization. Average use was approximately four days per week and approximately three actuations per day. Ipratropium use declined by 0.5 to 0.6 days per week more in the arformoterol treatment groups than in the placebo group during the double-blind period. Similarly, ipratropium use declined an average of 0.5 to 0.6 actuations per day more in the arformoterol groups than the change observed in the placebo group. The decline in ipratropium use in the salmeterol group versus placebo was similar to that of subjects treated with arformoterol

- Racemic Albuterol MDI Rescue Use

Prior to randomization, over 73% of subjects across treatment groups reported racemic albuterol MDI rescue use. Average use was approximately three days per week with two actuations per

day. A decline in rescue albuterol use in excess of that seen in the placebo group was observed throughout the 12-week duration of the trial, both for mean number of days used per week (0.4 to 0.9 days/week), as well as mean number of actuations used per day (0.5 to 0.8 actuations/day) for all active treatment groups.

- COPD Symptom Ratings

Across all treatment groups, morning ratings for the mean number of symptom-free days/week at baseline ranged between 3.5 and 3.9 days. Over the double-blind period, the arformoterol dose groups demonstrated an increase in symptom-free days/week that ranged between 0.54 days/week for arformoterol 50 μg QD and 0.83 days/week for arformoterol 15 μg BID. By comparison, placebo symptom-free days increased by 0.35 days/week and salmeterol increased by 0.70 days/week. When subjects assessed their symptoms in the evening, a majority (>80%) of subjects in all treatment groups reported no symptom-free days/week throughout the single-blind period. The mean number of symptom-free days increased for all active treatment groups and ranged from 0.24 days/week for the arformoterol 50 μg QD group to 0.31 days/week for the arformoterol 25 μg BID group; the salmeterol group increased by a mean of 0.29 days/week.

- St. George's Hospital Respiratory Questionnaire

After six weeks of double-blind treatment, total scores improved in all active treatment groups, with mean changes in total scores ranging between -2.6 and -3.6 units for arformoterol treated subjects. Salmeterol treated subjects had mean changes in total scores of -3.5. The placebo group, by comparison, changed by -1.2 units.

- Subject/Investigator Global Evaluations

Between 72 and 76% of subjects in active treatment groups reported that their symptoms were slightly-to-much improved, compared with approximately 55% of subjects in the placebo group. These patterns were similarly observed for the Investigator global evaluation data.

- Baseline Dyspnea Index/Transitional Dyspnea Index (BDI/TDI)

The BDI was assessed predose during the single-blind period (Visit 2); the baseline focal score (range, 0 to 12) was defined as the sum of the Functional Impairment, Magnitude of Task, and Magnitude of Effort scores. The TDI was assessed predose at Weeks 6 and 12. Mean TDI scores improved in all active treatment groups during the double-blind period: by 2.0 to 2.2 units in the arformoterol BID groups, by 2.1 units in the arformoterol 50 μg QD group and by 1.4 units in the salmeterol group.

- Six-Minute Walk

The results of the six-minute walk test suggested substantial exercise compromise in all groups, with the median distance walked at baseline ranging from 1000 to 1060 feet. Modest (45-67 feet) improvement in walk distance was observed after both three and nine weeks of double-blind

treatment, however, this improvement was similar in both the placebo and active treatment groups.

Pharmacokinetic Data

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

Pharmacokinetic assessments were performed on a subset of ITT subjects (approximately 20 to 30% of subjects) at identified sites. Blood for determination of plasma concentrations was drawn predose and at 10 minutes, two and six hours post-first dose at Weeks 0, 6, and 12. Plasma concentration-time profiles increased with administration of higher total daily doses of arformoterol. Trough plasma concentrations (predose concentrations at Weeks 6 and 12) obtained after a 50 µg QD dose were greater than those observed following a 25 µg BID dose. Using mean plasma concentrations at 0.17 hours to approximate the expected time of C_{max}, 20 to 60% accumulation was noted with multiple doses at six and 12 weeks, respectively. No apparent relationship was observed between time-matched plasma concentrations and percent change in FEV_1 from visit predose values when viewing the data in aggregate. Of not is that measurable concentrations of arformoterol were observed in three of 31 (10%) and four of 59 (7%) analyzed samples in the placebo group and salmeterol groups, respectively. In addition, in the arformoterol dosing groups, approximately 19% (20 of 106 samples) of predose samples at Visit 3 (baseline) had measurable concentrations (Appendix 16.1.14). The mean plasma concentrations of arformoterol in these samples were below or near the limit of quantification.
Reviewer's Comment: Unless there is some cross-reactivity in the assays for arformoterol and albuterol, it appears that some of the subjects were self medicating with formoterol. This may have been more prevalent in the placebo group. If so, this could possibly prejudice the efficacy outcomes against arformoterol. Since arformoterol won on the primary outcome for all doses and many secondary outcomes, these findings would not change the study results/interpretation.

Efficacy Conclusions

Primary Endpoint
All arformoterol doses were superior to placebo on the specified primary endpoint: per cent change in trough FEV_1 versus placebo from study baseline over the 12-week double-blind treatment period. While improvement in trough FEV_1 remained significant for all treatment groups compared with placebo, the percent improvement in mean FEV_1 trough values decreased between Weeks 0 to 6 (by approximately one-third for all active treatment groups), but remained relatively stable between Weeks 6 through 12.
Reviewer's Comment: The baseline FEV1 values for subjects was between 1.2 and 1.3 L and the percent change above placebo was 11% for the proposed dose 15 µg group. This would calculate out to about a 120-130 mL improvement in FEV1 which would also be a clinically significant improvement for subjects with COPD.

No statistically significant differences between any of the arformoterol dosages and salmeterol in percent improvement in trough FEV_1 were detected.

Secondary Endpoints
Arformoterol was statistically superior to placebo or trended toward improvement for many of the secondary endpoints.

A key secondary endpoint was FEV1 time-normalized area under the percent change from visit predose curve over 12 hours ($nAUC_{0\text{-}12\text{-}P}$). All arformoterol doses significantly improved FEV_1 $nAUC_{0\text{-}12\text{-}P}$ compared with placebo. All arformoterol doses demonstrated greater improvement in FEV_1 $nAUC_{0\text{-}12\text{-}P}$ than salmeterol over the 12 weeks of treatment.

For other secondary endpoints, all arformoterol doses demonstrated statistically significant improvement versus placebo at Week 12 for the following spirometry-derived secondary endpoints: FEV_1 $nAUC_{0\text{-}12\text{-}B}$, FEV_1, FEV_1 $nAUC_{0\text{-}24\text{-}B}$, mean peak percent of predicted FEV_1; and mean FEV_1 peak percent change from visit predose or baseline.

The proportion of subjects who required supplemental (ipratropium bromide or albuterol) medications during the double-blind treatment period was about 10% lower in all arformoterol groups than the placebo group. There was no difference compared to salmeterol.

Descriptive analysis of symptom and functional improvement assessed in the St. George's Hospital Respiratory Questionnaire, Subject & Investigator Global Evaluations, and Baseline/Transitional Dyspnea Indices (BDI/TDI), all supported a greater improvement in arformoterol treatment groups relative to placebo.

Safety Review
The safety findings from this study, along with the safety data from the other placebo-controlled studies, will be reviewed in depth in the Integrated Review of Safety section of this review. Brief observations are described below.

Of the 717 subjects in the ITT population, 587 subjects (81.9%) completed the full duration of treatment. The mean number of days that subjects received study medication was similar across treatment groups (73 to 79 days) and the median number of days in each treatment group was 85 days. The extent of exposure for individual subject is shown in the following table.

Study 091-050: Extent of Exposure During the Double-Blind Treatment Period (ITT Population)

	Placebo (N=143)	ARF 15 µg BID (N=141)	ARF 25 µg BID (N=143)	ARF 50 µg QD (N=146)	Salmeterol 42 µg BID (N=144)
Duration (days)					
Mean (SD)	73.2 (25.8)	78.9 (19.3)	74.1 (24.6)	78.2 (18.9)	75.2 (22.8)
Median	85.0	85.0	85.0	85.0	85.0
Cumulative Dose (µg)*					
Mean (SD)	--	2317.3 (587.6)	3620.8 (1205.3)	3841.1 (952.1)	6147.2 (1997.4)
Median	--	2535	4175	4200	7056

*Cumulative dose not calculated for placebo subjects.

The overall occurrence of treatment-emergent adverse events in the ITT population during the double-blind period was similar across treatment groups (from 67.4 to 72.0%). Respiratory infection was reported by >10% of subjects in all treatment groups. Other frequently reported events (>5% in any of the treatment groups) were tremor, chest pain, headache, pain, nausea, bronchitis, COPD, pharyngitis, sinusitis, and urinary tract infection. Adverse events assessed as severe occurred with the highest frequency in the arformoterol 25 µg BID group (11.9%), followed by placebo-treated subjects (10.5%). The occurrence of potentially related adverse events was similar across treatment groups, ranging from 24.1 to 32.2%, and was highest in the arformoterol 50 µg QD group.

Adverse events that occurred in ≥2% of subjects in any treatment group during the double-blind treatment period are presented in the following Table.

Study 091-050: Adverse Events Occurring in ≥ 2% of Subjects in any Treatment Group During the Double-Blind Period (ITT Population)

BODY SYSTEM Preferred term	Placebo (N=143)	ARF 15 µg BID (N=141)	ARF 25 µg BID (N=143)	ARF 50 µg QD (N=146)	Salmeterol 42 µg BID (N=144)
	n (%)	n (%)	n (%)	n (%)	n (%)
ANY EVENT	103 (72.0)	95 (67.4)	101 (70.6)	104 (71.2)	99 (68.8)
BODY AS A WHOLE					
Abdominal pain	2 (1.4)	1 (0.7)	3 (2.1)	1 (0.7)	1 (0.7)
Accidental injury	3 (2.1)	3 (2.1)	5 (3.5)	7 (4.8)	5 (3.5)
Asthenia	1 (0.7)	1 (0.7)	4 (2.8)	6 (4.1)	1 (0.7)
Back pain	1 (0.7)	7 (5.0)	3 (2.1)	4 (2.7)	1 (0.7)
Chest pain	9 (6.3)	7 (5.0)	3 (2.1)	6 (4.1)	7 (4.9)
Chills	2 (1.4)	3 (2.1)	0	2 (1.4)	0
Fever	1 (0.7)	3 (2.1)	2 (1.4)	5 (3.4)	3 (2.1)
Flu syndrome	2 (1.4)	7 (5.0)	4 (2.8)	4 (2.7)	1 (0.7)
Headache	12 (8.4)	10 (7.1)	9 (6.3)	13 (8.9)	15 (10.4)
Infection	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	3 (2.1)
Neck pain	2 (1.4)	2 (1.4)	3 (2.1)	0	1 (0.7)
Pain	6 (4.2)	11 (7.8)	9 (6.3)	14 (9.6)	10 (6.9)
CARDIOVASCULAR					
Hypertension	3 (2.1)	3 (2.1)	3 (2.1)	3 (2.1)	1 (0.7)
Migraine	0	0	0	3 (2.1)	0
Palpitation	2 (1.4)	0	3 (2.1)	1 (0.7)	3 (2.1)
Tachycardia	2 (1.4)	1 (0.7)	1 (0.7)	1 (0.7)	3 (2.1)
Ventricular extrasystoles	4 (2.8)	0	1 (0.7)	1 (0.7)	3 (2.1)
Ventricular tachycardia	4 (2.8)	0	2 (1.4)	1 (0.7)	1 (0.7)
DIGESTIVE					
Diarrhea	5 (3.5)	7 (5.0)	7 (4.9)	2 (1.4)	0
Dyspepsia	7 (4.9)	3 (2.1)	5 (3.5)	1 (0.7)	4 (2.8)
Gastrointestinal disorder	3 (2.1)	1 (0.7)	0	1 (0.7)	1 (0.7)
Nausea	9 (6.3)	7 (5.0)	6 (4.2)	5 (3.4)	1 (0.7)
Vomiting	1 (0.7)	4 (2.8)	4 (2.8)	3 (2.1)	1 (0.7)
HEMIC & LYMPHATIC					
Anemia	0	0	3 (2.1)	0	1 (0.7)
Leukocytosis	0	0	2 (1.4)	3 (2.1)	0
METABOLIC & NUTRITIONAL					
Hyperkalemia	3 (2.1)	1 (0.7)	1 (0.7)	2 (1.4)	3 (2.1)
Hypokalemia	2 (1.4)	2 (1.4)	4 (2.8)	1 (0.7)	0
Peripheral edema	1 (0.7)	3 (2.1)	3 (2.1)	2 (1.4)	3 (2.1)
MUSCULO-SKELETAL					
Arthralgia	0	1 (0.7)	1 (0.7)	3 (2.1)	0
Leg cramps	2 (1.4)	2 (1.4)	6 (4.2)	4 (2.7)	3 (2.1)
Myalgia	0	1 (0.7)	2 (1.4)	5 (3.4)	0
NERVOUS					
Anxiety	2 (1.4)	3 (2.1)	2 (1.4)	3 (2.1)	0
Dizziness	3 (2.1)	2 (1.4)	5 (3.5)	3 (2.1)	4 (2.8)
Hypertonia	0	0	3 (2.1)	1 (0.7)	1 (0.7)
Hypesthesia	0	0	0	0	3 (2.1)
Insomnia	2 (1.4)	4 (2.8)	7 (4.9)	4 (2.7)	1 (0.7)
Nervousness	0	2 (1.4)	2 (1.4)	5 (3.4)	0
Tremor	0	1 (0.7)	2 (1.4)	15 (10.3)	0

Study 091-050: Adverse Events Occurring in ≥ 2% of Subjects in any Treatment Group During the Double-Blind Period continued

BODY SYSTEM Preferred term	Placebo (N=143)	ARF 15 µg BID (N=141)	ARF 25 µg BID (N=143)	ARF 50 µg QD (N=146)	Salmeterol 42 µg BID (N=144)
	n (%)	n (%)	n (%)	n (%)	n (%)
RESPIRATORY					
Bronchitis	8 (5.6)	8 (5.7)	9 (6.3)	7 (4.8)	3 (2.1)
COPD	12 (8.4)	8 (5.7)	9 (6.3)	10 (6.8)	15 (10.4)
Cough increased	3 (2.1)	5 (3.5)	7 (4.9)	4 (2.7)	7 (4.9)
Dyspnea	1 (0.7)	5 (3.5)	4 (2.8)	5 (3.4)	5 (3.5)
Infection	23 (16.1)	21 (14.9)	19 (13.3)	17 (11.6)	16 (11.1)
Lung disorder	1 (0.7)	3 (2.1)	2 (1.4)	1 (0.7)	1 (0.7)
Pharyngitis	11 (7.7)	4 (2.8)	4 (2.8)	8 (5.5)	13 (9.0)
Pneumonia	3 (2.1)	0	3 (2.1)	0	0
Rhinitis	7 (4.9)	7 (5.0)	4 (2.8)	5 (3.4)	7 (4.9)
Sinusitis	6 (4.2)	7 (5.0)	9 (6.3)	3 (2.1)	8 (5.6)
Voice alteration	3 (2.1)	3 (2.1)	2 (1.4)	1 (0.7)	0
SKIN					
Rash	2 (1.4)	3 (2.1)	4 (2.8)	0	2 (1.4)
SPECIAL SENSES					
Conjunctivitis	3 (2.1)	0	2 (1.4)	1 (0.7)	0
UROGENITAL					
Hematuria	0	2 (1.4)	2 (1.4)	4 (2.7)	2 (1.4)
Urinary tract infection	7 (4.9)	8 (5.7)	1 (0.7)	4 (2.7)	9 (6.3)
Urine abnormality	2 (1.4)	3 (2.1)	2 (1.4)	2 (1.4)	1 (0.7)

The incidence of cardiovascular events ranged from 7.1 to 16.0% (Table 14.3.1.3). None of these cardiovascular events appeared to increase with increasing doses of arformoterol, and were similar to placebo. The occurrence of respiratory events was evenly distributed across all treatment groups, and ranged from 33.6 to 39.9%. The rates of bronchitis, cough increased, dyspnea, and lung disorder (pulmonary congestion, chest congestion, upper respiratory congestion, or increased congestion) did not increase with increasing doses of arformoterol. Respiratory infection rates were greater than 10% for all treatment arms with the highest rate reported in the placebo group (16.1%). Adverse events considered by the Investigator to be potentially related to treatment occurred at roughly the same rate (24.1 to 25.9%) across treatment groups, except for the arformoterol 50 µg QD group (32.2%). Potentially related adverse events that were reported for ≥ 2% of subjects in the arformoterol 50 µg QD group and greater than placebo include tremor (9.6%), COPD exacerbation (4.1%), respiratory infection (3.4%), headache (2.7%), nervousness (2.7%), pharyngitis (2.7%), and dyspnea (2.1%). Only two events were assessed by the Investigator as definitely related to study medication: hypokalemia and tremor, both in the arformoterol 25 µg BID group.

Pivotal Study 091-051

Title of Study: A Double-Blind, Double-Dummy, Randomized, Placebo- and Active-Controlled, Multicenter, Parallel-Group Study of Arformoterol in the Treatment of Subjects with Chronic Obstructive Pulmonary Disease.

Study Description
This second pivotal study was performed under a protocol that was identical to the protocol for Study 091-050. The reader is referred to the description of the protocol discussed in the section above. This study was performed between April 16, 2002 and March 8, 2004. The study centers were all in the US and were located in the following states: AL, AZ, CA, CO, CT, FL, GA, IL, IN, KY, LA, MA, MO, MI, MT, NC, ND, NE, NJ, NV, OH, OK, OR, PA, RI, SC, TN, VA, WA, WI, TX, and the District of Columbia. A total of 451 patients were included, 271 assigned to tiotropium and 180 assigned to placebo.

The test product lot numbers were: placebo for arformoterol 2 mL: 05301B; arformoterol 15 mcg/2mL: 03501A and 00902B; arformoterol 25 mcg/2mL: 03501B and 00902C; arformoterol 50 mcg/2mL: 03501C and 00902D; Soya Lecithin Placebo MDI CFC: 1H947; Atrovent 14 g (supplemental): 010584W; Serevent 14.0 g: 1ZP1966; Ventolin 6.8 g (reversibility): 1ZP1408; Ventolin 17 g (rescue) 1ZP1205.

A total of 741 subjects with relatively stable, moderately severe COPD were randomized into the study with 739 analyzed (ITT). A total of 591 completed the study 118, placebo; 110, arformoterol 15 μg BID; 114, arformoterol 25 μg BID; 121, arformoterol 50 μg QD; 128, salmeterol 42 μg BID).

Disposition of Subjects

A total of 912 subjects were enrolled at Visit 1 (screening) and entered the single-blind placebo run-in period. Of the 917 enrolled subjects, 171 subjects (18.8%) withdrew prior to randomization. Of the 171 subjects enrolled but not randomized, 95 (55.6%) did not meet the eligibility criteria; 29 (17.0%) experienced an adverse event; 32 (18.7%) voluntarily discontinued; 5 (2.9%) were lost to follow-up; 3 (1.8%) had a protocol violation; and 7 (4.1%) terminated for other reasons. Two randomized subjects were excluded from the ITT population because they did not take study medication. Therefore, the ITT population consisted of 739 subjects. Subject disposition for the ITT population is presented in the following Table .

Study 091-051: Subject Disposition

	Placebo	ARF 15 µg BID	ARF 25 µg BID	ARF 50 µg QD	Salmeterol 42 µg BID	All Treatment Groups
ITT Population	150	147	149	147	146	739
Subjects Withdrawn (%)*	32 (21.3)	37 (25.2)	35 (23.5)	26 (17.7)	18 (12.3)	148 (20.0)
Adverse event	13 (8.7)	15 (10.2)	19 (12.8)	16 (10.9)	9 (6.2)	72 (9.7)†
Protocol variance	3 (2.0)	5 (3.4)	3 (2.0)	2 (1.4)	0	13 (1.8)
Voluntary withdrawal	10 (6.7)	11 (7.5)	5 (3.4)	5 (3.4)	3 (2.1)	34 (4.6)
Lost to follow-up	1 (0.7)	1 (0.7)	2 (1.3)	0	1 (0.7)	5 (0.7)
Did not meet entry criteria	0	2 (1.4)	1 (0.7)	0	1 (0.7)	4 (0.5)
Other	5 (3.3)	3 (2.0)	5 (3.4)	3 (2.0)	4 (2.7)	20 (2.7)
Subjects Completed (%)	118 (78.7)	110 (74.8)	114 (76.5)	121 (82.3)	128 (87.7)	591 (80.0)

* After review of the clinical database, Sepracor determined that ten subjects who were discontinued from the study for reasons other than an adverse event had an adverse event near the time of study discontinuation that may have contributed to the reason for discontinuation. Narratives for these ten subjects are provided in Appendix 16.5.3.

† Narratives for subjects who discontinued the study due to an adverse event was derived from subject disposition data (Appendix 16.2.2.1).

Of the 739 subjects, 591 subjects (80.0%) completed the study and 148 subjects (20.0%) terminated early: 72 of 148 subjects (48.6%) experienced an adverse event, 34 (23.0%) voluntarily discontinued, 13 (8.8%) discontinued because of protocol violations, 5 (3.4%) were lost to follow-up, 4 (2.7%) did not meet entry criteria, and 20 (13.5%) discontinued for other reasons. The percentage of subjects who discontinued due to an adverse event was highest in the arformoterol 25 µg BID group and lowest in the salmeterol 42 µg BID group. Upon review of the clinical database, the Applicant determined that ten subjects who discontinued for reasons other than adverse events had an adverse event or other abnormality that may have contributed to study termination (two subjects each in the arformoterol 25 µg BID and 50 µg QD groups and three subjects each in the placebo and arformoterol 15 µg BID group).

The definition of important protocol deviations and the process for their review was specified prior to end of study unblinding. Important protocol deviations were applicable only to the ITT population. The first three categories of important protocol deviations were determined programmatically. For the "disallowed medication" deviations, all potentially disallowed coded medications were clinically reviewed on a per-subject basis. For the "other" important deviations, all investigator comments were clinically reviewed on a per-subject basis. The following Table lists and summarizes the defined categories of important protocol deviations by treatment group.

Study 091-051: Important Protocol Deviations (ITT Population)

Important Protocol Deviation*	Placebo (N=150)	ARF 15 µg BID (N=147)	ARF 25 µg BID (N=149)	ARF 50 µg QD (N=147)	Salmeterol 42 µg BID (N=146)
Any Important Deviation (%)	43 (29)	39 (26)	39 (26)	37 (25)	30 (20)
Did not meet inclusion/exclusion criteria (%)	16 (11)	23 (16)	13 (9)	16 (11)	12 (8)
Study medication compliance† (%)	17 (11)	15 (10)	11 (7)	10 (7)	8 (6)
Continuation criteria not met‡	1 (1)	0	5 (3)	5 (3)	1 (1)
Used disallowed medication (%)	7 (5)	7 (5)	10 (7)	5 (3)	5 (3)
Other important deviations§ (%)	11 (7)	10 (7)	13 (9)	14 (10)	17 (12)

*A subject may have had more than one IPD.
†Noncompliant subjects had compliance rates <80% or >120%.
‡At Visits 3, 5, or 7.
§ Important protocol deviations listed in the Investigator's comments log.

Of the 739 subjects in the ITT population, 188 (25.4%) subjects deviated from the protocol at least once during the double-blind treatment period; the placebo group had the highest percentage of protocol deviations. The most common important protocol deviation was failure to meet eligibility criterion (80/739, 10.8%), followed by noncompliance with study medication schedule (61/739, 8.2%).

Reviewer's Comment: Similar to the other pivotal study, 091-050, these protocol deviations were either fairly equally distributed across study treatment groups and/or were very small in number and would not be expected to influence the results or conclusions from the study.

Concurrent pulmonary medications used during the study were similar between treatment groups. Over 70% of subjects reported using at least one agent for COPD before Visit 1 which included albuterol (39 to 48%), salmeterol (14 to 21%), fluticasone (14 to 22%), ipratropium (15 to 24%), and Combivent® (25 to 34%).

Study Demographics

The following Table summarizes the demographic and baseline characteristics for the ITT population:

Study 091-051: Summary of Demographic and Other Baseline Characteristics

Parameter	Placebo (N=150)	ARF 15 µg BID (N=147)	ARF 25 µg BID (N=149)	ARF 50 µg QD (N=147)	Salmeterol 42 µg BID (N=146)
Age (yrs)					
Mean (SD)	63.3 (9.4)	63.2 (8.7)	63.7 (9.4)	62.1 (9.7)	62.3 (8.7)
25th percentile	57.0	57.0	57.0	55.0	57.0
Median	64.0	64.0	64.0	62.0	63.0
75th percentile	69.0	70.0	70.0	69.0	68.0
Sex (n,%)					
Male	86 (57.3)	94 (63.9)	94 (63.1)	87 (59.2)	83 (56.8)
Female	64 (42.7)	53 (36.1)	55 (36.9)	60 (40.8)	63 (43.2)
Race (n,%)					
Caucasian	146 (97.3)	138 (93.9)	142 (95.3)	139 (94.6)	138 (94.5)
Black	2 (1.3)	8 (5.4)	4 (2.7)	6 (4.1)	4 (2.7)
Asian	1 (0.7)	0	2 (1.3)	1 (0.7)	3 (2.1)
Hispanic	0	1 (0.7)	0	0	0
Other	1 (0.7)	0	1 (0.7)	1 (0.7)	1 (0.7)
Height (ins)					
Mean (SD)	67.0 (3.9)	67.6 (3.9)	67.2 (3.8)	67.1 (3.9)	67.2 (3.6)
25th percentile	63.8	65.0	64.5	64.2	64.2
Median	67.0	68.1	67.3	67.0	67.6
75th percentile	70.0	70.5	70.1	69.5	70.0
Weight (lbs)					
Mean (SD)	174.5 (43.2)	178.5 (40.3)	177.1 (41.1)	182.2 (46.4)	181.6 (44.7)
25th percentile	142.5	149.0	149.0	149.5	147.7
Median	167.6	175.9	174.2	174.0	176.9
75th percentile	195.0	203.0	198.2	213.8	209.4
FEV_1 (L)					
Mean (SD)	1.30 (0.4)	1.31 (0.5)	1.28 (0.5)	1.28 (0.4)	1.29 (0.5)
25th percentile	0.93	0.88	0.86	0.98	0.94
Median	1.25	1.20	1.18	1.22	1.18
75th percentile	1.60	1.56	1.57	1.50	1.54
FEV_1 % predicted† (%)					
Mean (SD)	43.6 (12.3)	42.3 (13.9)	41.6 (12.4)	42.4 (11.8)	42.6 (13.4)
25th percentile	34.5	31.0	32.0	32.4	32.5
Median	42.7	41.3	41.3	42.8	41.8
75th percentile	53.5	55.6	50.4	51.6	54.1
FEV_1/FVC ratio					
Mean (SD)	51.2 (10.7)	51.8 (11.1)	50.1 (9.6)	51.8 (10.3)	51.1 (10.4)
25th percentile	43.6	43.0	42.9	44.2	42.7
Median	51.6	52.4	51.1	51.6	51.2
75th percentile	57.9	60.4	57.4	59.6	59.4
FEV_1 % reversibility† (%)					
Mean (SD)	15.3 (13.5)	16.7 (14.7)	18.5 (16.4)	17.6 (13.7)	17.0 (14.1)
25th percentile	5.8	7.1	8.9	7.6	8.0
Median	13.4	14.8	16.3	16.8	14.7
75th percentile	23.4	23.4	24.2	25.2	23.7
Nonreversible subjects* (%)	19 (12.7)	28 (19.0)	21 (14.1)	27 (18.4)	20 (13.7)

* Subjects were classified as reversible if their FEV_1 percent reversibility was ≥10% for at least one of two (or three) visits prior to randomization; otherwise subjects were defined to be nonreversible.

† Predose FEV_1 and percent reversibility values provided are from the Week 1 visit.

Almost all the subjects in the study were Caucasian (95%). The male to female ratio was about 60:40 across all treatment groups. Age, and pulmonary characteristics, including reversibility, were fairly well balanced across treatment groups.

Reviewer's Comment: The Applicant knows that the lack of some diversity in the ethnic make-up of the studies is a review issue and will likely result in some type of post-market commitment on their part.

Analysis of Efficacy

The primary efficacy endpoint 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 groups and 24 hours post-dose for the QD treatment group) over 12 weeks of treatment. FEV1 trough data were also analyzed at individually for Visits 3, 5, and 7 (Weeks 0, 6, and 12). These data are summarized in the Table below.

Study 091-051: Percent Change in FEV1 from Study Baseline to the End of the Dosing Interval Over the 12-Week Double-Blind Period and at Weeks 0, 6, and 12 (ITT Population)

	Placebo (N=150)	ARF 15 µg BID (N=147)	ARF 25 µg BID (N=149)	ARF 50 µg QD (N=147)	Salmeterol 42 µg BID (N=146)
Baseline FEV_1 (L) (predose at Visit 3 [Week 0])					
n	147	145	148	144	143
Mean (SD)	1.21 (0.4)	1.21 (0.5)	1.19 (0.5)	1.16 (0.4)	1.21 (0.5)
Overall (Weeks 0 to 12)					
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)
Mean (SD)	6.4 (15.2)	17.2 (18.0)	22.7 (22.7)	19.4 (19.6)	18.3 (17.9)
Median	3.5	15.9	20.0	15.7	16.7
25th, 75th percentiles	-3.0, 11.3	5.7, 29.0	8.9, 34.7	7.3, 29.6	7.5, 28.3
P-value‡	--				
vs placebo	--	<0.001	<0.001	<0.001	<0.001
vs salmeterol	--	0.455	0.080	0.802	--
Week 0 (post-first dose)					
n	129	131	136	127	124
LS Mean (SE)*	6.3 (1.8)	20.8 (1.7)	26.3 (1.7)	21.7 (1.8)	20.7 (1.8)
Mean (SD)	6.3 (14.5)	21.8 (20.7)	27.1 (22.5)	23.1 (23.3)	21.7 (19.2)
Median	4.0	17.8	25.3	19.2	18.5
25th, 75th percentiles	-1.9, 12.3	6.5, 31.5	13.3, 39.9	8.5, 35.9	8.2, 33.9
P-value					
vs placebo	--	<0.001	<0.001	<0.001	<0.001
vs salmeterol	--	0.972	0.017	0.680	--
Week 6					
n	113	112	124	120	123
LS Mean (SE)*	4.9 (1.9)	13.4 (1.9)	20.4 (1.8)	16.6 (1.8)	16.7 (1.8)
Mean (SD)	5.4 (17.2)	14.0 (20.5)	21.8 (23.2)	18.2 (21.6)	17.4 (20.6)
Median	2.9	12.7	17.4	15.8	16.8
25th, 75th percentiles	-6.7, 12.7	2.8, 26.0	7.8, 32.0	4.6, 31.2	3.3, 28.8
P-value					
vs placebo	--	<0.001	<0.001	<0.001	<0.001
vs salmeterol	--	0.189	0.135	0.984	--
Week 12					
n	106	102	108	109	116
LS Mean (SE)*	4.6 (2.0)	12.9 (2.0)	16.2 (2.0)	15.2 (2.0)	14.5 (1.9)
Mean (SD)	4.7 (18.3)	14.0 (19.7)	17.8 (24.7)	16.4 (25.3)	15.7 (19.2)
Median	2.2	13.6	17.8	12.9	13.8
25th, 75th percentiles	-5.8, 12.3	0.5, 24.7	3.7, 29.8	1.4, 24.6	3.4, 27.3
P-value					
vs placebo	--	0.003	<0.001	<0.001	<0.001
vs salmeterol	--	0.544	0.521	0.807	--

Note: End of the dosing interval = 12 hours post-second dose for the BID treatment arms and 24 hours postdose for the QD treatment arm.

*From Repeated Measures Model: with fixed effects for treatment, time (Weeks 0, 6, and 12), treatment-by-time interaction, and site type, with baseline FEV_1 as a covariate, and treatment-by-baseline-FEV_1 interaction. P-values for the treatment-by-time interaction and treatment-by-baseline FEV_1 interaction were 0.069 and 0.185, respectively.

‡Bonferroni adjustment: comparison of 50 µg QD arformoterol dose versus placebo tested at the 0.0250 significance level, and two comparisons of each BID arformoterol dose versus placebo tested at the significance 0.0125 level. All other comparisons were tested at the 0.05 significance level.

Arformoterol at all 3 doses was statistically superior to placebo on the primary endpoint: FEV1 at trough from study baseline versus placebo over the 12-week double-blind treatment period (all p-values <0.001). The LS mean percent change in FEV1 from study baseline was greater for all arformoterol treatment groups than placebo, with treatment differences of 10.4% for arformoterol 15 µg BID, 15.7% for arformoterol 25 µg BID, and 12.5% for arformoterol 50 µg QD. A dose-response relationship in FEV1 at trough from study baseline was observed for the arformoterol BID dose groups. The mean percent change from study baseline in FEV1 for the salmeterol group was 12.0% greater than the placebo group. The percent improvement in FEV1 the end of the dosing interval demonstrated no significant differences between any of the arformoterol dosages and salmeterol. Arformoterol also won at each individual measurement time point (Weeks 0, 6, and 12). As would be expected, subjects whose FEV1 reversibility was < 10% prior to randomization improved less than those whose FEV1 reversibility was ≥ 10%. For nonreversible subjects, the overall mean improvement difference relative to placebo was 4.0 to 5.2% for the arformoterol dose groups, and 1% for the salmeterol dose group *[Table 11.4.1.1-2, clinstat\copd\091-051.pdf].*

Secondary Analyses

The Applicant listed a key secondary efficacy endpoint for the study as FEV1 time-normalized area under the percent change from visit predose curve over 12 hours ($nAUC_{0\text{-}12\text{-}P}$). The overall LS mean FEV_1 $nAUC_{0\text{-}12\text{-}P}$ was significantly improved for all arformoterol doses compared with placebo, and ranged from approximately 11 to 17% greater across the arformoterol groups compared with placebo. In addition, the mean FEV_1 $nAUC_{0\text{-}12\text{-}P}$ was significantly improved for all arformoterol doses compared to placebo at each study time point. Improvements in lung function appeared to increase with higher doses of arformoterol. *Reviewer's Comment: Similar to the 091-050 study, the 15 and 25 µg bid groups were very similar while the 50 µg qd group was about 5% greater than the lower doses. The fact that the measurement was taken at trough (12 hr) for the lower doses but after only half the dosing period had elapsed for the higher qd dose favored the high dose.*
Overall improvement in FEV_1 $nAUC_{0\text{-}12\text{-}P}$ was also approximately 3 to 9% greater for the arformoterol doses compared with salmeterol and was greater at each individual study time point as well. Salmeterol, however, was still significantly better than placebo (p = 0.02). *Reviewer's Comment: These differences were statistically different at the p < 0.05 level for all 3 formoterol doses. The high qd day dose would not be comparable for reasons given in the comment above. Salmeterol may be at a disadvantage in this type of measurement because it takes several hours to reach peak effect compared to formoterol.*

Subgroup analyses of subjects who demonstrated reversible (>10% response in FEV1 to albuterol) to those who were less reversible (< 10%) demonstrated greater responses in those who had demonstrated greater reversibility to albuterol. Again it appears that the arformoterol groups performed several percentage points higher than the salmeterol group.

Other Spirometric Secondary Analyses

- FEV_1 Time-normalized Area Under the Percent Change from Study Baseline Curve Over 12 Hours ($nAUC_{0\text{-}12\text{-}B}$)

All arformoterol doses had significantly (all p-values <0.001) greater increases in $nAUC_{0\text{-}12\text{-}B}$ compared with placebo, both averaged over the 12-week double-blind period and at Weeks 0, 6, and 12. Overall, improvement was statistically greater for the arformoterol 25 µg BID and 50 µg QD doses than for salmeterol.

- FEV_1 Time-normalized Area Under the Percent Change from Visit Predose Curve Over 24 hours ($nAUC_{0\text{-}24\text{-}P}$)

Approximately 20% of subjects remained in the clinic overnight and had at least one spirometry measurement taken at the 13, 14, or 16 hour time points. Subjects in all arformoterol treatment groups demonstrated significantly ($p<0.001$) greater FEV_1 AUC responses over 24 hours from visit predose over the double-blind period ($nAUC_{0\text{-}24\text{-}P}$) relative to placebo. Arformoterol also won at each individual time point (Weeks 0, 6, and 12). The extent of improvement in this small subset of subjects was not dose-dependent.

- FEV_1 Time-normalized Area Under the Percent Change from Study Baseline Curve Over 24 Hours ($nAUC_{0\text{-}24\text{-}B}$)

For this outcome variable, percent improvement in FEV_1 over 24 hours after dosing is compared to the FEV_1 value at the Week 0 (Visit 3) baseline. Again, approximately 20% of subjects remained in the clinic overnight and had at least one spirometry measurement taken at the 13, 14, or 16 hour time points. Subjects in all the arformoterol treatment groups had significantly improved time-normalized area under the FEV_1 percent change from study baseline curve over 24 hours ($nAUC_{0\text{-}24\text{-}B}$) compared with placebo over the double-blind period (all p values <0.001) and at Weeks 0, 6, and 12 (all p-values ≤ 0.012).

- Peak Percent of Predicted FEV_1

Subjects in all arformoterol treatment groups demonstrated significant (all p-values <0.003) improvement in mean peak percent of predicted FEV_1 compared with placebo, both over the double-blind period and at Weeks 0, 6, and 12.

- Peak Percent Change in FEV_1

Subjects in all arformoterol treatment groups demonstrated significant improvement in mean FEV_1 peak percent change from visit predose when compared with placebo both over the double-blind period and at Weeks 0, 6, and 12 (all p-values ≤ 0.001). There is evidence of a dose-response. All arformoterol treatments were significantly better than salmeterol (all p-values ≤ 0.007), except for arformoterol 15 µg BID at Weeks 0 and 6.

- Predose FEV_1 and Percent Predicted FEV_1

Mean predose FEV_1 values were between 1.16 and 1.21 L and mean predose FEV_1 percent predicted values were between 38.4 and 40.8% for all treatment groups at Week 0. Mean predose FEV_1 and mean predose percent predicted FEV_1 increased over the double-blind period for all treatment groups.

- Time Point Changes in FEV_1

Changes at specific FEV_1 time points were assessed for Weeks 0, 6, and 12. All subjects had spirometry assessments scheduled at all time points between predose and 12-hours post-dose, as well as at 23 and 24 hours post-dose while a subset of approximately 20% subjects had spirometry values scheduled at 13, 14, and 16 hours post-dose. All endpoints show that both the arformoterol and salmeterol BID doses achieved a second increase in FEV_1 values following the second daily dose after 12 hours.

- Time to Onset of Response

A responder was defined as a subject who achieved at least a 10% increase in FEV_1 from predose values within 12 hours after dosing. At Week 0, a 10% response in FEV_1 was achieved with a median of 2-3 minutes of dosing for all the arformoterol groups, compared with a median of approximately 13 minutes for the salmeterol group. At Weeks 6 and 12, the median time to achieve a 10% increase in FEV_1 for all arformoterol groups ranged from 3 to 25 minutes, compared with about 2.5 hours for salmeterol.

- Time to Peak Change in FEV_1

The median peak change in FEV_1 occurred from 178 to 212 minutes approximately for all dose groups after the first dose at Week 0. At Weeks 6 and 12, the median time to peak change decreased for all arformoterol treatment groups, occurring in about one hour.

- In-clinic and At-home Peak Expiratory Flow Rate (PEFR)

The in-clinic average PEFR values increased about 0.30 L/sec in the active treatment groups and 0.0-0.1 L/sec in the placebo group by 15 minutes after dosing. The morning and evening at-home average PEFR values increased in the first three weeks of the double-blind treatment (Weeks 0 to 3) for all active treatment groups. These increases (0.3-0.5 L/sec) were maintained throughout the 12-week double-blind treatment period.

- Ipratropium Bromide MDI Supplemental Use

Prior to randomization, ipratropium bromide use was similar across treatment groups. Over 83% of subjects across treatment groups used ipratropium bromide prior to randomization. Average use was approximately four days per week and approximately three actuations per day. Ipratropium use declined by about 0.5 days per week more in the active treatment groups than in the placebo group during the double-blind period. Similarly, ipratropium use declined by about 0.5-1.0 actuations per day more in the active treatment groups than the change observed in the

placebo group. The decline in ipratropium use in the salmeterol group versus placebo was similar to that of subjects treated with arformoterol.

- Racemic Albuterol MDI Rescue Use

Prior to randomization, over 78% of subjects across treatment groups reported racemic albuterol MDI rescue use. Average use was approximately three to four days per week with two actuations per day. A decline in rescue albuterol use in excess of that seen in the placebo group was observed throughout the 12-week duration of the trial, both for mean number of days used per week (0.6 to 0.8 days/week), as well as mean number of actuations used per day (0.6 to 1.0 actuations/day) for all active treatment groups.

- COPD Symptom Ratings

Across all treatment groups, morning ratings for the mean number of symptom-free days/week at baseline ranged between 3.5 and 3.8 days. Over the double-blind period, the arformoterol dose groups demonstrated an increase in symptom-free days/week that ranged between 0.55 days/week for arformoterol 15 μg BID and 0.78 days/week for arformoterol 25 μg BID. By comparison, placebo symptom-free days increased by 0.39 days/week and salmeterol increased by 0.75 days/week. When subjects assessed their symptoms in the evening, a majority (>75%) of subjects in all treatment groups reported no symptom-free days/week throughout the single-blind period. The mean number of symptom-free days increased for all active treatment groups and ranged from 0.11 days/week for the arformoterol 15 μg BID group to 0.35 days/week for the arformoterol 25 μg BID group; the placebo group increased by a mean of 0.08 days/week.

- St. George's Hospital Respiratory Questionnaire

After six weeks of double-blind treatment, total scores improved in all active treatment groups, with mean changes in total scores ranging between -2.6 and -3.5 units for arformoterol treated subjects. The placebo group, by comparison, changed by -0.2 units.

- Subject/Investigator Global Evaluations

Between 71 and 79% of subjects in active treatment groups reported that their symptoms were slightly-to-much improved, compared with approximately 65% of subjects in the placebo group. These patterns were similarly observed for the Investigator global evaluation data.

- Baseline Dyspnea Index/Transitional Dyspnea Index (BDI/TDI)

The BDI was assessed predose during the single-blind period (Visit 2); the baseline focal score (range, 0 to 12) was defined as the sum of the Functional Impairment, Magnitude of Task, and Magnitude of Effort scores. The TDI was assessed predose at Weeks 6 and 12. Mean TDI scores improved in all active treatment groups during the double-blind period: by 1.6 to 2.1 units in the arformoterol groups, by 2.2 units in the salmeterol group, and by 1.3 units in the placebo group.

- Six-Minute Walk

The results of the six-minute walk test suggested substantial exercise compromise in all groups, with the median distance walked at baseline ranging from 1015 to 1109 feet. By Week 9, modest (13-53 feet) improvement in walk distance was observed in the arformoterol-treated groups and salmeterol-treated group (72 feet). However, the placebo group had also improved by 47 feet at Week 9.

Pharmacokinetic Data

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

Pharmacokinetic assessments were performed on a subset of ITT subjects (approximately 50% of subjects) at identified sites. Blood for determination of plasma concentrations was drawn predose and at 10 minutes, two and six hours post-first dose at Weeks 0, 6, and 12. Plasma concentration-time profiles increased with administration of higher total daily doses of arformoterol. Trough plasma concentrations (predose concentrations at Weeks 6 and 12) obtained after a 50 µg QD dose were similar to those observed following a 25 µg BID dose. Using mean plasma concentrations at 0.17 hours to approximate the expected time of C_{max}, 30 to 105% accumulation was noted with multiple doses at six and 12 weeks, respectively. No apparent relationship was observed between time-matched plasma concentrations and percent change in FEV_1 from visit predose values when viewing the data in aggregate. Of note is that measurable concentrations of arformoterol were observed in 25%) and 27% of analyzed samples in the placebo group and salmeterol groups, respectively. In addition, in the arformoterol dosing groups, approximately 27% (56 of 207 samples) of predose samples at Visit 3 (baseline) had measurable concentrations.
Reviewer's Comment: Unless there is some cross-reactivity in the assays for arformoterol and albuterol, it appears that some of the subjects were self medicating with formoterol. The number of arformoterol positive samples was balanced between the treatment groups.

Efficacy Conclusions

Primary Endpoint
All arformoterol doses were superior to placebo on the specified primary endpoint: per cent change in trough FEV_1 from study baseline over the 12-week double-blind treatment period. Arformoterol also demonstrated superiority separately at Weeks 0, 6, and 12. While improvement in trough FEV_1 remained significant for all treatment groups compared with placebo, the percent improvement in mean FEV_1 trough values decreased over the course of the study treatment period.

The percent improvement in the trough FEV_1 was similar for all doses of arformoterol compared with salmeterol over the 12-week double-blind treatment period and separately at Weeks 0, 6, and 12.

Secondary Endpoints
Arformoterol was statistically superior to placebo or trended toward improvement for most of the secondary endpoints.

A key secondary endpoint was FEV1 time-normalized area under the percent change from visit predose curve over 12 hours ($nAUC_{0\text{-}12\text{-}P}$). All arformoterol doses significantly improved FEV_1 $nAUC_{0\text{-}12\text{-}P}$ compared with placebo. All arformoterol doses demonstrated greater improvement in FEV_1 $nAUC_{0\text{-}12\text{-}P}$ than salmeterol over the 12 weeks of treatment.

For other secondary endpoints, all arformoterol doses demonstrated significant overall improvement versus placebo for the following spirometry-derived secondary endpoints: FEV_1 $nAUC_{0\text{-}12\text{-}B}$, FEV_1 $nAUC_{0\text{-}24\text{-}P}$, FEV_1 $nAUC_{0\text{-}24\text{-}B}$, peak percent of predicted FEV_1, and peak percent change in FEV_1 from visit predose or baseline.

The proportion of subjects who required supplemental (ipratropium bromide or albuterol) medications during the double-blind treatment period was 8-11% lower in the arformoterol groups than the placebo group. There was no difference compared to salmeterol.

Descriptive analysis of symptom and functional improvement assessed in the St. George's Hospital Respiratory Questionnaire, Subject & Investigator Global Evaluations, and Baseline/Transitional Dyspnea Indices (BDI/TDI), all trended toward a greater improvement in arformoterol treatment groups relative to placebo.

Safety Review

The safety findings from this study, along with the safety data from the other placebo-controlled studies, will be reviewed in depth in the Integrated Review of Safety section of this review. Brief observations are described below.

Of the 717 subjects in the ITT population, 587 subjects (81.9%) completed the full duration of treatment. The mean number of days that subjects received study medication was similar across treatment groups (73 to 79 days) and the median number of days in each treatment group was 85 days. The extent of exposure for individual subject is shown in the following Table.

Study 091-051: Extent of Exposure During the Double-Blind Treatment Period (ITT Population)

	Placebo (N=143)	ARF 15 µg BID (N=141)	ARF 25 µg BID (N=143)	ARF 50 µg QD (N=146)	Salmeterol 42 µg BID (N=144)
Duration (days)					
Mean (SD)	73.2 (25.8)	78.9 (19.3)	74.1 (24.6)	78.2 (18.9)	75.2 (22.8)
Median	85.0	85.0	85.0	85.0	85.0
Cumulative Dose (µg)*					
Mean (SD)	--	2317.3 (587.6)	3620.8 (1205.3)	3841.1 (952.1)	6147.2 (1997.4)
Median	--	2535	4175	4200	7056

*Cumulative dose not calculated for placebo subjects.

The overall occurrence of treatment-emergent adverse events in the ITT population during the double-blind period was similar across treatment groups (from 67.4 to 72.0%). Respiratory infection was reported by >10% of subjects in all treatment groups. Other frequently reported events (>5% in any of the treatment groups) were tremor, chest pain, headache, pain, nausea, bronchitis, COPD, pharyngitis, sinusitis, and urinary tract infection. Adverse events assessed as severe occurred with the highest frequency in the arformoterol 25 µg BID group (11.9%), followed by placebo-treated subjects (10.5%). The occurrence of potentially related adverse events was similar across treatment groups, ranging from 24.1 to 32.2%, and was highest in the arformoterol 50 µg QD group.

Adverse events that occurred in ≥2% of subjects in any treatment group during the double-blind treatment period are presented for the ITT population in the following Table:

Study 091-051: Adverse Events Occurring in ≥ 2% of Subjects in any Treatment Group During the Double-Blind Period

BODY SYSTEM Preferred term	Placebo (N=143)	ARF 15 µg BID (N=141)	ARF 25 µg BID (N=143)	ARF 50 µg QD (N=146)	Salmeterol 42 µg BID (N=144)
	n (%)	n (%)	n (%)	n (%)	n (%)
ANY EVENT	103 (72.0)	95 (67.4)	101 (70.6)	104 (71.2)	99 (68.8)
BODY AS A WHOLE					
Abdominal pain	2 (1.4)	1 (0.7)	3 (2.1)	1 (0.7)	1 (0.7)
Accidental injury	3 (2.1)	3 (2.1)	5 (3.5)	7 (4.8)	5 (3.5)
Asthenia	1 (0.7)	1 (0.7)	4 (2.8)	6 (4.1)	1 (0.7)
Back pain	1 (0.7)	7 (5.0)	3 (2.1)	4 (2.7)	1 (0.7)
Chest pain	9 (6.3)	7 (5.0)	3 (2.1)	6 (4.1)	7 (4.9)
Chills	2 (1.4)	3 (2.1)	0	2 (1.4)	0
Fever	1 (0.7)	3 (2.1)	2 (1.4)	5 (3.4)	3 (2.1)
Flu syndrome	2 (1.4)	7 (5.0)	4 (2.8)	4 (2.7)	1 (0.7)
Headache	12 (8.4)	10 (7.1)	9 (6.3)	13 (8.9)	15 (10.4)
Infection	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	3 (2.1)
Neck pain	2 (1.4)	2 (1.4)	3 (2.1)	0	1 (0.7)
Pain	6 (4.2)	11 (7.8)	9 (6.3)	14 (9.6)	10 (6.9)
CARDIOVASCULAR					
Hypertension	3 (2.1)	3 (2.1)	3 (2.1)	3 (2.1)	1 (0.7)
Migraine	0	0	0	3 (2.1)	0
Palpitation	2 (1.4)	0	3 (2.1)	1 (0.7)	3 (2.1)
Tachycardia	2 (1.4)	1 (0.7)	1 (0.7)	1 (0.7)	3 (2.1)
Ventricular extrasystoles	4 (2.8)	0	1 (0.7)	1 (0.7)	3 (2.1)
Ventricular tachycardia	4 (2.8)	0	2 (1.4)	1 (0.7)	1 (0.7)
DIGESTIVE					
Diarrhea	5 (3.5)	7 (5.0)	7 (4.9)	2 (1.4)	0
Dyspepsia	7 (4.9)	3 (2.1)	5 (3.5)	1 (0.7)	4 (2.8)
Gastrointestinal disorder	3 (2.1)	1 (0.7)	0	1 (0.7)	1 (0.7)
Nausea	9 (6.3)	7 (5.0)	6 (4.2)	5 (3.4)	1 (0.7)
Vomiting	1 (0.7)	4 (2.8)	4 (2.8)	3 (2.1)	1 (0.7)
HEMIC & LYMPHATIC					
Anemia	0	0	3 (2.1)	0	1 (0.7)
Leukocytosis	0	0	2 (1.4)	3 (2.1)	0
METABOLIC & NUTRITIONAL					
Hyperkalemia	3 (2.1)	1 (0.7)	1 (0.7)	2 (1.4)	3 (2.1)
Hypokalemia	2 (1.4)	2 (1.4)	4 (2.8)	1 (0.7)	0
Peripheral edema	1 (0.7)	3 (2.1)	3 (2.1)	2 (1.4)	3 (2.1)
MUSCULO-SKELETAL					
Arthralgia	0	1 (0.7)	1 (0.7)	3 (2.1)	0
Leg cramps	2 (1.4)	2 (1.4)	6 (4.2)	4 (2.7)	3 (2.1)
Myalgia	0	1 (0.7)	2 (1.4)	5 (3.4)	0
NERVOUS					
Anxiety	2 (1.4)	3 (2.1)	2 (1.4)	3 (2.1)	0
Dizziness	3 (2.1)	2 (1.4)	5 (3.5)	3 (2.1)	4 (2.8)
Hypertonia	0	0	3 (2.1)	1 (0.7)	1 (0.7)
Hypesthesia	0	0	0	0	3 (2.1)
Insomnia	2 (1.4)	4 (2.8)	7 (4.9)	4 (2.7)	1 (0.7)
Nervousness	0	2 (1.4)	2 (1.4)	5 (3.4)	0
Tremor	0	1 (0.7)	2 (1.4)	15 (10.3)	0

Study 091-051: Adverse Events Occurring in ≥ 2% of Subjects in any Treatment Group During the Double-Blind Period continued

BODY SYSTEM Preferred term	Placebo (N=143)	ARF 15 µg BID (N=141)	ARF 25 µg BID (N=143)	ARF 50 µg QD (N=146)	Salmeterol 42 µg BID (N=144)
	n (%)	n (%)	n (%)	n (%)	n (%)
RESPIRATORY					
Bronchitis	8 (5.6)	8 (5.7)	9 (6.3)	7 (4.8)	3 (2.1)
COPD	12 (8.4)	8 (5.7)	9 (6.3)	10 (6.8)	15 (10.4)
Cough increased	3 (2.1)	5 (3.5)	7 (4.9)	4 (2.7)	7 (4.9)
Dyspnea	1 (0.7)	5 (3.5)	4 (2.8)	5 (3.4)	5 (3.5)
Infection	23 (16.1)	21 (14.9)	19 (13.3)	17 (11.6)	16 (11.1)
Lung disorder	1 (0.7)	3 (2.1)	2 (1.4)	1 (0.7)	1 (0.7)
Pharyngitis	11 (7.7)	4 (2.8)	4 (2.8)	8 (5.5)	13 (9.0)
Pneumonia	3 (2.1)	0	3 (2.1)	0	0
Rhinitis	7 (4.9)	7 (5.0)	4 (2.8)	5 (3.4)	7 (4.9)
Sinusitis	6 (4.2)	7 (5.0)	9 (6.3)	3 (2.1)	8 (5.6)
Voice alteration	3 (2.1)	3 (2.1)	2 (1.4)	1 (0.7)	0
SKIN					
Rash	2 (1.4)	3 (2.1)	4 (2.8)	0	2 (1.4)
SPECIAL SENSES					
Conjunctivitis	3 (2.1)	0	2 (1.4)	1 (0.7)	0
UROGENITAL					
Hematuria	0	2 (1.4)	2 (1.4)	4 (2.7)	2 (1.4)
Urinary tract infection	7 (4.9)	8 (5.7)	1 (0.7)	4 (2.7)	9 (6.3)
Urine abnormality	2 (1.4)	3 (2.1)	2 (1.4)	2 (1.4)	1 (0.7)

The incidence of cardiovascular events ranged from 7.1 to 16.0% (Table 14.3.1.3). None of these cardiovascular events appeared to increase with increasing doses of arformoterol, and were similar to placebo. The occurrence of respiratory events was evenly distributed across all treatment groups, and ranged from 33.6 to 39.9%. The rates of bronchitis, cough increased, dyspnea, and lung disorder (pulmonary congestion, chest congestion, upper respiratory congestion, or increased congestion) did not increase with increasing doses of arformoterol. Respiratory infection rates were greater than 10% for all treatment arms with the highest rate reported in the placebo group (16.1%). Adverse events considered by the Investigator to be potentially related to treatment occurred at roughly the same rate (24.1 to 25.9%) across treatment groups, except for the arformoterol 50 µg QD group (32.2%). Potentially related adverse events that were reported for ≥ 2% of subjects in the arformoterol 50 µg QD group and greater than placebo include tremor (9.6%), COPD exacerbation (4.1%), respiratory infection (3.4%), headache (2.7%), nervousness (2.7%), pharyngitis (2.7%), and dyspnea (2.1%). Only two events were assessed by the Investigator as definitely related to study medication, hypokalemia and tremor, both in the arformoterol 25 µg BID group.

B Supportive Studies

Long-term Safety Study 091-060

Title of Study: A Multicenter, Open-Label, Randomized, Active-Controlled, Parallel Group Chronic Safety Study of Arformoterol in the Treatment of Subjects with Chronic Obstructive Pulmonary Disease

Design
This was an open-label, multicenter, randomized, active-controlled, parallel group, outpatient, study of one year duration to evaluate the long-term safety of arformoterol in the treatment of subjects with COPD. Randomization was performed in a 2:1 ratio of arformoterol 50 μg QD by nebulization to salmeterol 42 μg BID by MDI.

Duration
The duration of active treatment was 12 months. The study was performed during the period of June 17, 2002, to December 30, 2004. The final study report is dated October 4, 2005.

Study Centers
The study was conducted at 85 US centers in the following states: AL, AR, AZ, CA, CO, FL, GA, ID, IL, IN, KS, LA, MA, ME, MI, MO, MN, MT, NC, ND, NM, NJ, NV, NY, OH, OK, OR, PA, SC, TN, TX, VA, WA, and WV.

Population
A total of 799 subjects with relatively stable, moderately severe COPD were randomized into the study with 793 analyzed (ITT). A total of 468 completed the study, 307 arformoterol 50 μg QD, and 161 salmeterol 42 μg BID.

Treatments Administered
Each study subject was randomized to receive either arformoterol tartrate inhalation solution in unit dose vials (UDVs) at a dose of 50 μg QD or salmeterol at a dose of 42 μg BID via MDI. Arformoterol solution was delivered via a PARI LC PLUS nebulizer and a PARI Dura-neb 3000 compressor.

Materials
The open-label study treatments were:

- Arformoterol inhalation solution of 50 μg in 2 mL volume
- Salmeterol MDI 42 μg/actuation

Commercially available salmeterol was provided as a 13-g canister containing 120 actuations. Commercially available racemic albuterol MDI (17-g canister/200 inhalations) was provided to each study site for use by subjects as rescue medication for bronchospasm and acute treatment of COPD symptoms as needed throughout the study. Commercially available ipratropium MDI

(Atrovent 14-g canister/200 inhalations) was also provided to each study subject for use as supplemental medication for COPD as needed throughout the study.

Study 091-060: Drug Supply Lot Numbers

Product	Lot #
Arformoterol 50 mcg/2 mL	03501C, 00902D, 02403C
Serevent® (salmeterol) 13.0 g MDI	1ZP2519, 3ZP0323
Albuterol 17.0 g MDI	17801, 05402, 04003
Atrovent® (ipratropium)14.0 g MDI	011090W, 030110W

Objectives
The primary objective of this study was to evaluate the long-term safety of arformoterol 50 μg QD over a period of 12 months in subjects with COPD.

The secondary objective was to monitor the long-term efficacy of arformoterol 50 μg QD in subjects with COPD.

Study-Specific Inclusion Criteria

- Male and female subjects ≥35 years of age that provided written informed consent prior to participation.
- Subjects with a confirmed diagnosis of COPD, which may have included components of chronic bronchitis and/or emphysema.
- Subjects with a minimum smoking history of 15 pack-years
- Subjects with a Medical Research Council (MRC) Dyspnea Scale Score ≥2.
- Subjects with a baseline FEV1 ≤65% of predicted normal value and >0.7 L documented prior to randomization.
- Subjects with an FEV1/forced vital capacity (FVC) ratio ≤70% documented prior to randomization.
- Subjects with a chest x-ray that was consistent with the diagnosis of COPD and taken ≤3 months prior to Visit 1. If there was not chest x-ray taken 3 months prior to Visit 1, a chest x-ray was performed prior to Visit 2. This requirement was waived for subjects who participated in 091-050 or 091-051.

Notable Exclusion Criteria

The following individuals were ineligible for study participation:

- Female subjects who were pregnant or lactating.
- Subjects who were currently using disallowed medications or were unable to complete the medication washout periods.
- Subjects with life-threatening/unstable respiratory status, including upper or lower respiratory tract infection, within the previous 30 days prior to Visit 1.

- Subjects who had a change in dose or type of any medications for COPD within 14 days prior to the screening visit.
- Subjects who were scheduled for in-patient hospitalization, including elective surgery (in-patient or out-patient) during the trial.
- Subjects with clinically significant abnormal laboratory values (hematology, blood chemistry, or urinalysis) at Visit 1.
- Subjects with a known history of asthma or any chronic respiratory disease (including a current history of sleep apnea) other than COPD (chronic bronchitis and/or emphysema).
- Subjects with a blood eosinophil count >5%.
- Subjects with clinically significant cardiac, hepatic, renal, gastrointestinal, endocrine, metabolic, neurologic, or psychiatric disorder that may have interfered with successful completion of this protocol.
- Subjects with a history of cancer except non-melanomatous skin cancer. Subjects with a history of cancer that was considered surgically cured and without a recurrence within the past 10 years were allowed to participate. History of hematologic/lymphatic malignancy treated with chemotherapy or radiation was not allowed.
- Subjects with a history of lung resection of more than one full lobe.
- Subjects who required continuous supplemental oxygen therapy (unless subject resided at elevations of ≥ 4000 feet). The use of supplemental oxygen, not to exceed 2 L/min, at nighttime only and/or only during exercise was allowed.
- Subjects with a known sensitivity to arformoterol, ipratropium, salmeterol, or albuterol, or any excipients contained in any of these formulations.
- Subjects with clinically significant abnormalities that may have interfered with the metabolism or excretion of the study drug (e.g., abnormalities of the renal, hepatic, metabolic, or endocrine function).
- Subjects with a history of substance abuse or drug abuse within 12 months of Visit 1 or with a positive urine drug screen at Visit 1.
- Subjects with clinically significant abnormal 12-lead ECG that may have jeopardized the subject's ability to complete the study.
- Subjects using any prescription drug for which concomitant Beta-agonist administration is contraindicated (e.g., Beta-blockers).

Study 091-060: Disallowed Medications

Disallowed Medication	Withdrawal Time Prior to Visit 1
albuterol	≥6 hours and study duration*
ipratropium	≥6 hours and study duration*
Combivent®	≥6 hours and study duration
levalbuterol	≥8 hours and study duration
pirbuterol	≥8 hours and study duration
salmeterol (or any inhaled long-acting bronchodilator)	≥24 hours and study duration
controlled-release theophylline preparations	≥48 hours and study duration
cromolyn sodium and nedocromil sodium	≥7 days and study duration
Foradil® (formoterol fumarate)	≥10 days and study duration
methylphenidate HCl	≥30 days and study duration
monoamine oxidase inhibitors	≥30 days and study duration
tricyclic antidepressants	≥30 days and study duration
protease inhibitors	≥30 days and study duration

* with the exception of use as directed in the event of worsening COPD

If the subject required one of the disallowed medications in the table above during the study, the subject was discontinued from the study and completed an Early Termination Visit.

Study Design and Conduct
The Study schedule is summarized in the following Tables.

Study 091-060 Schedule of Assessments */clinstat\copd\091-060, p. 29/*

	Visit 1 Screen (Visit 8 in previous study)	OR	Visit 1 Screen for *de novo* Subjects[a]	Visit 2[b] Randomize		Visit 3 Interim Safety		Visit 4 Interim Safety		Visit 5 Interim Safety		Visit 6 Interim Safety		Visit 7 Interim Safety		Visit 8 Interim Safety
Week	-7 to –5 days		-7 to –5 days	0	1&2	3	4&5	6	7&8	9	10,11, 12	13	19	26	32	39
ASSESSMENTS																
Informed consent[c]	X		X													
Inclusion/exclusion criteria (review)	X		X	X												
Prior/concomitant medications	X[d]		X[d]	X		X		X		X		X		X		X
Medical/COPD history COPD symptoms			X													
Medical Research Council (MRC) Dyspnea Scale			X													
Baseline Dyspnea Index (BDI)	X[d]		X													
Chest x-ray[e]			X													
Reversibility testing (albuterol)	X		X													
Serial spirometry[f]			X[d]	X								X		X		X
Record PEFSL				X												
Physical examination	X[d]		X[d]													
Weight/height[d]	X		X[d]													

[a] Visit 1 screen was also required for subjects who completed Studies 091-050 or 091-051 ≥1 month prior to participating in Study 091-060.

[b] Randomization occurred at Visit 2.

[c] Women of childbearing potential were also required to sign the Women of Childbearing Potential Addendum.

[d] Subjects who did not participate in Studies 091-050 or 091-051 had these assessments done at Visit 1. End of study procedures from the previous COPD studies (Studies could have served as baseline assessments at Visit 1. BDI for crossover subjects taken from Visit 2 of the pivotal study. The urine drug screen was done at Visit 2 if the positive.

[e] A chest x-ray was required if one had not been performed ≤3 months prior to study entry; a chest x-ray was not required for subjects previously enrolled in Studies 091-0

[f] PFTs were preformed during Visits 2, 6, 7, 8, and 9 predose, immediately postdose, and at 1, 2, 3, and 4 hours postdose.

Schedule of Assessments (continued)

	Visit 1 Screen (Visit 8 in previous study)	OR	Visit 1 Screen for *de novo* Subjects[a]	Visit 2[b] Randomize		Visit 3 Interim Safety		Visit 4 Interim Safety		Visit 5 Interim Safety		Visit 6 Interim Safety		Visit 7 Interim Safety		Visit 8 Interim Safety
Week	-7 to –5 days		-7 to –5 days	0	1&2	3	4&5	6	7&8	9	10,11, 12	13	19	26	32	39
ASSESSMENTS																
Vital signs (BP, HR, RR, oral temperature)[i]	X[d]		X[d]	X		X		X		X		X		X		X
12-lead ECG[j]	X[d]		X[d]	X		X		X		X		X		X		X
Attach/remove 24-hr Holter monitor[k]			X	X								X		X		X
Clinical laboratory evaluations (blood/urine)[l]	X[d]		X[d]	X		X		X		X		X		X		X
Glucose and potassium levels[m]	X[d]		X[d]	X		X		X		X		X		X		X
Serum theophylline levels[n]	X[d]		X[d]	X		X		X		X		X		X		X
Urine drug screen	X[d]		X[d]	X[d]												
Serum β-hCG[o]	X[d]		X[d]													
FSH level (if applicable)[o]			X													
Urine pregnancy test[p]														X		

[i] Vital signs were obtained once at Visits 1, 3, 4, 5, and 10, and predose, immediately postdose, and 1, 2, 3, and 4 hours postdose at Visits 2, 6, 7, 8, and 9.

[j] ECG was performed once at Visits 1 and 10, and predose and 2 hours postdose at Visits 2 through 9.

[k] The Holter monitor was placed at Visit 1 for *de novo* subjects, and at predose at Visits 2, 6, 7, 8, and 9 for all subjects. Subjects were required to return to the clinic 24 ho *novo* subjects) and at Visits 2, 6, 7, 8, and 9 (for all subjects) to remove the Holter monitor.

[l] Clinical laboratory tests were done once at Visits 1 through 10.

[m] Glucose and potassium levels were done predose and 2 hours post-first dose at Visits 2, 6, 7, 8, and 9, and once at Visits 1, 3, 4, 5, and 10.

[n] Serum theophylline levels were obtained (if the subject was taking theophylline preparations) once at Visits 1 through 10.

[o] Serum FSH for all applicable women (see Inclusion Criterion 3).

[p] Serum β-hCG and urine pregnancy tests for all women ≤65 years of age.

Schedule of Assessments (continued)

	Visit 1 Screen (Visit 8 in previous study)	OR	Visit 1 Screen for *de novo* Subjects[a]	Visit 2[b] Randomize		Visit 3 Interim Safety		Visit 4 Interim Safety		Visit 5 Interim Safety		Visit 6 Interim Safety		Visit 7 Interim Safety		Visit 8 Interim Safety
Week	-7 to -5 days		-7 to -5 days	0	1&2	3	4&5	6	7&8	9	10,11,12	13	19	26	32	39
ASSESSMENTS																
PK blood sample[a]				X										X		
Administer study medication				X		X		X		X		X		X		X
Dispense study medication				X		X		X		X		X		X		X
Re(dispense) supplemental/ rescue medication as needed	X		X	X		X		X		X		X		X		X
Dispense/collect COPD questionnaire[f]	X		X	X		X		X		X		X		X		X
Dispense/collect Medical Event Calendar	X		X	X		X		X		X		X		X		X
Dispense/collect PEF/study drug/rescue med logs	X		X	X		X		X		X		X		X		X
Subject/Investigator Global Evaluations[g]	X		X													
Transitional Dyspnea Index (TDI)																
St. George's Hospital Respiratory Questionnaire	X		X													
Assess adverse events[i]	X[a]		X[i]	X		X		X		X		X		X		X
Telephone contact[k]					X		X		X		X		X		X	

[a] One plasma sample for PK analysis was collected from subjects pre-first dose and 2 hours after study drug administration at the randomization visit (Visit 2) and at an inte once at the End of Study visit.

[f] COPD questionnaire was completed by the subject at home in the morning (upon rising) and in the evening (prior to bedtime) for the 2 days prior to Visits 2 through 9.

[g] The Subject and Investigator Global Evaluations were done at separate times and with no knowledge on the part of the Investigator of the Subject's ratings. The subject co at the beginning of the study visit; the Investigator completed their evaluation after review of medical history and concomitant medications, physical examination, and PF

[i] Ongoing adverse events at the end of study visit for ongoing Sepracor COPD studies (if applicable) were recorded as baseline medical conditions for Study 091-060.

[k] Telephone contact between visits were conducted directly with the subject.

Study participation consisted of a total of ten visits over12 months. Study participants consisted of subjects who previously completed one of the pivotal studies (019-050 or 091-051) (i.e., rollover subjects), and subjects who did not previously participate in 091-050 or 091-051 (i.e., de novo subjects).

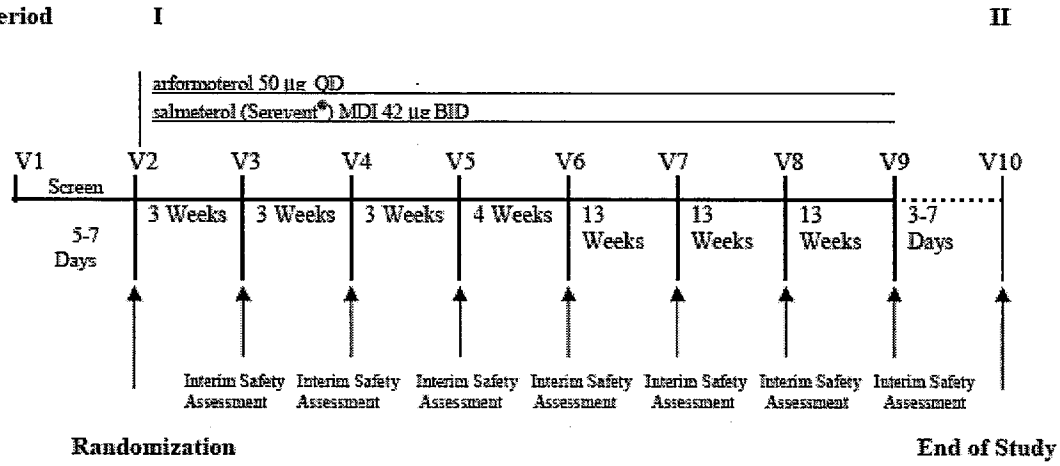
For Screening (Visit 1) procedures, the End of Study assessments from the previous COPD studies served as the baseline assessments for subjects who rolled over into the study after completion of one of the two pivotal trials (091-050 or 091-051). De novo subjects and subjects who completed Study 091-050 and 091-051 but enrolled ≥4 weeks after study completion had screening visit assessments completed at Visit 1. Period I (Visits 2-9) was a 12-month open-label treatment period wherein subjects were randomized in a 2:1 ratio to arformoterol 50 µg QD by nebulization or salmeterol 42 µg BID by MDI. During Period II (End of Study; Visit 10), subjects returned for an End of Study evaluation 3-7 days after Visit 9.

At Visits 3, 4, and 5, all subjects remained in the clinic for approximately 2 hours for safety evaluation and received their morning dose of study medication in the clinic. Vital signs were obtained prior to dosing at each visit. At Visits 2, 6, 7, 8, and 9, all subjects remained in the clinic for approximately five hours and received their morning dose of study medication in the clinic. Vital signs were obtained and pulmonary function tests (PFTs) were performed predose, immediately postdose, and at 1, 2, 3, and 4 hours postdose. Twenty-four (24)-hour Holter monitoring was performed at Visits 2, 6, 7, 8, and 9 for all subjects, and also at Visit 1 for de novo subjects. Standard 12-lead electrocardiograms (ECG) were performed once at Visits 1 and 10, and predose and two hours postdose at all other visits. Blood for pharmacokinetic (PK) analysis was collected predose and two hours postdose at Visits 2 and 7, and once at Visit 10. Clinical safety laboratory tests were done at every visit. The subject's COPD questionnaire, medical event calendar (MEC), and the peak expiratory flow (PEF)/study drug/rescue medication logs were reviewed.

Subjects were contacted by telephone at Weeks 1, 2, 4, 5, 7, 8, 10, 11, 12, 19, 32, and 45 (between study visits) to confirm adherence to and proper administration of study medications, to inquire about any adverse events and use of any concomitant medications, to remind subjects to complete the medical event calendar (MEC), study drug/rescue medication logs, peak expiratory flow rate (PEFR), and COPD questionnaire, to remind subjects to withhold the use of disallowed medications, and to confirm the next clinic appointment. An unscheduled visit could have been conducted between clinic visits if the subject experienced a significant or serious adverse event. An early termination visit was conducted if the subject was withdrawn from the study after Visit 2 or prior to completion of all study visits. For standardization, all study visits for each subject were scheduled to begin between 6 AM and 9 AM.

All study medications were self-administered (by nebulization or by MDI, depending on the assigned study medication) by subjects except during the in-clinic treatment visits (Visits 2, 3, 4, 5, 6, 7, 8, and 9).
A study schematic is shown below.

Study 091-060: Study Schematic



Concomitant Therapies

The following medications were allowed under the specified conditions:
Oral and inhaled corticosteroids and xanthines were allowed at study entry and for the study duration as long as the regimen was stable for at least 14 days prior to entry and during the subject's participation in the study. Subjects on concurrent oral corticosteroids at study entry were required to be taking ≤10 mg/day of prednisone or equivalent.

Three, 14-day courses of oral corticosteroids separated by at least 6 weeks could have been administered at a maximum dose of 40 mg/day. The decision to initiate or continue a course of oral corticosteroids was at the Investigator's discretion. If possible, in the case of a COPD exacerbation, FEV1 was measured before initiation of corticosteroid therapy. Subjects who required oral corticosteroids for more than 14 consecutive days and/or required >40 mg/day, or required any additional courses of oral corticosteroids was required to discontinue from the study (unless a special approval was granted).

Subjects who were maintained on a stable dose (at least 14 days prior to Visit 1) of a short acting theophylline (BID or TID regimen) or who were using such drugs intermittently at a stable dose were allowed to continue their regimen for the study. However, the subject was to avoid the use of a short-acting theophylline for at least 24 hours before Visits 2, 6, 7, 8, and 9. Once-a-day controlled-release theophylline preparations were not allowed during the study.

Subjects who were maintained on a stable dose (at least 14 days prior to Visit 1) of leukotriene inhibitors were allowed to continue their regimen for this study. However, the subject was to avoid the use of leukotriene inhibitors for at least 24 hours before Visits 2, 6, 7, 8, and 9.

Subjects were required to withhold Beta-agonists within 6 hours of pulmonary function testing and during the in-clinic treatment days. Other concurrent medications were permitted on a case-by-case basis and at stable doses for a minimum of 30 days prior to Visit 1.

No concurrent medications (including over-the-counter products), other than those meeting the above requirements, were permitted without prior approval.

Data Analysis

Study 091-060 was primarily a safety study with all efficacy analyses considered exploratory. Statistical methods were not used in determining sample size.

There were two populations in the study: the all subjects randomized population (RND) and the intent-to-treat (ITT) population. The All Subjects Randomized population (RND) was defined as those subjects who were randomized to open-label medication. All listings were performed using the RND population. The Intent-to-Treat population (ITT) was defined as those subjects who were randomized to treatment and received at least one dose of study medication. All safety and efficacy analyses were performed on the ITT population, according to treatment assigned.

No inferential testing was performed; summary statistics only were provided for all analyses by treatment group.

For continuous variables, statistical summaries included the number of subjects, means, standard deviations, medians, 25th percentiles, 75th percentiles, maxima, and minima. For categorical variables, statistical summaries included counts and percentages.

All change from visit predose calculations had the visit predose value subtracted from postdose values. All change from study baseline calculations had the study baseline values subtracted from the post-study baseline values.

Unless otherwise indicated, all tabular and graphical summaries were performed using the ITT population (by treatment group), and all data listings contained all randomized subjects.

Disposition of Subjects

Subject disposition for the ITT population is summarized in the Table below. A total of 799 subjects were randomized. Subjects who completed the pivotal trials (091-050 and 091-051) prior to participation in Study 091-060 (rollover subjects) comprised 65.5% of the arformoterol 50 µg QD group, and 58.9% of the salmeterol 42 µg BID group. Approximately 90% of rollover subjects in both groups began participation in Study 091-060 immediately upon completion of the prior study. Of those subjects who did not begin Study 091-060 immediately, the median time between the end of the prior study and the beginning of Study 091-060 was 16.0 days in the arformoterol group, and 18.0 days in the salmeterol group.

Of the 793 ITT subjects enrolled in the study, 468 (58%) completed through Visit 10 (52 weeks of treatment), with similar rates of completion for both the arformoterol 50 µg QD and salmeterol 42 µg BID groups. Of the 325 subjects who did not complete the study, half (163 subjects; 50.2%) discontinued due to adverse events. The rate of discontinuation due to adverse

events as reported on the study termination form was higher in the arformoterol 50 µg QD group (118/528; 22.3%) than in the salmeterol 42 µg BID group (45/265; 17.0%).
Reviewer's Comment: While there were a few more cardiovascular AEs that lead to discontinuation if the arformoterol group (6.1% vs 4.2% for the salmeterol group), the main reason for the increased discontinuations in the arformoterol group was a greater number of patients with tremor listed as an AE (4.5% for arformoterol vs 0% for salmeterol). [Table 12.3.1.3.1, clinstat\copd\091-060.pdf, pp. 129-30]

Study 091-060: Subject Disposition

	Treatment Group	
	Arformoterol 50 µg QD N=532	Salmeterol 42 µg BID N=267
	n (%)	n (%)
Number of Subjects in ITT Population [1]	528 (99.2)	265 (99.3)
Number of Subjects Completing [2]		
Visit 2 (Week 0)	527 (99.8)	265 (100)
Visit 3 (Week 3)	475 (90.0)	244 (92.1)
Visit 4 (Week 6)	458 (86.7)	234 (88.3)
Visit 5 (Week 9)	440 (83.3)	226 (85.3)
Visit 6 (Week 13)	423 (80.1)	215 (81.1)
Visit 7 (Week 26)	382 (72.3)	192 (72.5)
Visit 8 (Week 39)	337 (63.8)	170 (64.2)
Visit 9 (Week 52)	304 (57.6)	161 (60.8)
Visit 10 (End of Study)	307 (58.1)[3]	161 (60.8)
Number of Subjects Withdrawing Post-Randomization[1]	221 (41.5)	104 (39.0)
Reason for Post-Randomization Withdrawal [2]		
Adverse event	118 (22.3)	45 (17.0)
Protocol variance	20 (3.8)	8 (3.0)
Subject voluntarily withdrew	53 (10.0)	27 (10.2)
Lost to follow-up	15 (2.8)	7 (2.6)
Did not meet entry criteria	2 (0.4)	2 (0.8)
Other	13 (2.5)	15 (5.7)

[1] Percentages were based on the number of subjects randomized.
[2] Percentages were based on the number of subjects in the ITT population.
[3] Three subjects who completed Visit 10 (End of Study) did not have a Visit 9 but completed the Study.

Important Protocol Deviations

The definition of important protocol deviations was prespecified. Important protocol deviations were applicable only to the ITT population.

Important protocol deviations were reported for 212 subjects (26.7%) at least once during the treatment period. The distribution of protocol deviations was fairly even between the arformoterol and salmeterol groups. The most common important protocol deviations in both dose groups were disallowed concurrent medication, did not meet inclusion/exclusion criteria, and other important protocol deviation. For rollover subjects from the pivotal trials, review of inclusion/exclusion criteria from the pivotal trial was used in the determination of important protocol deviations. The most common inclusion/exclusion criteria for roll-over subjects that resulted in important protocol deviations were failing to have a FEV1/FVC ratio $\leq$70% or a blood eosinophil count $\leq$5%. For de novo subjects, failing to have a baseline FEV1 $\leq$65% of predicted and >0.7 L, or failing to have a FEV1/FVC ratio $\leq$70% were most common. Of the 28 subject who did not satisfy pre-randomization pulmonary function criteria, 13 had FEV1 values that were below the protocol specified minimum of 0.7 L, five had FEV1 values that were equal to or greater than the highest allowable percent predicted value (65% predicted).

The most common disallowed medications determined to be important protocol deviations were levalbuterol (Xopenex), Theophylline QD, Theo-Dur, Maxair, and Combivent. Some of the 71 deviations in the "other" important protocol deviation categories identified by review of the Investigator comments may have been cited in other categories, such as inclusion/exclusion

criteria or disallowed medications. The other important deviations not already discussed were primarily related to positive drug screens. The following Table lists and summarizes the defined categories of important protocol deviations by treatment group.
Reviewer's Comment: The types of important protocol deviations and the even distribution across treatment groups were such that they would not significantly impact the outcome of the study.

Study 091-060: Important Protocol Deviations *[Table 10.2-1, clinstat\copd\091-060.pdf]*

	Treatment Group	
	Arformoterol 50 µg QD N=528	Salmeterol 42 µg BID N=265
Protocol Deviation	n (%)	n (%)
Any Important Protocol Deviation	143 (27.1)	69 (26.0)
Did not meet Inclusion/Exclusion Criteria	46 (8.7)	27 (10.2)
Study Medication Compliance <70%	26 (4.9)	19 (7.2)
Disallowed Concurrent Medication	47 (8.9)	23 (8.7)
Other Important Protocol Deviation	49 (9.3)	22 (8.3)

NOTE: Subjects may have had important protocol violations in more than one category.

Concurrent medications use during the screening period was 93.9% in the arformoterol 50 µg QD treatment group and 91.3% in the salmeterol 42 µg BID treatment group. The types of concurrent medication taken by subjects in both groups reflect a study population with significant co-morbid conditions, including hypertension, diabetes, cardiac disease, and high cholesterol. More subjects in the arformoterol 50 µg QD group than in the salmeterol 42 µg BID group were using cardiac therapy drugs (5.3% and 3.8%, respectively), drugs for acid reflux-related disorders (26.9% and 15.5%, respectively), bronchodilators (41.5% and 37.0%, respectively), drugs for diabetes (6.8% and 2.3%, respectively), and serum lipid lowering agents (23.3% and 17.7%, respectively). Systemic corticosteroids (not including inhaled corticosteroids) were used by 2.8% of arformoterol subjects and 5.7% of salmeterol subjects, with the majority being oral prednisone (2.5% and 3.8% in the two groups). Approximately 24% of arformoterol subjects and 19% of salmeterol subjects were using inhaled corticosteroids at baseline [Table 10.3-1, clinstat\copd\091-060.pdf, p. 87]

Medications were initiated during the treatment period in 83.0% and 81.1% of subjects in the arformoterol 50 µg QD and salmeterol 42 µg BID treatment groups, respectively. In general, the majority of agents initiated during the treatment period were agents used to treat the underlying co-morbid medical conditions. The initiation of systemic corticosteroids, obstructive airway agents, and antibiotics during the treatment period was primarily used in the treatment of COPD exacerbations. Systemic corticosteroids were initiated during the treatment period by 27.8% of arformoterol subjects and 22.6% of salmeterol subjects. The rate of initiation of inhaled corticosteroids during the treatment period was low (approximately 5% for both groups). A slightly higher percentage of subjects in the arformoterol group (3.0%) compared with the salmeterol group (1.5%) required treatment with a diabetic agent. [Table 10.3-2, clinstat\copd\091-060.pdf, p. 88]

Past medical history or ongoing medical conditions were reported by 99.2% of subjects in the arformoterol 50 µg QD group, and 98.9% of subjects in the salmeterol 42 µg BID group. Overall rates of these medical history events were comparable in the two groups. Specifically, the presence of cardiac disorders, including cardiac arrhythmias and coronary artery disorders, hypertension, and nervous system disorders were much the same in the arformoterol group as the salmeterol group. Headaches were reported by more subjects in the arformoterol group (31.1%) compared with the salmeterol group (17.7%). [Table 10.4-1, clinstat\copd\091-060.pdf, p. 89-91]
Reviewer's Comment: The data presented support the fact that the study population was balanced between treatment groups with respect to protocol deviations, medication use, and co-morbid conditions.

Study Demographics

The following table summarizes the subject demographics for the ITT population:

Study 091-060: Summary of Subject Demographics *[Table 11.2-1, clinstat\copd\091-060.pdf]*

		Arformoterol 50 µg QD (N=528)	Salmeterol 42 µg BID (N=265)
Age (years)	n	528	265
	Mean (SD)	63.6 (8.9)	64.7 (8.8)
Gender n (%)	Female	224 (42.4)	102 (38.5%)
	Male	304 (57.6%)	163 (61.5%)
Race n (%)	Asian	2 (0.4%)	0
	Black	21 (4.0%)	4 (1.5%)
	Caucasian	500 (94.7%)	261 (98.5%)
	Hispanic	1 (0.2%)	0
	Other	4 (0.8%)	0
Height (in)	n	528	265
	Mean (SD)	66.8 (3.8)	67.2 (4.1)
Weight (lb.)	n	522	261
	Mean (SD)	178.1 (42.4)	172.6 (40.7)

NOTE: For rollover subjects, data were obtained from the prior pivotal study's Visit 1, with the exception of weight, which was obtained from the prior pivotal study's Visit 8.

Reviewer's Comment: The mean age of subjects in the 2 groups was about the same. Similar to the pivotal studies, there was a dearth of subjects from ethnic backgrounds other than Caucasian.

The following table summarizes the respiratory baseline characteristics for the ITT population:

Study 091-060: Baseline Respiratory Characteristics *[Table 11.2-2, clinstat\copd\091-060.pdf]*

		Arformoterol 50 µg QD (N=528)	Salmeterol 42 µg BID (N=265)
Visit 2 Predose FEV_1 (liters)	n	522	264
	Mean (SD)	1.15 (0.43)	1.11 (0.43)
Visit 2 Predose FEV_1, Percent of Predicted	n	522	264
	Mean (SD)	38.88 (12.82)	37.00 (13.31)
Visit 2 Predose Best FEV_1/Best FVC Ratio (%)	n	522	264
	Mean (SD)	49.20 (10.06)	47.63 (9.88)
COPD Duration n (%)	≥0 to <5 Years	268 (50.8)	140 (52.8)
	≥5 to <10 Years	133 (25.2)	72 (27.2)
	≥10 to <15 Years	67 (12.7)	24 (9.1)
	≥15 Years	60 (11.4)	29 (10.9)
Pack-years Smoked n (%)	≥15 to <25	41 (7.8)	10 (3.8)
	≥25 to <30	21 (4.0)	19 (7.2)
	≥30	466 (88.3)	236 (89.1)
Packs per Day Smoked n (%)	Not Current Smoker	293 (55.5)	151 (57.0)
	≥0 to 1 Pack	122 (23.1)	60 (22.6)
	≥1 to <2 Packs	77 (14.6)	36 (13.6)
	≥2 to <4 Packs	35 (6.6)	18 (6.8)
	≥4 Packs	1 (0.2)	0
Baseline Steroid Use*	n (%)	193 (36.6)	84 (31.7)
Baseline Oxygen Use	n (%)	26 (4.9)	6 (2.3)

NOTE: For rollover subjects, data were obtained from the prior pivotal study's Visit 1, with the exception of weight, which was obtained from the prior pivotal study's Visit 8.
* Includes subjects receiving systemic steroids (oral, inhaled, intravenous, intramuscular) at baseline.

The above data indicate that the subjects in each group had moderate to severe COPD. There was a slightly higher percentage of subjects using systemic steroids and oxygen at baseline in the arformoterol 50 µg QD group (36.6% and 4.9%, respectively) than in the salmeterol 42 µg BID group (31.7% and 2.3%, respectively).

Approximately 94% and 92% of subjects in the arformoterol 50 µg QD and salmeterol 42 µg BID groups, respectively, were compliant with treatment, as defined by compliance rates between 80% and 120% during the treatment period.

Analysis of Efficacy

Study 091-060 is an open label, active comparator safety study. All efficacy endpoints were exploratory in nature. No inferential testing was performed; summary statistics only were provided for all analyses. Although no formal evaluation for equivalency in the treatments was made, nevertheless, one would expect that with similar baseline demographics, the arformoterol group would perform similarly to that of the salmeterol group. Following is a brief summary of relevant efficacy findings.

- Both arformoterol 50 µg QD and salmeterol 42 µg BID improved predose FEV1 (i.e., trough) values to a similar extent, compared with study baseline. The percent change in

predose FEV1 from study baseline was 5.9% in the arformoterol group, and 6.2% in the salmeterol group at Week 52.

- Subjects in both the arformoterol and salmeterol groups demonstrated improvement in mean FEV_1 peak percent change from visit predose over four hours post-dose over the treatment period. The improvement ranged from 24.9% to 36.6% in the arformoterol 50 μg QD group, and from 14.4% to 26.2% in the salmeterol 42 μg BID group.

- Peak percent predicted FEV_1 over four hours ranged from 49.8% to 51.7% for subjects in the arformoterol 50 μg QD group, and from 43.8% to 45.9% for subjects in the salmeterol 42 μg BID group over the treatment period.

- Mean morning and evening at-home average PEFR values were improved in both groups compared to mean baseline values observed in the clinic prior to administration of study drug.

- Daytime COPD Symptom Ratings showed very slight, clinically insignificant increases in change from screening in symptom-free days/week during the 52 weeks of treatment duration with 0.2 days/week for the arformoterol 50 μg QD group and 0.1 days/week for the salmeterol 42 μg BID group.

- For both treatment groups, there was a slight increase in the mean change in number of symptom-free nights/week compared to screening for nocturnal awakenings over the treatment period. The increase in symptom-free nights/week for nocturnal awakenings was 0.5 nights/week for the arformoterol 50 μg QD group and 0.1 nights/week than for the salmeterol 42 μg BID group.

- Ipratropium bromide use declined by 1.3 and 1.4 days per week in the arformoterol 50 μg QD and salmeterol 42 μg BID groups, respectively.

- Racemic albuterol use declined by 1.1 and 0.9 days per week in the arformoterol 50 μg QD and salmeterol 42 μg BID groups, respectively.

Over the course of the study, the St. George Hospital Respiratory Questionnaire scores decreased by 0.7 and 0.8 in the arformoterol and salmeterol groups, respectively. Similarly, the transitional dyspnea index improved by 1.0 and 0.7 in the arformoterol and salmeterol groups, respectively.

Efficacy Conclusions

This was an open-label safety study of arformoterol 50 μg QD using salmeterol 42 μg BID as an active comparator. Subjects participating in this study had moderate to severe COPD and significant co-morbid medical conditions. Study populations were balanced with respect to the severity of pulmonary disease and co-morbid conditions between treatment groups. Important medical history included known cardiovascular disorders (20% to 22% of subjects), and/or

significant risk factors for cardiovascular disease, hypertension (37% to 39%), diabetes mellitus (8% to 11%), lipid disorders (20% to 24%), and smoking history (100%). No inferential testing was performed and, therefore, no formal evaluation for equivalency between arformoterol and salmeterol treatments can be made. However, as would be expected from the fact that arformoterol is an enantiomer of the well-characterized and marketed LABA, racemic formoterol, it appears that the arformoterol 50 µg QD group performed quite similarly to the approved comparator medication, salmeterol 42 µg BID group with respect to effecting improvement in pulmonary function and quality of life parameters.

Safety Review

The safety findings from this study will be reviewed in depth in the Integrated Review of Safety section of this Medical Officer Review. Brief observations are described below.

The duration of exposure, total number of doses administered, cumulative dose received, and days on medication are summarized in the following Table.

Study 091-060: Extent of Exposure (ITT Population) *[Table 12.1-1, clinstat\copd\091-060.pdf]*

	Treatment Group	
	Arformoterol 50 µg QD N=528	Salmeterol 42 µg BID N=265
Duration of Exposure		
<3 months	99 (18.8)	50 (18.9)
<2 days	16 (3.0)	7 (2.6)
≥2 days but <3 weeks	27 (5.1)	11 (4.2)
≥3 weeks but <6 weeks	18 (3.4)	9 (3.4)
≥6 weeks but <9 weeks	17 (3.2)	4 (1.5)
≥9 weeks but <13 weeks	21 (4.0)	19 (7.2)
≥3 but <6 months	46 (8.7)	21 (7.9)
≥6 but <9 months	47 (8.9)	18 (6.8)
≥9 but <12 months	133 (25.2)	71 (26.8)
≥39 weeks but <48 weeks	25 (4.7)	12 (4.5)
≥48 weeks but <49 weeks	3 (0.6)	1 (0.4)
≥49 weeks but <50 weeks	2 (0.4)	1 (0.4)
≥50 weeks but <51 weeks	12 (2.3)	4 (1.5)
≥51 weeks but <52 weeks	91 (17.2)	53 (20.0)
≥12 months	203 (38.4)	105 (39.6)
Total Number of Doses Administered		
n	528	265
Mean (SD)	259.0 (135.1)	528.3 (262.1)
Cumulative Dose Received (µg)		
n	528	265
Mean (SD)	12947.7 (6756.8)	22189.6 (11007.3)
Days on Medication		
n	528	265
Mean (SD)	266.4 (135.4)	273.6 (131.7)

The mean number of days that subjects received study medication was similar in the arformoterol 50 µg QD (266.4 days) and salmeterol 42 µg BID (273.6 days) treatment groups. In addition, a total of 383 subjects had arformoterol 50 µg QD for at least 6 months of exposure,

and 308 completed 12 months of exposure (defined as ≥49 weeks of exposure). Adverse events reported in ≥ 2% of subjects in either treatment group are summarized in the following Table.

Study 091-060: Adverse Events Reported in ≥ 2% of Subjects in Either Treatment Group During the Treatment Period *[Table 12.2.2-1, clinstat\copd\091-060.pdf]*

	Arformoterol 50 µg QD (N=528)		Salmeterol 42 µg BID (N=265)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
ALL ADVERSE EVENTS	**478 (90.5)**	**2543**	**234 (88.3)**	**1113**
BODY AS A WHOLE				
Abdominal Pain	18 (3.4)	20	8 (3.0)	12
Accidental Injury	53 (10.0)	68	31 (11.7)	37
Asthenia	25 (4.7)	27	10 (3.8)	36
Back Pain	34 (6.4)	50	19 (7.2)	23
Chest Pain	40 (7.6)	47	15 (5.7)	28
Fever	16 (3.0)	21	1 (0.4)	1
Flu Syndrome	20 (3.8)	21	15 (5.7)	15
Headache	54 (10.2)	93	23 (8.7)	35
Neck Pain	17 (3.2)	20	2 (0.8)	2
Pain	78 (14.8)	114	32 (12.1)	44
Viral Infection	29 (5.5)	32	17 (6.4)	17
CARDIOVASCULAR SYSTEM				
Hypertension	20 (3.8)	21	15 (5.7)	15
Palpitation	4 (0.8)	5	7 (2.6)	7
Ventricular extrasystoles	8 (1.5)	8	8 (3.0)	8
Ventricular tachycardia	11 (2.1)	11	3 (1.1)	3
DIGESTIVE SYSTEM				
Colitis	9 (1.7)	9	8 (3.0)	9
Constipation	10 (1.9)	11	7 (2.6)	7
Diarrhea	27 (5.1)	33	22 (8.3)	29
Dry Mouth	14 (2.7)	18	2 (0.8)	2
Dyspepsia	20 (3.8)	24	11 (4.2)	12
Gastroenteritis	11 (2.1)	11	2 (0.8)	2
Nausea	26 (4.9)	28	12 (4.5)	13
Vomiting	18 (3.4)	20	6 (2.3)	6
METABOLIC AND NUTRITIONAL DISORDERS				
Hyperglycemia	7 (1.3)	7	6 (2.3)	7
Hypokalemia	12 (2.3)	13	4 (1.5)	4
Peripheral Edema	21 (4.0)	23	4 (1.5)	4
MUSCULOSKELETAL SYSTEM				
Arthritis	16 (3.0)	18	5 (1.9)	5
Leg Cramps	28 (5.3)	47	6 (2.3)	16

Study 091-060: Adverse Events Reported in ≥ 2% of Subjects in Either Treatment Group During the Treatment Period continued *[Table 12.2.2-1, clinstat\copd\091-060. pdf]*

	Arformoterol 50 µg QD (N=528)		Salmeterol 42 µg BID (N=265)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
ALL ADVERSE EVENTS	478 (90.5)	2543	234 (88.3)	1113
NERVOUS SYSTEM				
Depression	11 (2.1)	13	7 (2.6)	7
Dizziness	40 (7.6)	48	7 (2.6)	7
Hypertonia	12 (2.3)	13	4 (1.5)	6
Insomnia	25 (4.7)	25	7 (2.6)	7
Nervousness	25 (4.7)	28	3 (1.1)	3
Paresthesia	13 (2.5)	23	2 (0.8)	2
Tremor	71 (13.4)	81	3 (1.1)	3
RESPIRATORY SYSTEM				
Bronchitis	66 (12.5)	84	47 (17.7)	66
COPD	104 (19.7)	147	46 (17.4)	64
Cough Increased	38 (7.2)	50	25 (9.4)	34
Dyspnea	28 (5.3)	33	14 (5.3)	15
Epistaxis	11 (2.1)	12	1 (0.4)	1
Infection	132 (25.0)	211	62 (23.4)	93
Lung Disorder	14 (2.7)	16	5 (1.9)	5
Pharyngitis	33 (6.3)	38	14 (5.3)	16
Pneumonia	26 (4.9)	29	11 (4.2)	11
Rhinitis	53 (10.0)	63	28 (10.6)	35
Sinusitis	36 (6.8)	54	21 (7.9)	27
SKIN AND APPENDAGES				
Herpes Zoster	3 (0.6)	3	7 (2.6)	8
Rash	18 (3.4)	21	6 (2.3)	7
UROGENITAL SYSTEM				
Hematuria	15 (2.8)	21	10 (3.8)	12
Urinary Tract Infection	25 (4.7)	36	13 (4.9)	19

The incidence of adverse events during the treatment period was similar in the two groups. Overall, 90.5% of subjects in the arformoterol 50 µg QD group and 88.3% of subjects in the salmeterol 42 µg BID group experienced at least one adverse event. The most frequently reported events (>5% in either of the treatment groups) were accidental injury, back pain, chest pain, flu syndrome, headache, pain, viral infection, hypertension, diarrhea, leg cramps, dizziness, tremor, bronchitis, COPD, cough increased, dyspnea, respiratory infection, pharyngitis, rhinitis, and sinusitis *[Table 14.3.1.3, clinstat\copd\091-060, pdf.].*

The overall incidence of nervous system adverse events was higher in the arformoterol 50 µg QD group (32.0%) than in the salmeterol 42 µg BID group (15.5%). This difference was driven by a higher incidence of Beta-mediated nervous system events in the arformoterol 50 µg QD group compared with the salmeterol 42 µg BID group, including dizziness (7.6% versus 2.6%,

respectively), insomnia (4.7% versus 2.6%, respectively), leg cramps (5.3% versus 2.3%, respectively), nervousness (4.7% versus 1.1%, respectively), paresthesia (2.5% versus 0.8%, respectively), and tremor (13.4% versus 1.1%, respectively). The following Table summarizes the nervous system related AEs during the treatment period.

Study 091-060: Central Nervous System Adverse Events During the Treatment Period
[Table 12.3.1.4.3-1, clinstat\copd\091-060.pdf]

n (%)	Arformoterol 50 µg QD (n=528)	Salmeterol 42 µg BID (n=265)
Overall CNS AE Rate	169 (32.0)	41 (15.5)
Mild	96 (18.2)	20 (7.5)
Moderate	59 (11.2)	17 (6.4)
Severe	14 (2.7)	4 (1.5)
CNS AEs Leading to Discontinuation	33 (6.3)	4 (1.5)
Serious CNS AEs	5 (0.9)	1 (0.4)

The incidence of CNS adverse events assessed as severe was slightly higher in the arformoterol 50 µg QD group (2.7%) than in the salmeterol 42 µg BID group (1.5%). Five arformoterol subjects experienced tremor assessed as severe, compared with no salmeterol subjects.

The incidence of CNS adverse events resulting in study discontinuation was higher in the arformoterol 50 µg QD group (6.3%) than in the salmeterol 42 µg BID group (1.5%). This difference was driven by a higher incidence of discontinuation due to Beta-mediated tremor in the arformoterol group (4.5%), compared with no discontinuations due to tremor in the salmeterol group [Table 14.3.1.10].

The overall incidence of cardiovascular adverse events was 18.2% in the arformoterol 50 µg QD group, and 18.9% in the salmeterol 42 µg BID group. The rates of hypertension, palpitation, and ventricular extrasystoles were higher in the salmeterol 42 µg BID group, while the rate of ventricular tachycardia was higher in the arformoterol 50 µg QD group. The following Table presents the treatment-emergent cardiovascular adverse events reported during the treatment period.

Study 091-060: Cardiovascular Adverse Events During the Treatment Period *[Table 12.3.1.4.1-1, clinstat\copd\091-060.pdf]*

	Arformoterol 50 µg QD (N=528)	Salmeterol 42 µg BID (N=265)
Overall CV AE Rate (%)	96 (18.2)	50 (18.9)
Ischemic Events*	11 (2.1)	9 (3.4)
Arrhythmic Events†	44 (8.3)	17 (6.4)
CV AEs Leading to Discontinuation (%)	32 (6.1)	11 (4.2)
Serious CV Adverse Events	14 (2.7)	7 (2.6)
Severe CV Adverse Events	17 (3.2)	7 (2.6)

Reviewer's Comment: It does not appear that there was a meaningful increase in cardiovascular AEs in the arformoterol group. However, AEs associated with the nervous system such as tremor and dizziness, while mostly rated mild or moderate in severity, were higher with arformoterol and are the main reason that 5% more people who received arformoterol discontinued from the study due to an AE. See Table 12.3.1.3, clinstat\copd\091-060. pdf, p130-1.

The overall incidence of spontaneously reported COPD adverse events was similar between the two treatment groups during the treatment period, as were the numbers of COPD events assessed as severe, and those resulting in study discontinuation. There was a slightly higher rate of COPD events that met the definition of serious in the arformoterol 50 µg QD group (2.7%) than in the salmeterol 42 µg BID group (1.9%). The number and percentages of subjects with COPD exacerbations during the treatment period are summarized in the following Table.

Study 091-060: Number and Percentages of Subjects with COPD Adverse Events During the Treatment Period *[Table 12.3.1.4.2-1, clinstat\copd\091-060. pdf*

	Arformoterol 50 µg QD (N=528)	Salmeterol 42 µg BID (N=265)
Overall COPD AE Rate	104 (19.7)	46 (17.4)
Mild	24 (4.5)	10 (3.8)
Moderate	66 (12.5)	30 (11.3)
Severe	14 (2.7)	6 (2.3)
COPD AEs Leading to Discontinuation	21 (4.0)	10 (3.8)
Serious COPD AEs	14 (2.7)	5 (1.9)

The proportion of subjects who withdrew due to an adverse event was 22.2% in the arformoterol 50 µg QD group and 17.0% in the salmeterol 42 µg BID group.

One hundred subjects experienced 130 serious adverse events during the treatment period. The incidence of serious adverse events in the ITT population occurring during the treatment period was 12.7% in the arformoterol 50 µg QD group, and 12.5% in the salmeterol 42 µg BID group. SAEs were fairly well balanced between treatment groups for all organ systems, including the nervous system, which had a greater number of AEs leading to study discontinuation in the arformoterol group.
Reviewer's Comment: This is presumably because, while AEs of tremor and nervousness due to arformoterol were significant enough to result in withdrawing from the study, they did not meet the regulatory definition of an SAE.

There were five deaths during the treatment period, three in the arformoterol 50 µg QD group, and two in the salmeterol 42 µg BID group. Subject 0194-S506 (arformoterol 50 µg QD) died of cryptococcal meningitis 93 days after the last documented dose of study medication. Subject 0197-S503 (arformoterol 50 µg QD) died of a myocardial infarction after 201 days of treatment, and Subject 0844-S909 (arformoterol 50 µg QD) died of cardiac ischemia after 309 days of treatment. Subject 0254-S507 (salmeterol 42 µg BID) lung cancer after 20 days of treatment, and

Subject 0681-S503 (salmeterol 42 µg BID) died of lung cancer three months after the end of treatment. Narratives for these subjects are provided in *clinstat\copd\091-060, pdf, Section 12.3.2.1.*

Clinical laboratory evaluations included hematology, blood chemistry, and urinalysis assessments; these were collected at Visits 2 through 10 [Weeks 0, 3, 6, 9, 13, 26, 39, 52, and 53 (End of Study or Early Termination)]. Laboratory parameters of interest included serum potassium and serum glucose because the use of β-agonists has been associated with hypokalemia and hyperglycemia. During the treatment period, 8.4% of subjects in the arformoterol 50 µg QD treatment group, and 2.7% of subjects in the salmeterol 42 µg BID treatment group had serum potassium values that were <3.5 mEq/L two hours after dosing. One subject in the arformoterol 50 µg QD group experienced serum potassium levels <3 mEq/L. Overall, 15.7% of arformoterol treated subjects experienced a potentially clinically significant glucose elevation compared with 12.5% of salmeterol treated subjects.

There were no meaningful changes in mean values over time, or differences between the treatment groups in the ECG parameters of ventricular heart rate, PR interval, QRS duration, QT interval, QTc interval, or RR interval.

New ECG abnormalities meeting alert criteria and not present at baseline were reported in 18.4% of arformoterol subjects and 16.6% of salmeterol subjects. The most common alerts (reported in ≥3% of subjects in either group) included 1st degree AV block (1.3% versus 3.0%), bradycardia (3.4% versus 1.5%), QTc-B >450 ms and 25% change from baseline (4.4% versus 2.3%), ventricular ectopy (4.9% versus 5.3%), and new T wave inversions (3.0% versus 0.8%).

Mean changes from baseline for Holter monitoring heart rate parameters were similar throughout the study for both treatment groups. New Holter monitor abnormalities meeting alert criteria and not present at baseline were reported in 13.3% of arformoterol subjects and 11.3% of salmeterol subjects. The most common alert (reported in ≥3% of subjects in either group) included ventricular ectopy (>6000 in 24 hours; 3.2% versus 3.0%), and VE runs (>4 beats at >80 beats per minute; 8.5% versus 8.7%). Holter alerts for sustained ventricular tachycardia (runs of >10 beats) occurred in 15 subjects (2.8%) in the arformoterol 50 µg QD group, and five subjects (1.9%) in the salmeterol 42 µg BID group. The length of the ventricular tachycardia episodes for the 15 arformoterol subjects ranged from 11 to 32 beats, with all but one episode being less than 30 beats. Three arformoterol subjects discontinued from the study due to the sustained ventricular tachycardia (one additional arformoterol subject discontinued due to a non-sustained ventricular tachycardia event). The length of the ventricular tachycardia episodes in the five salmeterol subjects ranged from 11 to 26 beats. Three salmeterol subjects discontinued from the study due to the ventricular tachycardia.

Safety Summary

This study was a multicenter, open-label, randomized, active-controlled, parallel-group, long-term safety evaluation of arformoterol in the treatment of subjects with chronic obstructive pulmonary disease. The primary objective was to obtain long-term safety data following

treatment with arformoterol 50 μg QD over a period of 12 months in this subject population. In this study, 383 subjects completed at least 6 months of exposure to arformoterol, and 308 subjects completed at least 12 months. The marketed LABA, salmeterol, given at the approved dose, was used as an active comparator. As the 50 μg QD dose of arformoterol is over 2 times the proposed dose of 15 μg BID, the salmeterol group is important in that it establishes a baseline level of side effects/adverse events in the indicated COPD population to which the high dose arformoterol group can be compared.

The sponsor is correct in concluding that the overall incidence of adverse events, including cardiovascular events and COPD exacerbations, was similar between treatment groups. However, there was clearly a higher incidence of Beta-mediated adverse events related to the CNS such as tremor and dizziness that resulted in more subjects dropping out of the study due to adverse events (6.3% vs 1.5% for arformoterol and salmeterol, respectively). In addition Beta-mediated decreases in serum potassium and increases in serum glucose were more frequent in the arformoterol group than salmeterol group.

Three deaths were reported in the arformoterol group, of which two were cardiac ischemic events. Both were elderly subjects with cardiovascular risk factors present at study entry. There were 2 deaths reported in the salmeterol group, both due to lung cancer. Overall, however, the number of deaths reported in this study is not unexpected. In information supplied by the sponsor, based on approximately 583 person-years of total exposure time during the treatment period, the National Vital Statistics report for 2003 estimate of 900.4 deaths/100,000 person-years for Caucasians 55 to 64 years of age (slightly younger than the mean age of the study population) would predict 5.25 deaths for this study.

In conclusion, high dose arformoterol (50 μg QD) possessed a clinically significant increase in treatment related side effects than salmeterol given at the standard indicated dose for COPD. These were related to increased CNS effects due to excess Beta receptor stimulation rather than direct cardiovascular side effects. Overall, the safety profile of 50 μg QD of arformoterol would not, in my opinion, be adequate to support approval of that dose for clinical use. However, the use of high dose arformoterol in this safety trial demonstrates that there do not appear to be increases in side effects seen with R-formoterol that would not be predicted based on the mechanism of action of formoterol and clinical use of racemic formoterol.

Study 091-026: Multi-Dose, Dose-Ranging Study

Title of Study: A Double-Blind, Randomized, Multicenter, Two-Part, Parallel-Group, Dose-Ranging Study of Twice-Daily and Once-Daily Arformoterol in the Treatment of Subjects With Chronic Obstructive Pulmonary Disease (COPD).

Design
This was a double-blind, multicenter study 2-part study parallel group dose-ranging study of the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics of arformoterol when administered at doses of 5, 15, and 25 μg BID (Part A) or at doses of 15, 25, and 50 μg QD (Part B) to subjects with COPD. Part A and Part B of the study each constituted 1) a 7 ± 1-day, single-blind, placebo run-in period, 2) a 14 ± 4-day randomized, double-blind treatment period during which the subjects received treatment with arformoterol (either BID in Part A or QD in Part B) or placebo (either BID in Part A or QD in Part B), and 3) a 7 ± 1-day washout period. The same subjects participated in both parts of the study. Randomization in Parts A and B was done independently.

Duration
The duration of active treatment was 14 days for both Parts A and B. The study was performed during the period of October 2, 2003 to May 5, 2004.

Study Centers
The study was conducted at 31 US centers in the following states: CA, FL, GA, KS, LA, NC, NE, NJ, OH, OR, PA, SC, TX, and WA.

Population
A total of 215 subjects with relatively stable, moderately severe COPD were randomized into Part A of the study (54, 54, 54, and 53 subjects in the placebo and arformoterol 5, 15, and 25 μg BID groups, respectively) and 191 re-randomized into Part B of the study after a 7 day washout period and 7 day placebo run-in period (49, 48, 47, and 47 subjects in the placebo and arformoterol 15, 25, and 50 μg QD groups, respectively).

Treatments Administered
Each study subject was randomized to receive arformoterol tartrate inhalation solution in unit dose vials (UDVs) at doses of 5, 15, or 25 μg or placebo BID (Part A) or 15, 25, or 50 μg or placebo QD (Part B). Arformoterol solution was delivered via a PARI LC PLUS nebulizer and a PARI Dura-neb 3000 compressor.

Treatments/Materials
The blinded study treatments were:

- Arformoterol inhalation solution of 5, 15, 25, and 50 μg in 2 mL volume
- Placebo (citrate buffer)

Commercially available racemic albuterol MDI (17-g canister/200 inhalations) and ipratropium MDI (Atrovent 14-g canister/200 inhalations) were provided to each study site for use by

subjects as rescue medication for bronchospasm and acute treatment of COPD symptoms as needed throughout the study.

Objectives
Part A: To evaluate relevant airway function endpoints compared to placebo for arformoterol over a 14-day treatment period when administered at doses of 5, 15, and 25 μg BID for 14 days.

Part B: To evaluate relevant airway function endpoints compared to placebo for arformoterol over a 14-day treatment period when administered at doses of 15, 25, and 50 μg QD for 14 days.

The secondary objectives for both parts of the study were:

- To compare the safety and tolerability of arformoterol with those of placebo in subjects with COPD
- To characterize the effect of inhaled arformoterol on cardiovascular safety outcomes in subjects with COPD (especially its effects on electrocardiographic (ECG) parameters, including QTc interval)
- To evaluate any dose-response trend among the doses of arformoterol
- To evaluate the clinical effects of withdrawal from therapy
- To explore the relationship between plasma concentrations of arformoterol and selected pharmacodynamic endpoints

Efficacy Variables

The primary efficacy endpoints were:

Part A: The time-normalized area under the curve for FEV1 percent change from predose over 12 hours (nAUC0-12-P) at Visit 4 (after 14 days of double-blind treatment)

Part B: The time-normalized area under the curve for FEV1 percent change from predose over 24 hours (nAUC0-24-P) at Visit 7 (after 14 days of double-blind treatment)

A key secondary efficacy endpoint in Parts A and B was the percent change in the FEV1 24-hour trough value after 14 days of double-blind treatment.

Other secondary efficacy endpoints include:

- time normalized AUC for FEV1 percent change from predose over 24 hours (nAUC0 - 24-P) for the 24-hour clinic visit (Visit 4) in Part A or the time-normalized AUC for FEV1 percent change from predose over 12 hours (nAUC0-12-P) for the 24-hour clinic visit (Visit 7) in Part B
- time-normalized AUC for FEV1 percent change from predose over 6 hours (nAUC0-6-P) for the 6-hour clinic visit (Visit 3 in Part A and Visit 6 in Part B)
- percent change in FEV1 from predose to each time point after dosing

- peak percent change in FEV1
- peak percent of predicted FEV1 after dosing
- ipratropium bromide and racemic albuterol use
- morning and evening peak expiratory flow rate (PEFR)
- exacerbations of COPD
- COPD symptom ratings
- the effects of withdrawal of therapy
- the relationship between plasma concentrations of arformoterol and selected pharmacodynamic parameters.

Post hoc analyses of the time-normalized area under the FEV1 percent change from baseline curve over 12 hours (nAUC0-12-B) and over 24 hours (nAUC0-24-B) after 14 days of double-blind treatment in Part A (Visit 4) and Part B (Visit 7) of the study were also derived.

Safety Variables

Safety assessments included adverse events; ECG findings, QTc-M; 24-hour Holter Monitoring; clinical laboratory parameters including serum potassium and glucose; vital signs; and physical examination findings.

Study-Specific Inclusion Criteria

- Subject gave written informed consent and privacy authorization for release of health information before participation. If the subject was a woman of childbearing potential, she signed the Women of Childbearing Potential Addendum.
- Subject was aged ≥35 years on the day the informed consent was signed. Both males and females were eligible for the study.
- Subject had a primary diagnosis of COPD, which may have included components of chronic bronchitis and/or emphysema.
- Subject had a minimum smoking history of 15 pack-years
- Subject had a score of ≥2 on the Medical Research Council (MRC) Dyspnea Scale.
- Subject had a baseline FEV1 that was ≤65% of the predicted normal value and >0.70 L before randomization
- Subject had an FEV1/forced vital capacity (FVC) ratio (calculated as the highest FEV1 obtained divided by the highest FVC obtained from 2 efforts conducted) of ≤70% before randomization
- Subject demonstrated reversible disease (≥10% improvement in FEV1 within 15 to 30 minutes after inhalation of 2 puffs (180 μg) of racemic albuterol MDI before randomization
- Subject had a chest x-ray within 6 months of Visit 1 that was consistent with the diagnosis of COPD (e.g., not diagnostic of pneumonia, other infection, atelectasis, or pneumothorax). If no chest x-ray had been taken ≤6 months before Visit 1, a chest x-ray was performed at Visit 1.

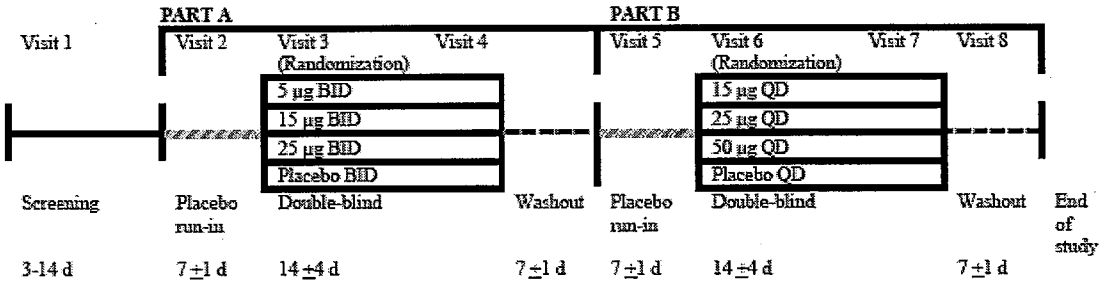
Study Specific Exclusion Criteria

The following individuals were ineligible for study participation:

- Subject was currently using disallowed medications (see Section 9.4.7.1) or was unable to complete the medication washout periods
- Subject was scheduled for in-patient hospitalization, including elective surgery (inpatient or outpatient), during the study.
- Subject had a life-threatening or unstable respiratory status, including upper or lower respiratory tract infection, within 30 days before Visit 1.
- Subject had a known history of asthma (except childhood asthma) or chronic respiratory disease (including a current history of sleep apnea) other than COPD (chronic bronchitis and/or emphysema).
- Subject had a known history of α-1 antitrypsin deficiency-related emphysema.
- Subject had a blood eosinophil count of >5% of total white blood cell (WBC) count.
- Subject had a history of lung resection of more than 1 full lobe or had been the recipient of a lung or major organ transplant.
- Subject required continuous supplemental oxygen therapy (unless subject resided at an elevation ≥4000 feet). Use of supplemental oxygen (not to exceed 2 L/minute) at nighttime only and/or only during exercise was allowed.
- Subject had a change in dose or type of any medications for COPD within 14 days before the screening visit (Visit 1 or 2).
- Subject had a known sensitivity to arformoterol, ipratropium, or albuterol or to any of the excipients contained in any of their formulations.
- Subject had clinically significant abnormalities that may have interfered with the metabolism or excretion of the study drug (e.g., abnormalities of renal, hepatic, metabolic, or endocrine function)
- Subject had clinically significant abnormal laboratory values at Visit 1 (hematology, blood chemistry, and urinalysis)
- Subject had a clinically significant abnormal 12-lead ECG that could have jeopardized completion of the study
- Subject was using any prescription drug for which concomitant Beta-agonist administration was contraindicated (e.g., Beta-blockers).

Study Design and Conduct
A study schematic is summarized in the following Figure.

Study 091-026: Schematic *[Figure 9.1-1, clinstat\copd\091-026.pdf]*



This study was a placebo-controlled, double-blind, randomized, multicenter, 2-part, parallel group, dose-ranging study of the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics of arformoterol when administered at doses of 5, 15, and 25 µg BID (Part A) or at doses of 15, 25, and 50 µg QD (Part B) to subjects with COPD. Part A and Part B of the study each constituted 1) a 7 ± 1-day, single-blind, placebo run-in period, 2) a 14 ± 4-day randomized, double-blind treatment period during which the subjects received treatment with arformoterol (either BID in Part A or QD in Part B) or placebo (either BID in Part A or QD in Part B), and 3) a 7 ± 1-day washout period. The same subjects participated in both parts of the study. Randomization in Parts A and B was done independently.

Study participation constituted 8 study visits over an approximate 10-week period. The study visits consisted of 1) a screening visit (Visit 1), which was conducted 3 to 14 days before randomization to confirm the subject's eligibility for the study; 2) a visit to initiate the Part A, single-blind, placebo run-in period (Visit 2); 3) a visit to randomize the subject to treatment and to initiate the Part A, double-blind, treatment period (Visit 3; 6-hour in-clinic visit); 4) a 24-hour in-clinic visit after 14 days of double-blind treatment (Visit 4); 5) a visit to initiate the Part B, single-blind, placebo run-in period (Visit 5); 6) a visit to randomize the subject to treatment and to initiate the Part B, double-blind, treatment period (Visit 6; 6-hour in-clinic visit); 7) a 24-hour in-clinic visit after 14 days of double-blind treatment (Visit 7); and 8) a final end-of-study visit (Visit 8). An early termination visit was conducted for any subject who withdrew from the study after Visit 2.

In addition to the scheduled study visits (i.e., Visits 1-8), the subjects were required to return to the clinic at 36 and 60 hours after administration of the second dose of study medication at the Visit 4 in-clinic visit (Part A) and at 48 and 72 hours after administration of the dose of study medication at the Visit 7 in-clinic visit (Part B) so that additional blood samples could be obtained for PK analysis. The subjects were also required to return to the clinic 24 hours after Visits 2, 3, 5, and 6 for removal of the Holter Monitor.

During Part A, placebo or arformoterol was self-administered BID (approximately every 12 hours) by nebulization for 3 weeks (including the 1-week, placebo run-in period and the 2-week double-blind treatment period) except during Visits 2 (first dose), 3 (first dose), and 4 (first and second doses) when the study medication was administered in the clinic by study site staff. During Part B, placebo or arformoterol was self-administered QD (approximately every 24 hours) by nebulization for 3 weeks (including the 1-week, placebo run-in period and the 2-week

double-blind treatment period) except during Visits 5, 6, and 7 when the study medication was administered in the clinic by study site staff. Study drug was to be administered at the same time each day (±1 hour). All subjects were provided with ipratropium bromide metered-dose inhalers (MDI) to be used as needed as supplemental treatment for COPD and with racemic albuterol MDIs to be used as rescue medication for bronchospasm and for the acute treatment of COPD symptoms.

Subjects were required to complete COPD questionnaires; Medical Event Calendars (MEC); and peak expiratory flow (PEF), study drug use, and supportive or rescue medication use logs during the study. Subjects were required to withhold the use of certain medications for the duration of the study and during specific, defined time frames before study visits. A schedule of study assessments is depicted in the following Table.

Study 091-026: Schedule of Study Assessments *[Table 9.1-1, clinstat\copd\091-026.pdf]*

		Part A[1]			Part B[1]			
	Screening	Single-blind	Rand/Dose	Washout	Single-Blind	Rand/Dose	Washout	EOS/ET
Assessments	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	V8
Informed consent[2]	X							
Inclusion/exclusion criteria (review)	X	X	X					
Medical/COPD history/COPD symptoms	X							
Review prior/concomitant medications	X	X	X	X	X	X	X	X
Physical examinations[3]	X		X	X		X	X	X
Vital signs (HR, BP, PR, and oral temperature)[4]	X	X	X	X	X	X	X	X
Chest x-ray[5]	X							
12-lead ECG[6]	X	X	X	X	X	X	X	X
Serum β-hCG (pregnancy test)[7]	X							X
FSH level[7]	X							
Urine drug screen	X				X			
Medical Research Council (MRC) Dyspnea Scale	X							
Clinical laboratory evaluations (blood/urine)[8]	X		X	X		X	X	X
Glucose and potassium levels [9]	X		X	X		X	X	X
Serum theophylline levels[10]	X	X	X	X	X	X	X	X
Pharmacokinetic samples[11]			X	X		X	X	

		Part A[1]			Part B[1]			
	Screening	Single-Blind	Rand/Dose	Washout	Single-Blind	Rand/Dose	Washout	EOS/ET
Assessments	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	V8
Bioanalytical urine samples[12]						X	X	
Reversibility testing (albuterol)[13]	X	(X)[13]						
Spirometry/serial spirometry[14]	X	(X)[13]	X	X	X	X	X	X
Calculate PEFSL			X					
Holter Monitor attach/remove[15]		X	X	X	X	X	X	X
Administer study medication		X	X	X	X	X	X	
Dispense single-blind placebo medication		X			X			
Randomize via IVRS/dispense double-blind study medication			X			X		
(Re)dispense supportive and rescue medications as needed	X	X	X	X	X	X	X	
Collect unused SB/DB study medication			X	X		X	X	
Dispense/collect COPD questionnaire[16]		X	X	X	X	X	X	X
Dispense/collect Medical Event Calendar	X	X	X	X	X	X	X	X
Dispense/collect PEF/study drug/rescue med logs	X	X	X	X	X	X	X	X
Assess adverse events		X	X	X	X	X	X	X
First Postdose meal[17]			X	X		X	X	

Data Analysis

The primary efficacy parameter was the time-normalized area under the FEV1 percent change from predose curve at the 24-hour clinic visit (Visit 4 for Part A and Visit 7 for Part B). Predose

was defined as the last FEV1 measurement that was collected before administration of the first double-blind dose at the 24-hour in-clinic visit (i.e., Visit 4 for Part A and Visit 7 for Part B).

For Part A, the primary efficacy parameter was defined over the first 12 hours (nAUC0-12-P). The primary analyses of the nAUC0-12-P were to compare arformoterol BID doses versus placebo and to make comparisons between the 3 arformoterol BID doses.

For Part B, the primary efficacy parameter was defined over the entire 24 hours (nAUC0-24-P). The primary analyses of the nAUC0-24-P were to compare arformoterol QD doses versus placebo and to make comparisons between the 3 arformoterol QD doses.

The primary efficacy analysis was performed using the ITT population and consisted of a linear model of nAUC at the 24-hour double-blind treatment clinic visit (Visit 4 for Part A or Visit 7 for Part B), with the predose FEV1 (i.e., predose value at Visit 4 for Part A or Visit 7 for Part B) as a covariate and treatment group as a fixed effect.

The pairwise comparisons between each arformoterol group and placebo and between the arformoterol groups were performed using the least-square means from the above model. No adjustments for multiple comparisons were performed. The least-square means and associated standard errors (SE) from the above linear model were presented for each of the double-blind treatment groups. To assess the dose-response relationship, a graphical display of the least-square means (±1 SE) for each treatment dose, in ascending order, was produced. In addition, the number of subjects, the mean, standard deviation, median, 25th and 75th percentiles, and the minimum and maximum values for nAUC at the 24-hour clinic visit were provided.

For the key secondary endpoint, the percent change in FEV1 from predose to 24 hours postdose (trough) value for Parts A and B, the analysis used the same model as defined for the primary efficacy endpoint with the exception that the covariate was the last FEV1 measurement that was collected before the first dose of double-blind medication was administered at the 6-hour in-clinic visit (Visit 3 for Part A or Visit 6 for Part B).

Other secondary endpoints used either the same linear model as defined for the primary endpoint or were summarized descriptively by visit and treatment group.

Disposition of Subjects

For Part A, 226 subjects were enrolled with 215 randomized to one of the 4 BID dosing treatment groups. Two hundred subjects completed Part A, 7 of the withdrawals were due to adverse events (4/7 were in the placebo group). One hundred ninety four of the 200 subjects who completed Part A were enrolled in Part B with 191 being randomized into one of the 4 QD treatment groups. Of the 191 subjects randomized, 7 did not complete Part B, 6 of which were due to adverse events (3/6 withdrawals were in the arformoterol 50 µg QD group). Study subjects in both Parts A and B were fairly well balanced between groups with regard to age, severity of pulmonary disease, and presence of co-morbid conditions. Males representation was slightly higher than female (55-60%), approximately 90% of subjects were Caucasian.

Analysis of Efficacy

Primary Efficacy Endpoint

Part A

For Part A (BID dosing), the primary efficacy endpoint in Part A was the time-normalized area under the FEV1 percent change from predose curve over 12 hours (nAUC0-12-P) after 14 days of double-blind treatment (Visit 4).

Arformoterol at all 3 BID dosing levels was superior to placebo with p values of 0.011, 0.019, and 0.036 vs placebo for the 5, 15, and 25 µg dosing groups, respectively. There was no dose response relationship observed for the nAUC0-12-P endpoint at the dose levels tested. Results are summarized in the following Table.

Study 091-026: Time-Normalized Area Under the FEV1 Percent Change From Predose Curve Over 12 Hours (nAUC0-12-P) After 14 Days of Double-Blind Treatment in Part A (Visit 4) of the Study (ITT Population) *[Table 11.1.4.1.1-1, clinstat\copd\091-026.pdf]*

$nAUC_{0\text{-}12\text{-}P}$[1]	Placebo BID N=54	ARF 5 µg BID N=54	ARF 15 µg BID N=54	ARF 25 µg BID N=53
n	46	49	50	47
Mean (SD)	1.9 (12.7)	6.9 (10.4)	6.3 (11.0)	5.8 (11.8)
LS Mean (SE)	0.9 (1.9)	7.1 (1.4)	6.7 (1.5)	6.4 (1.7)
Median	0.5	6.8	6.7	4.6
25th, 75th Percentiles	-5.8, 9.1	0.0, 10.8	-0.1, 12.6	-2.8, 13.5
P-value[2] vs				
Placebo	—	0.011	0.019	0.036
5 µg BID	—	—	0.845	0.747
15 µg BID	—	—	—	0.890

[1] The analysis consisted of a linear model of nAUC over the first 12 hours after dosing at the 24-hour, double-blind treatment clinic visit (Visit 4), with the Visit 4 predose FEV_1 as a covariate and treatment group as a fixed effect.

[2] Pairwise comparisons were performed using the least squares (LS) means from the above model; no adjustments were made for multiple comparisons.

An ad hoc analysis of the time-normalized area under the FEV1 percent change from baseline curve over 12 hours (nAUC0-12-B) after 14 days of double-blind treatment (Visit 4) was conducted.

Reviewer's Comment: This analysis was probably performed in an attempt to look for a dose response relationship. The change in FEV1 from baseline values would be greater than those from after 14 days of dosing thus allowing a larger range of FEV1 values from which to look for a dose-response. In fact, as seen in the table below, a small dose response is seen between the 5 and 15 µg BID treatment groups when this analysis is used. Taken into account with the safety analyses in larger studies 091-050 and 051, where 25 µg BID had more treatment related adverse events such as tremor, dizziness, and insomnia than the 15 µg group, the data support the use of 15 µg as the proposed clinical dose.

Study 091-026: Time-Normalized Area Under the FEV1 Percent Change From Baseline Curve Over 12 Hours (nAUC0-12-B) After 14 Days of Double-Blind Treatment in Part A (Visit 4) of the Study (ITT Population) *[Table 11.1.4.1.1-2, clinstat\copd\091-026.pdf]*

$nAUC_{0\text{-}12\text{-}B}$[1]	Placebo BID N=54	ARF 5 µg BID N=54	ARF 15 µg BID N=54	ARF 25 µg BID N=53
n	45	44	49	47
Mean (SD)	-0.1 (13.2)	17.7 (20.5)	20.0 (19.7)	20.5 (20.5)
LS Mean (SE)	-1.3 (2.0)	18.0 (2.8)	20.5 (2.5)	20.8 (2.9)
Median	-2.4	17.2	18.8	19.2
25^{th}, 75^{th} Percentiles	-9.3, 6.2	5.6, 28.1	8.0, 26.4	6.3, 30.2
P-value[2] vs Placebo	—	<0.001	<0.001	<0.001

[1] The analysis consisted of a linear model of nAUC over the first 12 hours after dosing at the 24-hour, double-blind treatment clinic visit (Visit 4), with the Visit 3 pre-first dose FEV_1 as a covariate and treatment group as a fixed effect.

[2] Pairwise comparisons were performed using the least squares (LS) means from the above model; no adjustments were made for multiple comparisons.

Although statistical analyses were not performed, by looking at the Mean, Median, and 75^{th} percentile values for the 3 arformoterol dose groups, a small dose-response seems likely.

Part B

For Part B (QD dosing), the primary efficacy endpoint was the time-normalized area under the FEV1 percent change from predose curve over 24 hours (nAUC0-24-P) after 14 days of double-blind treatment (Visit 7).

Arformoterol at all 3 QD dosing levels (15, 25, and 50 µg) was significantly more effective than placebo in increasing pulmonary function after 14 days of double-blind treatment. Again, no dose response was observed with the arformoterol QD doses. Results are summarized in the following Table.

Study 091-026: Time-Normalized Area Under the FEV1 Percent Change From Predose Curve Over 24 Hours (nAUC0-24-P) After 14 Days of Double-Blind Treatment in Part B (Visit 7) of the Study (ITT Population) *[Table 11.2.4.1.1-1, clinstat\copd\091-026.pdf]*

$nAUC_{0\text{-}24\text{-}P}$[1]	Placebo QD N=49	ARF 15 µg QD N=48	ARF 25 µg QD N=47	ARF 50 µg QD N=47
n	47	44	44	44
Mean (SD)	-2.4 (12.8)	8.5 (12.3)	6.0 (14.6)	8.1 (13.0)
LS Mean (SE)	-2.9 (1.9)	8.8 (1.7)	6.5 (2.2)	7.9 (1.8)
Median	-2.1	7.1	4.3	4.6
25^{th}, 75^{th} Percentiles	-10.7, 3.8	1.1, 12.6	-0.8, 11.2	-0.4, 15.4
P-value[2] vs				
Placebo	—	<0.001	0.001	<0.001
15 µg QD	—	—	0.407	0.736
25 µg QD	—	—	—	0.611

[1] The analysis consisted of a linear model of nAUC over the first 24 hours after dosing at the 24-hour, double-blind treatment clinic visit (Visit 7), with the Visit 7 predose FEV_1 as a covariate and treatment group as a fixed effect.

[2] Pairwise comparisons were performed using the least squares (LS) means from the above model; no adjustments were made for multiple comparisons.

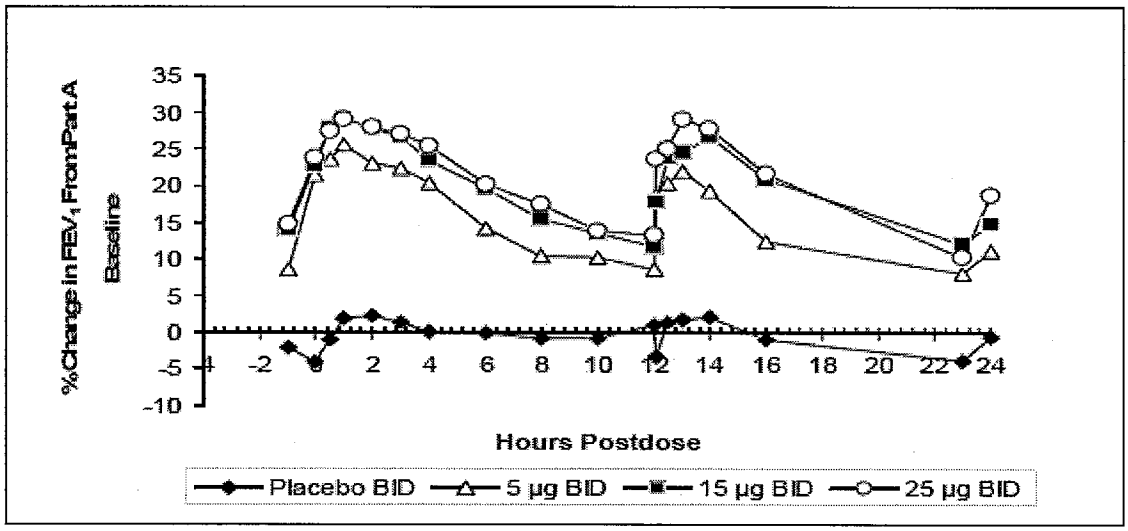
Reviewer's Comment: A similar ad hoc analysis was performed in Part B as was done in Part A; the time-normalized area under the FEV1 percent change from baseline curve over 24 hours (nAUC0-24-B) after 14 days of double-blind treatment. In Part B, unlike Part A, no dose relationship could be established using this analysis [Table 11.2.4.1.1-2].

Secondary Efficacy Endpoints

A key secondary endpoint for Parts A and B was percent change in FEV1 24-hour trough value after 14 days of double-blind treatment.

For Part A, the percent of improvement in the FEV1 trough value after 14 days of double-blind treatment was significantly higher in the arformoterol 5, 15, and 25 µg BID groups (11.1, 14.7, and 18.8 %, respectively) than in the placebo group. Higher doses of arformoterol resulted in greater improvement, thus supporting a dose-response relationship. See the Figure below.

Study 091-026: Mean Percent Change in FEV1 from Baseline Over 24 Hours After 14 Days of Dosing (Visit 4) in Part A of the Study [Figure 11.1.4.1.2-1, clinstat\copd\091-026. pdf]



For Part B, the percent of improvement in the FEV1 trough value after 14 days of double-blind treatment was significantly higher in the arformoterol 15 µg QD group than in the placebo group. While trough FEV1 values in the 25 and 50 µg doses were higher than for placebo, neither of these differences was statistically significant at the $p<0.05$ level.
Reviewer's Comment: The 15 µg QD dose had unexpectedly greater efficacy than either of the 2 higher arformoterol doses. The sponsor could not reconcile the large improvement observed with the 15 µg QD dose of arformoterol with data developed throughout the rest of the clinical development program. Investigation of this result, including analyses by gender, reversibility, current smoking status, steroid use at study entry, and concomitant rescue medication use were conducted but did not provide an explanation.

Other Secondary Endpoints
Evaluation of the many pulmonary function related secondary outcomes demonstrated that arformoterol at all BID and QD doses produced relatively rapid bronchodilation that was clinically and statistically superior to placebo.

In both Parts A and B there was also a slight decreased use of ipratropium bromide and racemic albuterol and increased morning and evening PEFR in all arformoterol treatment groups. There was also no clinically significant adverse withdrawal effects observed during the washout periods in either Parts A or B after discontinuation of arformoterol based on FEV1, FVC, or ipratropium bromide or racemic albuterol use. *[Sections 11.1.4.1.3 and 11.2.4.1.3, clinstat\copd\091-026. pdf]*

There was no meaningful difference in COPD symptom scores in any of the groups in either Parts A or B.

In Part A, a dose-response relationship was evident as the dose was increased from 5 µg BID to 25 µg BID, as evidenced by the mean increase in FEV1 trough values and the percentage of subjects who attained ≥15% improvement in FEV1 at trough. *[Section 11.1.4.1.2, clinstat\copd\091-026.pdf]*

Reviewer's Comment: It is no surprise that arformoterol was better than placebo in improving FEV1 based pulmonary function endpoints. The sponsor was able to establish a dose-response relationship in the BID dosing regimen of the study (Part A) but not with QD dosing (Part B). Other secondary endpoints, although not likely to be clinically significant, generally trended toward improvement in the arformoterol treated groups.

Summary of Efficacy

Arformoterol, at all doses tested in both BID and QD dosing regimens provided significant increases in FEV1 derived endpoints. In general, the BID dosing regimen appeared to produce more consistent results in pulmonary function endpoints and a dose-response relationship was able to be elicited in that group. Secondary, symptom-related, endpoints generally trended on the side of improvement with arformoterol although these changes were not really clinically meaningful.

Safety Review

This dose-ranging study was primarily reviewed for efficacy and to assess the ability to establish a dose-response relationship. The safety data provided in the study report was reviewed. Considering the safety database included in the Integrated Summary of Safety, this data did not provide any additional insight into the safety of arformoterol. It does, however, support the notion that there are no new or unforeseen treatment related adverse events seen with arformoterol that would not be predicted based on the mechanism of action of the drug product, Beta-receptor stimulation.

Study 091-021: Single-Dose, Dose-Ranging Study

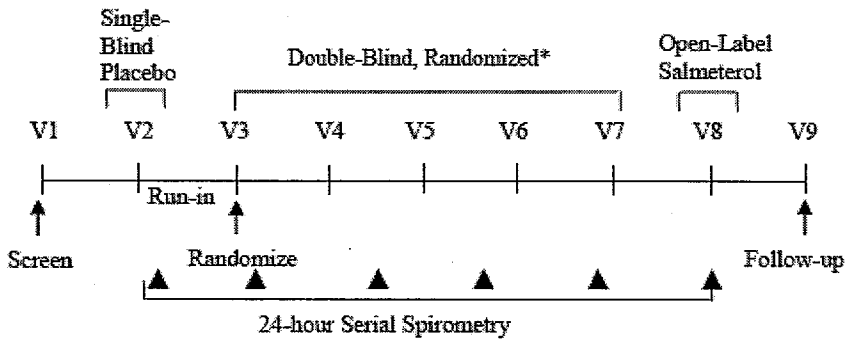
Reviewer's Note: This was a relatively small single-dose, cross-over design study in which study subjects had a large degree of reversibility to Beta-2 agonists at baseline (20%). As such, it is not surprising that it won on virtually all pulmonary function dependent endpoints. The lowest dose used, 9.6 µg QD, while having some activity, was shown to be a less efficacious than the higher doses of arformoterol or salmeterol.

Title of Study: A multicenter, randomized, placebo and active-controlled, five-way crossover study of arformoterol tartrate inhalation solution and salmeterol in subjects with chronic obstructive pulmonary disease (COPD)

Study Design and Conduct

This was a multicenter, randomized, placebo- and active-controlled, five-way crossover study consisting of four phases. In the screening period (Visit 1), subjects were assessed for enrollment eligibility. During the single-blind run-in period (Visit 2), eligible subjects received placebo treatment, their baseline COPD symptoms were recorded, and their compliance in completing the COPD questionnaire was assessed. In the double-blind/open-label treatment period (Visits 3-8), subjects received five individual double-blinded treatments (placebo, arformoterol 9.6 µg QD, 24 µg BID, 48 µg QD, and 96 µg QD) at Visits 3 through 7 and open-label treatment (salmeterol 42 µg BID) at Visit 8. All in-clinic treatment visits (Visits 2 to 8) were separated by 6- to 13-day washout intervals. At each treatment visit vital signs, ECGs, Holter monitoring, clinical chemistries including troponin values, serial spirometry, PK sampling, and COPD and AE assessments were performed [Table 9.1.1, clinstat\copd\091-021. pdf]. A safety evaluation was performed during the follow-up period (Visit 9). A study schematic is shown below.

Study 091-021: Schematic *[Figure 9.1.1, clinstat\copd\091-021. pdf]*



*Random-order of five treatments

Duration

This was a single-dose, 5-way cross-over study. The study was performed during the period of October 16, 2000 to May 18, 2001.

Study Centers
The study was conducted at 8 centers located in the United States.

Population
A total of 75 were randomized to treatment with 68 subjects completing the study and 7 terminating early

Treatments Administered
Subjects received five individual double-blinded treatments (placebo, arformoterol 9.6 μg QD, 24 μg BID, 48 μg QD, and 96 μg QD) at Visits 3 through 7 and open-label treatment (salmeterol 42 μg BID) at Visit 8. While the original protocol specified a total nebulization volume of 3 mL for each treatment, the nebulization volume was reduced to 2 mL after 13 subjects were randomized. Arformoterol solution was delivered via a PARI LC PLUS nebulizer and a PARI Dura-neb 3000 compressor. Since the study included instances of BID dosing with active drug (arformoterol 24 μg BID and salmeterol 42 μg BID), all QD dosing consisted of study medication (arformoterol or placebo) in the morning followed by placebo in the evening to maintain the blind.

Treatments/Materials
The blinded study treatments were:

- Arformoterol inhalation solution of 5, 15, 25, and 50 μg in 2 mL volume
- Salmeterol MDI 42 μg BID
- Placebo (citrate buffer)

Concomitant Medications
The use of oral prednisolone ≤ 10 mg/day or equivalent or intranasal or inhaled corticosteroids was allowed if the dose had been stable for at least 60 days prior to Visit 1 and would remain stable during participation. Leukotriene inhibitors could also be used but the dose had to be stable for at least 30 days prior to Visit 1 and remain stable throughout the study. Short-acting theophylline preparations were allowed but were to be withheld for 24 hours prior to Visits 2 through 8. Ipratropium bromide was to be used as needed throughout the study for supportive treatment.

Objectives
The primary objective was to compare the efficacy, safety, and tolerability of four different single-dose regimens of arformoterol (9.6 μg once daily [QD], 24 μg twice daily [BID], 48 μg QD, and 96 μg QD) with placebo in subjects with COPD.

Secondary objectives include:

- To determine any dose-effect trend among arformoterol 9.6 μg QD, 48 μg QD, and 96 μg QD

- Subject demonstrated reversible disease (≥ 10% improvement in FEV1 within 15 to 30 minutes after inhalation of 2 puffs (180 μg) of racemic albuterol MDI before randomization
- Subject had a chest x-ray within 2 months of Visit 1 that was consistent with the diagnosis of COPD (e.g., not diagnostic of pneumonia, other infection, atelectasis, or pneumothorax)

Study Specific Exclusion Criteria

The following individuals were ineligible for study participation:

- Subject was currently using disallowed medications or was unable to complete the medication washout periods
- Subject was scheduled for in-patient hospitalization, including elective surgery (inpatient or outpatient), during the study.
- Subject had a life-threatening or unstable respiratory status, including upper or lower respiratory tract infection, within 4 weeks of study entry
- Subject had a known history of asthma (except childhood asthma) or chronic respiratory disease (including a current history of sleep apnea) other than COPD (chronic bronchitis and/or emphysema)
- Subject had a history of lung resection of more than 1 full lobe
- Subject required continuous supplemental oxygen therapy. Use of supplemental oxygen (not to exceed 2 L/minute) at nighttime was allowed
- Subject had a change in dose or type of any medications for COPD within 4 weeks before the screening visit.
- Subject had a known sensitivity to arformoterol, salmeterol, ipratropium, or albuterol or to any of the excipients contained in any of their formulations.
- Subject had clinically significant abnormalities that may have interfered with the metabolism or excretion of the study drug (e.g., abnormalities of renal, hepatic, metabolic, or endocrine function)
- Were using any prescription drug for which concomitant Beta agonist administration was contraindicated (e.g., β-blockers)
- Had Familial Long QT Syndrome as suggested by subject reports of an unexplained sudden death of a relative less than 30 years of age, including non-traumatic sudden infant death syndrome (SIDS), or of a relative under the age of 55 years with unexplained bradycardia.

Data Analysis

Analyses of demographic and other baseline characteristics were performed for the 2 mL and entire ITT populations. All efficacy analyses were performed for the 2 mL ITT population, and selected efficacy analyses were repeated for the entire ITT population. The efficacy results are reported primarily in terms of the 62 subjects in the 2 mL ITT population because of the uniform nebulization volume and the fact that results from this group and those of the entire ITT population (that included 13 subjects who received 3 mL nebulization volumes) were similar.

- To compare the efficacy of arformoterol 24 μg BID and 48 μg QD
- To explore the relationship between plasma concentrations of arformoterol and selected pharmacodynamic and safety measures
- To compare the efficacy of four different single-dose regimens of arformoterol (9.6 μg QD, 24 μg BID, 48 μg QD, and 96 μg QD) with salmeterol 42 μg BID

Efficacy Variables

The primary efficacy endpoint was time-normalized area under the curve (nAUC) for the percent change from predose FEV1 over a 24-hour period expressed as FEV1 nAUC(0-24).

Secondary efficacy endpoints included the following:

- 24-hour mean FEV1.
- Percent change in FEV1 from predose to 24 hours postdose.
- Time to onset of response.
- Duration of response.
- Time to peak FEV1.
- Other analyses of FEV1 (during Visits 3 through 8, FEV1 at each time point, the change in FEV1 from pre-first dose, and percent change in FEV1 from pre-first dose).
- Peak expiratory flow (PEF).
- COPD symptom ratings.
- Ipratropium bromide use.
- Exacerbations of COPD.
- Subject/Physician Global Evaluation.
- Oxygen saturation.

Safety Variables
Safety assessments included adverse events; ECG findings, 24-hour Holter Monitoring; clinical laboratory parameters; vital signs; and physical examination findings.

Study-Specific Inclusion Criteria

- Subject gave written informed consent and privacy authorization for release of health information before participation
- Subject was aged ≥ 35 years on the day the informed consent was signed
- Subject had a primary diagnosis of COPD, which may have included components of chronic bronchitis and/or emphysema
- Subject had a minimum smoking history of 15 pack-years
- Subject had a baseline FEV1 that was ≤ 65% of the predicted normal value and > 0.70 L at either Visit 1 or 2
- Subject had an FEV1/forced vital capacity (FVC) ratio of ≤ 70% before randomization at either Visit 1 or 2

When the analyses by nebulization volume yielded differing results, those differences are described.

An adjustment was made for predose spirometry values when calculating AUC. All changes from predose calculations had the predose values subtracted from the postdose values. All changes from study baseline calculations had the study baseline values subtracted from the post-study baseline values. No other covariate adjustments were made.

For the primary efficacy analysis, the four pairwise tests of each arformoterol dose versus placebo were performed at the 0.0125 level. No adjustment for multiple comparisons was performed for any other analysis.

Disposition of Subjects

The mean age of subjects in the 2 mL ITT population was 63.2 years. The majority of subjects were male (67.7%) and most were Caucasian (98.4%).Study subjects had moderate to severe COPD with % predicted FEV1 of 40-43%. The study subjects had a mean FEV1 reversibility to short-acting bronchodilator of 20%.
Reviewer's Note: This was a cross-over study with all subjects received all treatments so treatment groups were inherently balanced with regard to pulmonary function, co-morbid conditions, etc. The subjects were highly reversible to administration of Beta-2 agonists. This subject selection benefited the pulmonary function related study endpoints, including the primary endpoint.

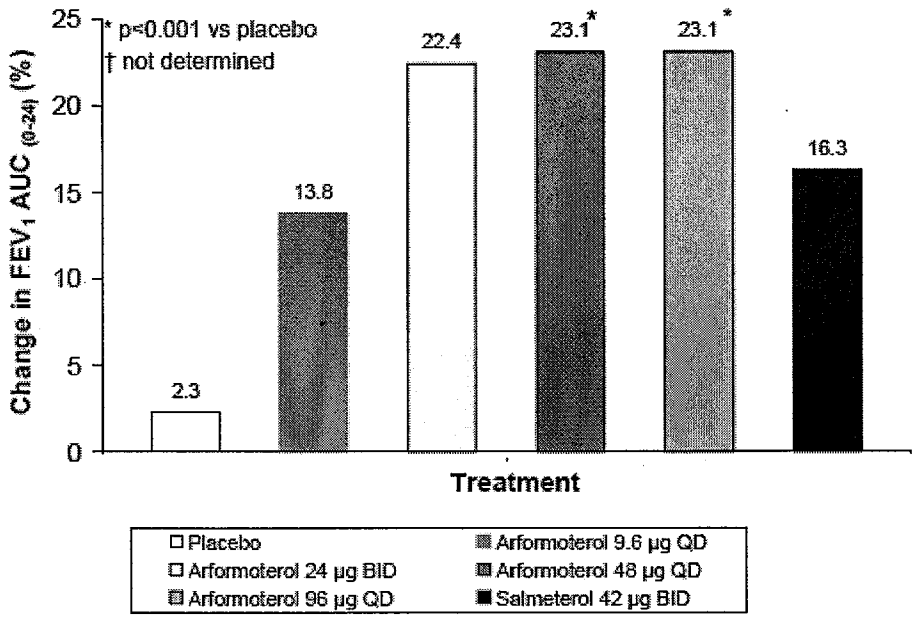
Analysis of Efficacy

Primary Efficacy Endpoint

The primary efficacy parameter was FEV1 nAUC(0-24). All arformoterol doses significantly ($p<0.001$) improved FEV1 nAUC(0-24) compared to placebo. The mean FEV1 nAUC(0-24) for arformoterol ranged from 13.8% with 9.6 μg QD to 23.1% with 48 μg QD and 96 μg QD. A dose-effect trend was evident up to 48 μg total daily dose but further increasing the dose to 96 μg QD did not further improve pulmonary function. Comparable improvement in FEV1 nAUC(0-24) was achieved with the 24-μg BID and 48-μg QD doses. Statistical comparisons were not performed for the salmeterol dosing group, however, it appears it would also show significant improvement over placebo. The following Figure displays the results for the primary endpoint in graphic form.

Appears This Way
On Original

Study 091-021: Mean FEV1 nAUC(0-24) (2 mL ITT Population) *[Figure 11.4.1.1-1, clinstat\copd\091-021.pdf]*



Results of the primary efficacy analysis for the entire ITT population were similar to those for the 2 mL ITT population, with all arformoterol doses significantly ($p<0.001$) improving FEV1 nAUC(0-24) compared to placebo *[Table 14.2.1.1A, clinstat\copd\091-021.pdf].*

Secondary Endpoints

For pulmonary function related endpoints, all arformoterol groups demonstrated significant improvement compared to placebo except the 9.6 µg QD group in trough mean % change in FEV1. In general, the 9.6 µg QD group did not perform as well as other groups and the 48 µg BID group did not perform better than the 24 µg BID group. The 96 µg QD performed similarly to the 24 and 48 µg BID groups. Salmeterol performed similarly to the arformoterol groups. Analysis of the total ITT population did not differ from that of the 2mL ITT population. Changes in COPD global evaluation score and symptom ratings were small but also supportive *[Section 11.4.1.2, clinstat\copd\091-021.pdf].*

Pharmacokinetic Analysis

The pharmacokinetic evaluation suggests that, although a large degree of inter-subject variability was seen, plasma concentration-time profiles generally increased with administration of higher total doses and the 24 µg BID dose results in higher total exposure to arformoterol as compared to 48 µg QD dose. Plasma concentrations of arformoterol were frequently BLQ following treatment; therefore, the concentration-dose relationship could not be adequately evaluated *[Table 11.4.4-1, clinstat\copd\091-021.pdf].*

Efficacy Conclusion

All arformoterol doses won on the primary endpoint of FEV1 nAUC(0-24) vs to placebo. There was some evidence of a dose-response relationship as the 9.6 µg QD group did not perform as well as the 48 and 96 µg QD groups. Higher dose groups of 48 µg BID and 96 µg QD offered no benefit over the 24 µg BID dose group. Analysis of the total ITT population did not differ from that of the 2mL ITT population. Secondary endpoints generally supported the primary endpoint.

Safety Review
This dose-ranging study was primarily reviewed for efficacy. The safety data provided in the study report was reviewed. There were relatively few AEs in this small study. However, it did appear that there was a higher incidence of Nervous System related side effects (nervousness and tremor in the 48 and 96 QD dosing groups. *[Table 12.2.3.1-1, clinstat\copd\091-021.pdf]*

Considering the safety database included in the Integrated Summary of Safety, the data in this small study did not provide any additional insight into the safety of arformoterol. It does, however, support the notion that there are no new or unforeseen treatment related adverse events seen with arformoterol that would not be predicted based on the mechanism of action of the drug product, Beta-receptor stimulation.

10.2 Line-by-Line Labeling Review

At the time of this Medical Officer Review specific labeling discussions had not yet been initiated with the Applicant

REFERENCES

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

/s/

Anthony Durmowicz
8/31/2006 01:48:35 PM
MEDICAL OFFICER

Badrul Chowdhury
9/1/2006 09:46:18 AM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Products

APPLICATION #:	21-912	**APPLICATION TYPE:**	NDA
SPONSOR:	Sepracor	**PROPRIETARY NAME:**	NA
INVESTIGATOR:	Multiple	**USAN NAME:**	arformoterol tartrate
CATEGORY:	Bronchodilator	**ROUTE:**	Oral Inhalation
MEDICAL OFFICER:	Anthony Durmowicz, MD Eugene Sullivan, MD FCCP	**REVIEW DATE:**	2006

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
December 8, 2005	January 4, 2006	NDA	Paper volume 1 stamp date was 12/12/05 however the electronic NDA was unreadable and had to be resubmitted twice. The final stamp date for the submission in the EDR was 1/4/06.

REVIEW SUMMARY:

This is a 45-day Filing Review of NDA 21-912. This NDA is submitted in support of the use of the bronchodilator, arformoterol tartrate inhalation solution, 15mcg, twice daily for the long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Arformoterol tartrate is the (R,R)-enantiomer of racemic formoterol (e.g., Foradil), a long-acting beta-2 agonist (LABA). The Sponsor has identified two pivotal clinical trials. Supporting studies include two dose-ranging studies and one long-term safety study. The submission appears complete enough to allow for a further more complete review, and is therefore considered "fileable." The Division does not plan to present this NDA to the Pulmonary-Allergy Drugs Advisory Committee. Audits of clinical centers will be requested of the Division of Scientific Investigations.

Note: This review was drafted by Dr. Durmowicz. The draft was then modified and entered into the Division File System by Dr. Sullivan in Dr. Durmowicz' absence.

OUTSTANDING ISSUES:

Comments to be sent to Applicant in 74-day letter.

RECOMMENDED REGULATORY ACTION

__X__ **FILEABLE** _____ **NOT FILEABLE**

REVIEWERS

Medical Reviewer: Anthony G. Durmowicz, MD

Deputy Division Director: Eugene J. Sullivan, MD

I. General Information

Drug Substance

Trade Name:	NA
US Adopted Name:	arformoterol tartrate
International Non-proprietary Name:	arformoterol tartrate
Molecular Formula:	$C_{23}H_{30}N_2O_{10}$
Molecular Weight:	494.5
Manufacturer:	Sepracor, Marlborough, MA, USA

This NDA is submitted in support of the use of Arformoterol Tartrate Inhalation Solution, 15mcg, twice daily for the long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Arformoterol is the (R,R)-enantiomer of racemic formoterol, a long-acting $beta_2$-agonist (LABA), that binds to beta-adrenergic receptors in the lung resulting in smooth muscle relaxation with resultant bronchodilation. A formulation of the racemic formoterol, Foradil Aerolizer (Novartis), is currently approved for COPD and asthma.

As of August 17, 2005, the NDA clinical cutoff date, a total of 16 clinical trials have been completed, including two trials proposed as being "pivotal", two dose-ranging studies, and a 12-month safety study. One additional trial is ongoing.

II. Background and Rationale

Formoterol is a selective, potent LABA presently marketed in a dry powder inhalation formulation (Foradil Aerolizer, Novartis). Formoterol has two chiral centers and has four potential stereoisomers with the marketed product containing equal amounts of the (R,R) and (S,S) enantiomers. Arformoterol tartrate contains only the more active (R,R) enantiomer of formoterol. The sponsor notes that the other two LABAs available to treat bronchoconstriction associated with COPD are available only as dry powder inhalers and

that arformoterol tartrate solution was developed as an alternative LABA to the DPI products. **Reviewer's Comment: The sponsor does not appear to plan to market arformoterol as a safer or more effective form of formoterol but in it's rationale concentrates on the idea that it is being offered in a dosing format that may be more acceptable to the older COPD population (inhaled solution vs. a single-dose DPI).** The sponsor has previously developed and marketed levalbuterol (Xopenex), a short acting beta$_2$-agonist bronchodilator containing only the (R) enantiomer of albuterol, for asthma.

Recently, studies of other LABAs (Serevent Inhalation Aerosol, and Foradil Aerolizer) in patients with asthma have suggested that this class of drugs may be associated with an increased risk of severe asthma exacerbation and asthma-related death. As a result of these findings, the product labels of approved LABAs, both of which are indicated for asthma and for COPD, have been modified to highlight the risk. This application is for a COPD indication, and the Applicant has stated that it does not intend to develop the product for asthma. There are insufficient data to determine whether the risk observed in asthma patients may also be present in COPD. It is quite likely that, even if the asthma indication is not sought, this product will be commonly used off-label for asthma. **Reviewer's Comment: During the course of the review, the Division will address the ramifications of the known asthma risk for this product. Considerations may include specific labeling language, or possibly a request for a large, simple safety study designed to examine the risk in COPD patients.**

III. Regulatory and Foreign Marketing History

A. Regulatory History

Arformoterol tartrate inhalation solution was developed under IND 55,302, which was submitted on February 20, 1998. Initially, the drug was being studied for COPD [redacted] b(4)

An End-of-Phase-2 meeting was held on September 6, 2001. A Pre-NDA meeting was held on March 7, 2005. Other significant Pre-NDA communications occurred at an August 17, 2005, teleconference. At this teleconference, the lack of racial/ethnic subgroup data in the pivotal trials was discussed. The Applicant was informed that this is an issue that will be considered during the NDA review.

B. Foreign Marketing History

As of January 2006, arformoterol inhalation solution is not marketed in any country. This NDA is the first global regulatory submission for arformoterol.

IV. Items Required for Filing and Reviewer Comments

A. Necessary Elements (21 CFR 314.50)

The table below lists the necessary elements for an NDA and their location within the electronic submission.

Necessary Elements		
Type	**Status**	**Location (Item #: Folder from Main Table of Contents)**
Application Form (FDA 356h):	Present	N21912\cover.pdf
Investigator Debarment Certification:	Present	N21912\other\debar.pdf
Financial Disclosure:	Present	N21912\other\financial.pdf
Statements of Good Clinical Practice:	Present	Volume 1
Environmental Assessment:	Present	
Proposed label:	Present	N21912\labeling\.pdf
Integrated Summary of Efficacy	Present	N21912\clinstat\ise\ise.pdf
Integrated Summary of Safety:	Present	N21912\clinstat\iss\iss.pdf
Integrated Summary of Benefits and Risks:	Present	N21912\clinstat\riskben\riskben .pdf
Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures:	Present	N21912\clinstat\clinsum.pdf (p69/411)
Statistical Analyses:	Present	N21912\clinstat\clintoc.pdf
Pediatric Use Section:	Pediatric Waiver Requested	N21912\other\reghistory.pdf
Case Report Tabulations:	Present	N21912\crftoc.pdf
Case Report Forms (for patients who died or did not complete study):	Present	N21912\crftoc.pdf
Patent Information:	Present	N21912\other\patinfo.pdf N21912\other\patcert.pdf

V. Preliminary Review of Package Insert

Draft labeling is included in the electronic submission. The Clinical Studies section of the proposed label refers to the two identical, placebo-controlled proposed "pivotal" trials that also had a salmeterol active control group. **Reviewer's Comment: The safety section of the label only lists the adverse events seen with the proposed 15 mcg bid dose. The study also had 25 mcg bid and 50 mcg qd dosing groups.** In both pivotal 12-week trials, arformoterol, 15 mcg twice daily, significantly improved post-dose bronchodilation as measured by the percent increase in FEV_1 at the end of the 12-hour dosing interval (the primary endpoint) over the entire 12 week trial period and at each specific assessment time point (Weeks 0, 6, and 12). The median time to achieve a 10% improvement in FEV_1 from

the visit predose level was three minutes after the first dose and 10 minutes after 12 weeks of daily treatment. With regard to salmeterol being used as an active control, the text of the proposed label makes no claim of superiority to salmeterol. **Reviewer's Comment: The claims being proposed in the label appear to be very similar to those made for the racemic formoterol product. That is, there are no overt attempts to make claims that arformoterol is any safer or is more effective than racemic formoterol.**

VI. Clinical Studies

As of the cutoff date (August 17, 2005), 16 clinical trials have been completed with doses ranging from 5 mcg bid to 96 mcg qd. Other than one study that used an oral, radiolabeled formulation of arformoterol, two similar formulations of nebulized solution were used in the trials, one with the delivered dose diluted to 3 mL and another where the dose was diluted to 2 mL. The 16 completed trials include:

- Five Phase 1 studies in healthy subjects (091-001, 091-007, 091-012, 091-013, and 091-018).
- Two Phase 1 studies conducted in subjects with renal (091-014) and hepatic impairment (091-015) versus healthy subjects.
- Two Phase 1 and 2 Phase 2 studies in subjects with asthma (091-002, 091-016, 091-003, and 091-004)
- Two Phase 2 trials in subjects with COPD (single-dose, 091-021 and a 4 week placebo-controlled, multi-dose trial, 091-026)
- Three Phase 3 trials in subjects with COPD, two identical, 12 week, placebo-controlled pivotal studies that included a salmeterol comparator group (091-050 and 091-051) and a 1 year open-label safety trial in which subjects received 50 mcg of formoterol qd (091-060)

Another study (091-010), a phase 2 multi-center, randomized, open-label study of arformoterol tartrate inhalation solution and salmeterol in subjects with COPD, was planned to enroll 52 subjects but the sponsor terminated the study after 11 subjects were screened and 1 subject randomized and who received one dose of 45 mcg of arformoterol. The study was terminated because it was determined by the sponsor that the objectives of the study would be better addressed in the pivotal program.

In addition to these trials, one additional COPD trial is ongoing, an open-label, randomized, multiple-dose, 3-way crossover study of arformoterol and racemic formoterol in subjects with mild to moderate COPD (091-019). **Reviewer's Comment: The protocol for another study, 091-061, a 6-month safety study of 15 and 25mcg arformoterol bid, is included in the NDA filing but, as of yet, no reference has been found to it.**

The main clinical program consists of:

- Two Phase 2 dose-ranging studies dose-ranging trials (091-021 and 091-026)
- Two pivotal, Phase 3 placebo-controlled 12 week studies (091-050 and 091-051)
- One Phase 3, open-label, 1-year safety and efficacy trial (091-060)

The Applicant proposes that the five clinical trials listed above be considered to represent the primary support for efficacy and safety. Other studies, including 4 studies in asthmatic

subjects (091-002, 003, 004, and 016) will provide supportive evidence of safety in a different disease population.

A total of 3,200 subjects participated in the 16 completed trials. This includes 146 healthy volunteers, 2,539 COPD patients, 435 asthmatic patients, 40 subjects with renal impairment, and 40 subjects with hepatic impairment. A total of 2,399 subjects were exposed to arformoterol, including 1,637 COPD patients, and 342 asthma patients. At least 500 were exposed to 50mcg once daily for one year. **Reviewer's Comment: The proposed dose for marketing is 15mcg bid while the dose in the one year safety study was 50mcg given once daily. Because the total daily dose used in the safety study (50mcg) is higher than the total daily dose proposed for marketing (30mcg, as 15mcg BID), this safety study may be adequate to support the proposed marketed dose, as the Division has previously indicated to the Applicant. Although the total daily dose would suggest adequate support, there is one potential additional consideration in this regard. It has been postulated that tonic beta-adrenergic receptor agonist activity may result in receptor desensitization, and that such desensitization may be associated with adverse effects of chronically administered beta-agonists. It is possible that BID dosing might result in more continuous receptor binding than QD dosing and therefore might be associated with more adverse effects. These, if any, would be expected to be local effects, not systemic (e.g. cardiac). This issue will be considered during the review.**

A. Pivotal Studies

As discussed above, two "pivotal" studies are submitted. These include identical 12-week studies (091-050 and 051), both conducted in the United States.

The same inclusion criteria were used for the 2 pivotal studies. Subjects were ≥ 35 years old, had a smoking history of >15 pack-years, an FEV_1 ≤65% of normal predicted value and >0.70 L, and an FEV_1/FVC of ≤0.70. Subjects with a history of asthma or any chronic respiratory disease other than COPD, including a current history of sleep apnea, the need for continuous oxygen therapy, or a total blood eosinophil count > 5% of total white blood cell count were excluded.

The primary endpoint was the percent change in trough FEV_1 from study baseline to the end of the dosing interval (12 hours post second dose for the BID treatment and 24 hours post dose for the QD treatment arm) over the double-blind period. Secondary endpoints included the time-normalized area under the percent change from visit pre-dose curve for FEV_1 over 12 hours, peak percent predicted FEV_1, time-normalized area under the percent change in FEV_1 from study baseline, time to peak change in FEV_1, etc. Symptom and patient functioning endpoints included supplemental ipratropium bromide use, rescue albuterol use, COPD exacerbations, SGRQ, distance walked in 6 minutes, and baseline and transitional dyspnea index.

In addition to a placebo group, the pivotal studies included an active control group that used salmeterol, 42mcg BID.

Of note is that during the pivotal trials, 091-050 and 051, the sponsor unblinded itself and the DMSB to 24 patients who had adverse events related to either cardiac or respiratory systems. 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 50mcg of arformoterol QD than the group receiving the active comparator salmeterol at 42mcg BID. The sponsor took

it upon itself to unblind these 24 patients and assess the safety data only. When informed, the Division noted concern that this unblinding could undermine the integrity of the pivotal studies. The Division stated in a Pre-NDA meeting with the sponsor on 3/7/05 that a convincing case concerning blind breaking must be made in the NDA and it should be included as an appendix to NDA Section 8, including a detailed explanation of the course of events, step by step, day by day that provides a convincing substantiation that the studies were not compromised. **Reviewer's Comment: This issue has been discussed with the sponsor several times and they have been notified that during NDA review we will be looking carefully at the unblinding issue.**

Summary of Applicant's Proposed Pivotal Studies

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 FEV_1 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

B. Supporting Studies

In addition to the 2 proposed "pivotal" studies, the sponsor states that the clinical program in support of efficacy consists of 2 Phase 2 dose-ranging studies dose-ranging trials (091-021 and 091-026) and 1 Phase 3, open-label, 1-year safety and efficacy trial (091-060). The table below summarizes the features of these 3 "supporting" studies.

Study # Country/ Dates	Design	Treatments	Duration	# of Subjects	Population	Primary Endpoint
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
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
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

C. Other Studies

In addition to those that are mentioned in Sections A and B above, other clinical studies have been conducted with arformoterol. These include:

- four studies in asthma subjects
- two adult/elderly normal volunteer PK studies
- two studies in subjects with either impaired renal or hepatic function
- three metabolism/drug interaction studies

Summaries of these studies are included in the Appendix to this Review.

VII. Advisory Committee Meeting

There are no issues at present that would require input from the Pulmonary Allergy Drugs Advisory Committee.

VIII. DSI Review / Audit

Pending review of the data from the pivotal studies by the Biometrics reviewer (Dr. Ted Guo) to assess for evidence of treatment-by-site interaction, there are no plans to otherwise request audits by the Division of Scientific Investigation. This decision is based on the facts that the molecular entity is not a new NME but is the active enantiomer of racemic formoterol which is already approved for the treatment of both asthma and COPD, the efficacy data are as would be expected for the product, and the sponsor is not making any novel claims for the product.

IX. Summary

This NDA is submitted in support of the use of the bronchodilator, arformoterol tartrate inhalation solution, 15mcg, twice daily for the long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The Sponsor has identified two pivotal clinical trials. Supporting studies include two dose-ranging studies and one long-term safety study. The submission appears complete enough to allow for a further, more complete review, and is therefore considered "fileable." There are no plans at present to present this NDA to the Pulmonary-Allergy Drugs Advisory Committee. At present, no audits of clinical centers will be requested.

A. Decision

The submission appears adequate from a clinical standpoint to allow for further review, and is therefore fileable.

B. Comments to Sponsor for the 74-Day Letter

1) As discussed during the telephone conference on August 15, 2005, the limited available data in racial and ethnic subgroups will be considered during the NDA review. We encourage you to generate safety and efficacy data in these populations.

2) On November 18, 2005, the FDA issued a public health advisory regarding risks associated with long-acting $beta_2$-agonists in patients with asthma (http://www.fda.gov/cder/drug/advisory/LABA.htm). This advisory states that manufacturers of marketed long-acting $beta_2$-agonists indicated for the treatment of asthma were asked to update their existing product labels with new warnings and a Medication Guide. The advisory also states that information is not available to know whether there are similar concerns in patients with COPD. During the course of the review of your NDA we will consider how this issue should be addressed in the product label, and whether further data to explore this issue, such as a large, simple safety study, will be requested.

Reviewed by:

Anthony G. Durmowicz, MD
Medical Officer, DPAP

Eugene J. Sullivan, MD
Deputy Director, DPAP

X. Appendix: Additional Clinical Trials Conducted with Arformoterol

Study No. Report No.	Description of Study	Total No. Subjects	Country
091-001	Tolerability and pharmacokinetics of single increasing doses in normal volunteers (6-96 mcg).	16	USA
091-002	Tolerability and pharmacokinetics of single increasing doses in subjects with mild to moderate asthma (6-96 mcg).	6	USA
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
091-012	Metabolism and pharmacokinetics of a single oral radio-labeled dose in normal volunteers (50mcg po dose)	8	USA
091-013	Tolerability and pharmacokinetics after a single 50mcg dose in healthy elderly subjects	48	USA
091-014	Tolerability and pharmacokinetics of a single 50mcg dose in subjects with mild to severe renal insufficiency	40	USA
091-015	Tolerability and pharmacokinetics of a single 50mcg dose in subjects with mild to severe hepatic insufficiency	40	USA
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
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
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
091-004	Safety, efficacy, and tolerability of multiple once-daily doses in subjects with asthma (24, 48, 72mcg)	357	USA

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/s/

Eugene Sullivan
2/14/2006 10:51:52 AM
MEDICAL OFFICER