CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-912

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA: 21-912	Submission Date: April 18, 2006
Brand Name	[ ]
Generic Name	Arformoterol tartrate Inhalation Solution
Reviewer	Shinja R. Kim, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D.
Sponsor	Sepracor Pharmaceuticals, Inc.
OCP Division	DCP 2
ORM Division	Division of Pulmonary and Allergy Drug Products (DPADP)
Submission Type; Code	NME; 3S
Formulation; Strength(s)	Oral Inhalation Solution, 15 mcg/2 mL Unit-Dose
Indication	Long term treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema

b(4)

Background: Arformoterol is a selective long-acting β_2-adrenergic receptor agonist indicated for twice daily long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The study report (#091-019) was included when the 120-Day Safety Update Report for NDA 21-912 was submitted however the study was not reviewed by me with the other NDA studies. Thus this review is addendum to the original review (dated August 4, 2006).

Study 091-019: This was an open-label, randomized, multiple-dose, 3-way crossover study in subjects with mild to moderate Chronic Obstructive Pulmonary Disease (COPD). The primary objective of this study was to compare systemic exposure of (R,R)-formoterol after administration of arformoterol tartrate inhalation solution and Foradil® dry powder inhaler (DPI) at steady state in these subjects. The study involved 3 dose periods and 3 washout periods.

Eligible subjects received 3 different treatments in random order, each for 13 consecutive days twice daily and a single dose on the morning of the 14th day. The 3 treatments are consisted of 12 μg of racemic formoterol fumarate (Foradil® Aerolizer™) (Treatment A), 15 μg of nebulized arformoterol tartrate inhalation solution (Treatment B), and 24 μg of racemic formoterol fumarate (Foradil® Aerolizer™) (Treatment C).

The results from this study are summarized as follows:

- After 14 days, arformoterol 15 μg inhalation solution BID produced similar (R,R)-formoterol plasma exposure (Cmax and AUC) to that from racemic formoterol 12 μg BID and lower than that with racemic formoterol 24 μg BID.
- Treatment with arformoterol 15 μg BID for 14 days provided similar accumulation of (R,R)-formoterol plasma concentrations (approximately 2.5 fold) compared with racemic formoterol 12 or 24 μg BID.
- There were insignificant differences in absorption rate across treatments after 14 days, with a median tmax of 0.92 hr in the arformoterol, 0.64 hr in the Foradil 12 μg, and 0.75 hr in the Foradil 24 μg, groups, respectively.
- The elimination rate (based on median $t_{1/2}$) of (R,R)-formoterol after arformoterol treatment for 14 days was similar to that obtained after racemic formoterol treatments (median $t_{1/2}$ range across treatments: 14 to 17 hrs).

- The amount of (R,R)-formoterol recovered in the urine (Ae) after 14 days was similar following treatment with arformoterol 15 μg and racemic formoterol 12 μg; these results are consistent with the exposures in plasma.
- There was an overall positive association between (R,R)-formoterol plasma concentration and percent change in FEV1.

In conclusion, the systemic exposure to (R,R)-formoterol following 15 μg of arformoterol inhalation solution is similar to that following 12 μg of racemic formoterol inhalation Aerosol (Foradil® Aerolizer™). Detailed review of the study results is provided in the Attachment.

Recommendation: The Office of Clinical Pharmacology has reviewed the Study and found that it is acceptable. No further action is indicated.

Shinja R. Kim, Ph.D, DCP 2

Emmanuel Fadiran, Ph.D., Team Leader

ATTACHMENT

Study No. 091-019

Study Type: Multiple-dose PK in patients with COPD.

Title: An Open-Label, Randomized, Multiple Dose, 3-Way Crossover Study of Arformoterol Tartrate Inhalation Solution and Foradil® (Racemic Formoterol) in Subjects with Mild to Moderate Chronic Obstructive Pulmonary Disease (COPD).

Investigators: Multi-centers

Objectives:

Primary Objective: To compare systemic exposure to (R,R)-formoterol after administration of arformoterol tartrate inhalation solution and Foradil® dry powder inhaler (DPI) at steady state in subjects with COPD.

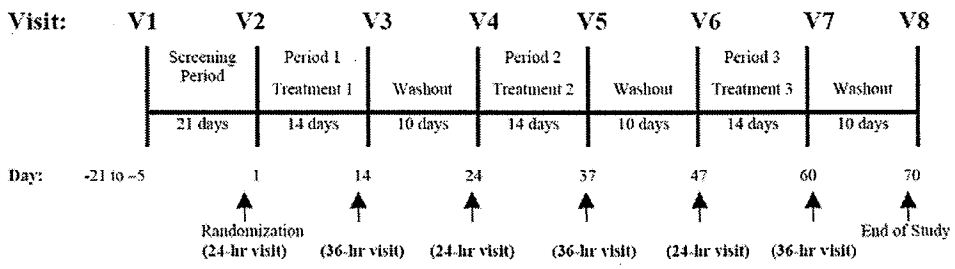
Secondary Objectives:

- To calculate the accumulation ratio and terminal half-life (t½) of (R,R)-formoterol following administration of arformoterol tartrate inhalation solution and Foradil.
- To characterize and describe airway function (spirometry) changes with treatment.
- To characterize the PK profile of (S,S)-formoterol following administration of Foradil.

Methodology: This was an open-label, randomized, mutiple-dose, 3-way cross-over study in male and female subjects with COPD. Thirty-nine subjects were randomized to ensure that a minimum of 24 subjects completed the study. The study involved 3 dosing periods and 3 washout periods. Subjects received the following 3 different treatments in random order twice daily (BID) for 13 consecutive days, and a single dose on the morning of the 14th day:

- Treatment A: 12 µg of racemic formoterol fumarate (Foradil® Aerolizer™) BID (lot#S4A016E and S4A0Z0E).
- Treatment B: 15 µg of nebulized arformoterol tartrate inhalation solution BID (lot#02904B).
- Treatment C: 24 µg (2 capsules of 12 µg) of racemic formoterol fumarate (Foradil® Aerolizer™) BID (lot#S4A016E and S4A0Z0E).

The study schematic is shown below:



Diagnosis and Main Criteria for Inclusion: Males and females at least 35 years old with a primary clinical diagnosis of COPD, a baseline FEV_1 of ≤65% of predicted, an FEV_1 >0.70 L, and an FEV_1/forced vital capacity (FVC) ratio of <70%.

PK measurements:

Blood: At Visit 2, 4, and 6 after receiving the morning dose, were as follows: pre-first dose and post first dose at 15, 30 and 45 min and at 1, 2, 6, and 12 hrs (pre-2nd dose). In addition, blood samples for steady-state determination were obtained on the 12th and 13th days of each dose period at 264 and 288 hrs post first dose. At Visit 3, 5, and 7, after receiving the single morning dose, blood samples were collected for up to 96 hrs as follows: pre-last morning dose and post last dose at 15, 30 and 45 min and at 1, 2, 6, 12, 16, 24, 48, 72 and 96 hrs.

Urine: Samples were collected as follows: at Visit 2, 4, and 6 pre-first dose, 0-6, and 6-12 hrs post first dose (and pre-2nd dose), and at Visit 3, 5, and 7 at 0-6, 6-12, and 12-24 hrs post last morning dose.

Efficacy measurements: Spirometry assessments were performed during screening Visit 1, at Visits 2, 4, and 6 pre-first dose and post first dose at 15 minutes, and 1, 2, 4, 6, and 12 hrs (pre-second dose). Additional spirometry assessments were performed during Visits 3, 5, and 7 at 11 and 12 hrs post the admission evening dose (the latter is pre-last morning dose) and at 15 minutes and 1, 2, 4, 6, and 12 hrs.

Criteria for Evaluation:

Pharmacokinetic: The primary endpoint for this study was exposure to (R,R)-formoterol, measured by the PK parameters AUC(0-τ) and Cmax. Additional PK parameters included tmax, t½, AUC(0-∞), and accumulation ratios as measured by RCmax (ratio of Cmax for the last and the first dosing periods of the multiple dosing regimen) and RAUC(0-τ) [ratio of AUC(0-τ) for the last and first dosing periods of the multiple dosing regimen]. In addition, the same PK parameters as those for (R,R)-formoterol were determined for (S,S)-formoterol following Foradil® administration.

Efficacy: Airway function (spirometry) endpoints included FEV_1 and % predicted FEV_1.

Safety: Safety assessments included adverse events (AEs), vital signs, physical examination findings, 12-lead ECG findings, clinical laboratory parameters.

Statistical Methods:

PK:
Primary: The (R,R)-formoterol parameters AUC(0-τ) and Cmax , in logarithmic scale, were analyzed using a linear model with sequence, treatment group, and period as fixed effects and subject nested within sequence as a random effect. From this linear model, the following were derived: least squares (LS) means of each treatment, treatment differences, and 90% confidence intervals (CI) of the differences for AUC(0-τ) and Cmax between 15 µg of nebulized arformoterol tartrate inhalation solution BID and 12 µg of racemic formoterol fumarate BID or 24 µg of racemic formoterol fumarate BID. These results were transformed to the original scale by exponentiation to obtain geometric least squares means, treatment ratios, and 90% CIs of these ratios.

Secondary: Using the same approach as described in the primary analysis above, (R,R)-formoterol AUC(0-∞) was analyzed. PK parameters were summarized descriptively by treatment group, both after a single dose (post-first dose) and at steady state (post-last dose). In addition to descriptive statistical summaries, the 95% CI of RCmax and RAUC(0-τ) of (R,R)-formoterol for arformoterol tartrate inhalation solution and racemic formoterol were presented. The achievement of steady state was confirmed by visual examination of the graphical displays of mean trough drug concentrations.

PD/safety: Descriptive statistics were generated. Safety and efficacy summaries were based on the Intent-to-Treat (ITT) population (PK analyses were based on the PK population). Subjects were analyzed by treatment received.

Note: Intent-to-treat (ITT) population: consisted of all subjects who received at least 1 dose of study medication. The PK population consisted of all subjects who were in the ITT population and had evaluable PK data available.

RESULTS

Disposition of Subjects: Thirty-nine subjects were randomized in this study. Of the 39 dosed, 6 subjects (15.4%) discontinued during the course of the study. Two subjects (5.1%) voluntarily withdrew (both receiving Foradil 24 μg), 2 subjects (5.1%) discontinued due to an adverse event (1 on Foradil 12 μg and 1 on Foradil 24 μg), and 2 subjects (5.1%) withdrew due to a protocol violation (1 received arformoterol in the first treatment period, and mistakenly received the same treatment in the second treatment period). A total of 33 subjects (84.6%) completed the study.

Protocol Deviations: Sponsor reported that 16 subjects (41.0%) in the ITT population had important protocol deviations (IPD) during the study, and the most common IPD was failure to meet the inclusion/exclusion criteria.

Pharmacokinetics:

(R,R)-formoterol:

Mean single and multiple dose concentration-time profiles are shown in Figure 1. Descriptive statistics after single and multiple doses are presented in Table 1 and Table 2, respectively. Statistical analysis of steady-state of plasma (R,R)-Formoterol is presented in Table 3.

Figure 1: Mean (R,R)-Formoterol Plasma Concentration-Time Profiles following single dose (left panel) and steady state (right panel) of Arformoterol and Racemic Formoterol in COPD Subjects

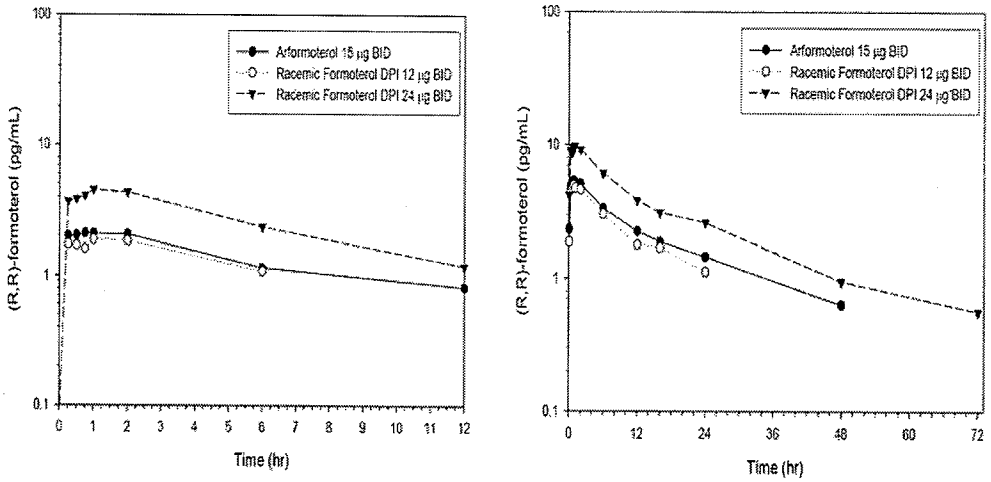


Table 1: Descriptive Statistics of Plasma (R,R)-Formoterol PK Parameters following Single Doses of Arformoterol or Racemic Formoterol in COPD Subjects

Treatment/ Parameter	Statistics	Arformoterol 15 µg N=35	Racemic Formoterol 12 µg DPI N=35	Racemic Formoterol 24 µg DPI N=36
$AUC_{(0-\tau)}$ (pg*hr/ml)	n	13	9	21
	Mean (SD)	34.9 (28.2)	28.3 (16.9)	46.3 (30.7)
	Median (Range)	21.6 (5.0, 97.7)	22.8 (12.5, 57.8)	37.1 (16.4, 145.3)
C_{max} (pg/ml)	n	27	28	34
	Mean (SD)	3.16 (2.58)	3.00 (1.97)	5.68 (3.31)
	Median (Range)	2.15 (1.01, 12.50)	2.26 (0.98, 7.83)	5.09 (1.21, 16.30)
t_{max} (hr)	n	27	28	34
	Mean (SD)	1.41 (2.23)	1.01 (0.70)	1.09 (1.05)
	Median (Range)	0.75 (0.25, 12.02)	0.85 (0.22, 2.08)	0.93 (0.25, 6.00)

$AUC_{(0-\tau)} = AUC_{(0-12\ hr)}$
NOTE: N represents the number of subjects in PK population and n represents the number of subjects with evaluable data for the indicated parameter.
Cross Reference: Table 14.2.3.1

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Table 2: Descriptive Statistics of Plasma (R,R)-Formoterol PK Parameters following BID administration of Arformoterol or Racemic Formoterol in COPD Subjects

Treatment/ Parameter	Statistics	Arformoterol 15 µg N=35	Racemic Formoterol 12 µg DPI N=35	Racemic Formoterol 24 µg DPI N=36
$AUC_{(0-\tau)}$ (pg*hr/ml)	n	26	26	31
	Mean (SD)	56.5 (67.84)	46.3 (37.00)	83.6 (61.64)
	Median (Range)	31.9 (13.0, 323)	28.4 (19.2, 152)	59.7 (32.3, 293)
C_{max} (pg/ml)	n	33	30	34
	Mean (SD)	6.49 (7.70)	6.16 (4.31)	10.8 (7.00)
	Median (Range)	4.72 (0.911, 40.1)	4.33 (1.5, 19.5)	8.98 (2.13, 37.8)
Rc_{max}	n	27	25	32
	Mean (SD)	2.40 (1.29)	2.46 (1.25)	2.08 (0.53)
	Median (Range)	2.41 (0.404, 5.22)	2.23 (0.462, 5.24)	2.02 (0.828, 3.42)
$RAUC_{(0-\tau)}$	n	12	8	20
	Mean (SD)	2.78 (1.78)	2.29 (1.69)	2.41 (0.67)
	Median (Range)	2.76 (0.475, 6.15)	1.88 (0.373, 4.87)	2.53 (0.590, 3.52)
$t_{1/2}$ (hr)	n	23	17	20
	Mean (SD)	21.6 (23.0)	15.0 (7.7)	18.0 (7.5)
	Median (Range)	15.6 (2.93, 99.6)	13.9 (5.98, 35.5)	17.4 (6.41, 33.6)
t_{max} (hr)	n	33	30	34
	Mean	1.08 (1.05)	0.89 (0.70)	0.92 (0.67)
	Median (Range)	0.92 (0.4, 6.1)	0.64 (0.25, 2.25)	0.75 (0.25, 2.25)

NOTE: N represents the number of subjects in PK population and n represents the number of subjects with evaluable data for the indicated parameter.
Cross Reference: Table 14.2.3.1

Summary of PK parameters of (R,R)-formoterol at steady-state (Tables 2-3):

- Plasma concentrations of (R,R)-formoterol after 14 days of treatment, as measured by AUC(0-τ) were on average about 16% greater in COPD subjects given a nebulized dose of 15 µg of arformoterol as compared to those given 12 µg of racemic formoterol as a DPI product.
- (R,R)-formoterol exposure [AUC(0-τ)] after treatment with arformoterol 15 µg BID was 42% lower than that after racemic formoterol 24 µg BID.
- Arformoterol 15 µg BID produced an $AUC_{(0-\infty)}$ 22% higher than that after racemic formoterol 12 µg and 38% lower of that after racemic formoterol 24 µg BID.
- Cmax after arformoterol 15 µg BID and racemic formoterol 12 µg BID was similar. Cmax after arformoterol 15 µg BID was 53% lower than after racemic formoterol 24 µg BID.
- A dose proportional change in (R,R)-formoterol exposure was observed when the dose of racemic formoterol increased from 12 µg BID to 24 µg BID.
- Estimates of drug accumulation based upon $RAUC_{(0-\tau)}$ and RCmax was similar across treatments and was approximately 2.5 fold greater at Day 14 (Table 2). These observations were consistent with a median terminal $t_{1/2}$ of about 14-17 hours after 14 days of treatment. It is noted that drug accumulation based on urinary excretion of unchanged Foradil® was 1.6-2.1 and 1.2-1.4 for patients with asthma and COPD, respectively.

Table 3: Statistical Analysis of Effect of Treatment on Primary Steady State Plasma (R,R)-Formoterol Pharmacokinetic Parameters after 14 Days in Subjects with COPD (PK Population)

Parameter	Treatment Group	Geometric LS Mean	Treatment Comparison	Ratio	90% CI
$AUC_{(0-\tau)}$ (pg*hr/mL)	Racemic Formoterol 12 µg DPI BID	33.93	Arformoterol 15 µg / Foradil 12 µg	1.16	1.00, 1.35
	Arformoterol 15 µg BID	39.33	NA	NA	NA
	Racemic Formoterol 24 µg DPI BID	67.69	Arformoterol 15 µg / Foradil 24 µg	0.58	0.50, 0.67
C_{max} (pg/mL)	Racemic Formoterol 12 µg DPI BID	4.75	Arformoterol 15 µg / Foradil 12 µg	0.91	0.76, 1.09
	Arformoterol 15 µg BID	4.30	NA	NA	NA
	Racemic Formoterol 24 µg DPI BID	9.14	Arformoterol 15 µg / Foradil 24 µg	0.47	0.39, 0.56

Note 1: Geometric LS mean for $AUC_{0-\infty}$ at steady-state following 15 µg of arformoterol, Foradil® 12 µg and Foradil® 24 µg was 83.8, 68.8 and 136.3 pg*hr/mL, respectively.
Note 2: The median (range) values of Cmax at steady-state following 15 µg of arformoterol and Foradil® 12 µg were 4.72 (0.911, 40.1) and 4.33 (1.5, 19.5), respectively (Table 2). When these values were estimated using the linear model with sequence, treatment group, and period as fixed effects, and subjects nested within sequence as a random effect, the Cmax values were slightly different as shown in Table 3. Thus, overall, $C_{max,ss}$ was similar between arformoterol 15 µg and Foradil® 12 µg.

(S,S)-Formoterol: Descriptive statistics for plasma concentrations of (S,S)-formoterol for the racemic treatment groups at each measured time point are presented in Table 4 and Table 5 on Day 1 and Day 14, respectively.

Table 4: Descriptive Statistics of Plasma (S,S)-Formoterol PK Parameters Following Single Doses of Racemic Formoterol in COPD Subjects

Treatment/ Parameter	Statistics	Racemic Formoterol 12 µg DPI N=35	Racemic Formoterol 24 µg DPI N=36
$AUC_{(0-\tau)}$ (pg*hr/ml)	n	10	25
	Mean (SD)	28.07 (8.05)	59.0 (29.61)
	Median (Range)	27.28 (17.4, 41.3)	52.51 (24.1, 142.8)
C_{max} (pg/ml)	n	32	35
	Mean (SD)	4.05 (1.50)	9.29 (4.00)
	Median (Range)	4.06 (1.4, 7.6)	8.34 (2.57, 20.60)
t_{max} (hr)	n	32	35
	Mean (SD)	1.17 (0.60)	1.07 (0.58)
	Median (Range)	1.00 (0.25, 2.08)	0.98 (0.25, 2.33)

NOTE: N represents the number of subjects in PK population and n represents the number of subjects with evaluable data for the indicated parameter.
References Table 14.2.3.2 and Appendix 16.2.23.1.1

Table 5: Descriptive Statistics of Plasma (S,S)-Formoterol PK Parameters Following BID Administration of Racemic Formoterol 12 µg and Racemic Formoterol 24 µg After 14 Days in Subjects with COPD

Treatment/ Parameter	Statistics	Racemic Formoterol 12 µg DPI N=35	Racemic Formoterol 24 µg DPI N=36
$AUC_{(0-\tau)}$ (pg*hr/ml)	n	28	33
	Mean (SD)	48.5 (26.03)	89.66 (44.70)
	Median (Range)	37.41 (26.2, 127.5)	79.25 (29.3, 219.7)
C_{max} (pg/ml)	n	33	34
	Mean (SD)	7.60 (3.62)	14.5 (5.62)
	Median (Range)	6.54 (1.7, 18.4)	13.4 (4.5, 29.9)
RC_{max}	n	30	33
	Mean (SD)	2.13 (0.98)	1.74 (0.54)
	Median (Range)	1.98 (0.9, 4.8)	1.74 (0.8, 3.1)
$RAUC_{(0-\tau)}$	n	9	24
	Mean (SD)	1.88 (0.72)	1.87 (0.61)
	Median (Range)	1.93 (0.9, 2.8)	1.75 (0.9, 3.5)
$t_{1/2}$ (hr)	n	20	28
	Mean (SD)	6.67 (3.48)	12.9 (6.58)
	Median (Range)	6.53 (2.9, 17.9)	12.06 (4.2, 32.3)
t_{max} (hr)	n	33	34
	Mean (SD)	1.0 (0.7)	1.0 (0.6)
	Median (Min-Max)	0.75 (0.5, 2.5)	0.86 (0.5, 2.0)

NOTE: N represents the number of subjects in PK population and n represents the number of subjects with evaluable data for the indicated parameter.
Cross References Table 14.2.3.2

As shown in Tables 4 and 5;

- The change in systemic exposure to (S,S)-formoterol was nearly dose proportional.
- Cmax values for (S,S)-formoterol tended to be slightly higher than those observed for (R,R)-formoterol, while AUC(0-τ) values were similar following a single administration of racemic formoterol 12 µg and 24 µg treatments (e.g., Table 2 *vs.* 5).
- There was no apparent impact of dose upon tmax. The median tmax was approximately 1 hour post dose across all treatments; (S,S)-formoterol tmax values were similar to that of (R,R)-formoterol after racemic formoterol 12 µg and 24 µg treatments (Table 4).
- An estimate of drug accumulation based upon RAUC(0-τ) and RCmax (Ratio of Day 14/Day 1) was similar and was approximately 2-fold higher on Day 14 than on Day 1.
- Median tmax for (S,S)-formoterol was 0.8 to 0.9 hours after racemic formoterol treatments (12 µg and 24 µg), suggesting rapid absorption of (S,S)-formoterol (Table 5).

Urine Pharmacokinetic Analysis

(R,R)-Formoterol Urine Parameters: The mean urine-derived PK parameters following a single dose are presented in Table 6 and at steady state are presented in Table 7.

Table 6: Mean (SD) Urine (R,R)-Formoterol PK Parameters Following Single Doses of Arformoterol and Racemic Formoterol in COPD Subjects

Treatment/ Parameter	Arformoterol 15 µg N=35	Racemic Formoterol 12 µg DPI N=35	Racemic Formoterol 24 µg DPI N=36
$A_{e\ (0\text{-}12\ hr)}$ (ng)	n=34 92.3 (50.5)	n=35 92.6 (27.3)	n=34 219 (79.0)
fe (%)	n=34 0.62 (0.34)	n=35 1.89 (0.56)	n=34 2.22 (0.80)
Cl_r (L/hr)	n=20 5.91 (4.19)	n=21 6.06 (3.81)	n=27 7.56 (4.45)

NOTE: N represents the number of subjects in PK population and n represents the number of subjects with evaluable data for the indicated parameter.

After a single dose;

- Similar amounts of (R,R)-formoterol were excreted after a single dose of arformoterol 15 µg or racemic formoterol 12 µg.
- When subjects were treated with racemic formoterol 24 µg, the amounts excreted were approximately doubled.
- The fraction of dose excreted was higher with racemic formoterol (DPI formulation) than with the arformoterol tartrate inhalation solution.

Table 7: Mean (SD) Urine (R,R)-Formoterol PK Parameters Following BID Administration of Arformoterol and Racemic Formoterol in COPD Subjects After 14 Days

Treatment/ Parameter	Arformoterol 15 µg N=35	Racemic Formoterol 12 µg DPI N=35	Racemic Formoterol 24 µg DPI N=36
$A_{e\ (0\text{-}12\ hr)}$ (ng)	n=35 389 (200)	n=33 396 (124)	n=32 703 (228)
fe (%)	n=35 2.59 (1.33)	n=33 8.07 (2.53)	n=32 7.15 (2.32)
Cl_r (L/hr)	n=30 9.03 (5.33)	n=29 8.36 (4.26)	n=33 9.71 (8.01)

NOTE: N represents the number of subjects in PK population and n represents the number of subjects with evaluable data for the indicated parameter.

Cross Reference: Table 14.2.4.1

After the multiple doses;

- (R,R)-formoterol amounts excreted into urine were similar for the arformoterol 15 µg BID and racemic formoterol 12 µg treatments.
- The amount of (R,R)-formoterol recovered after the 12 µg dose of racemic formoterol was approximately half of that recovered after racemic formoterol 24 µg. These results are consistent with the exposures in plasma.
- Renal clearance of unchanged (R,R)-formoterol accounts for less than 10% of the administered dose and appeared to be independent of treatment group.
- Renal clearance of unchanged (R,R)-formoterol was similar following all 3 treatments. Labeling for Foradil® stated that CLr was 150 ml/min (i.e., 9 L/hr).
- Amounts of (R,R)-formoterol in urine were approximately 4-fold higher after 14 days of dosing than after single doses.

(S,S)-Formoterol Urine PK Parameters: The mean urine-derived PK parameters for (S,S)-formoterol are presented in Tables 8 (single dose) and 9 (steady state). Note that subjects dosed with arformoterol were assayed for (S,S)-formoterol concentrations in urine but no measurable amounts were found.

Table 8: Mean (SD) Urine (S,S)-Formoterol PK Parameters Following Single Doses of Racemic Formoterol in COPD Subjects

Treatment/ Parameter	Racemic Formoterol 12 µg DPI N=35	Racemic Formoterol 24 µg DPI N=36
$A_{e(0\text{-}12\ hr)}$ (ng)	n=35 163 (52.6)	n=34 388 (151.6)
fe (%)	n=35 3.31 (1.07)	n=34 3.95 (1.54)
Cl_r (L/hr)	n=23 7.90 (4.53)	n=32 8.56 (4.11)

NOTE: N represents the number of subjects in PK population and n represents the number of subjects with evaluable data for the indicated parameter.

Cross Reference: Table 14.2.4.2

Table 9: Mean (SD) Urine (S,S)-Formoterol PK Parameters at Steady State Following BID Administration of Racemic Formoterol in COPD Subjects After 14 Days

Treatment/ Parameter	Racemic Formoterol 12 µg DPI N=35	Racemic Formoterol 24 µg DPI N=36
$A_{e\ (0\text{-}24\ hr)}$ (ng)	n=33 522 (173)	n=32 970 (362)
fe (%)	n=33 10.6 (3.52)	n=32 9.87 (3.68)
Cl_r (L/hr)	n=33 10.9 (7.51)	n=33 10.3 (6.42)

NOTE: N represents the number of subjects in PK population and n represents the number of subjects with evaluable data for the indicated parameter.

Cross Reference: Table 14.2.4.2

After 14 days of dosing the change in the amount of (S,S)-formoterol recovered in the urine after racemic formoterol treatments was dose proportional. Higher amounts of (S,S)-formoterol than (R,R)-formoterol were recovered in the urine after single or 14 days of dosing (Tables 6-7).

Pharmacodynamic Analysis

Correlation between PK Parameters and Efficacy Parameters: The relationship between mean time-matched percent change in FEV_1 from study baseline and plasma concentrations of (R,R)-formoterol following single and multiple doses of arformoterol and racemic formoterol in COPD subjects is presented in Figures 2 and 3.

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Figure 2: Mean % Change in FEV1 from Study Baseline and Mean (R,R)- Formoterol Plasma Concentrations Versus Time Following a Single Dose of Arformoterol and Racemic Formoterol in COPD Subjects

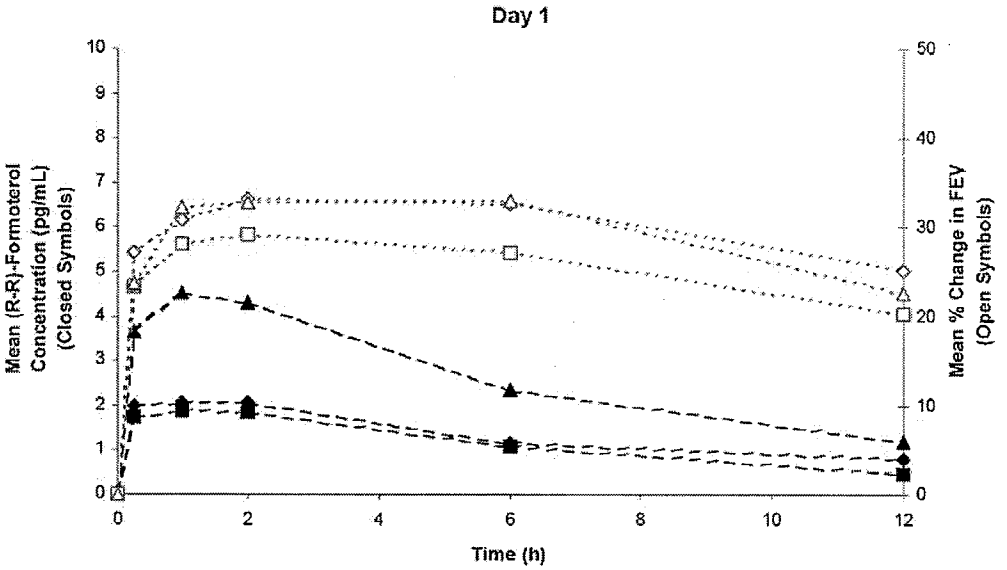
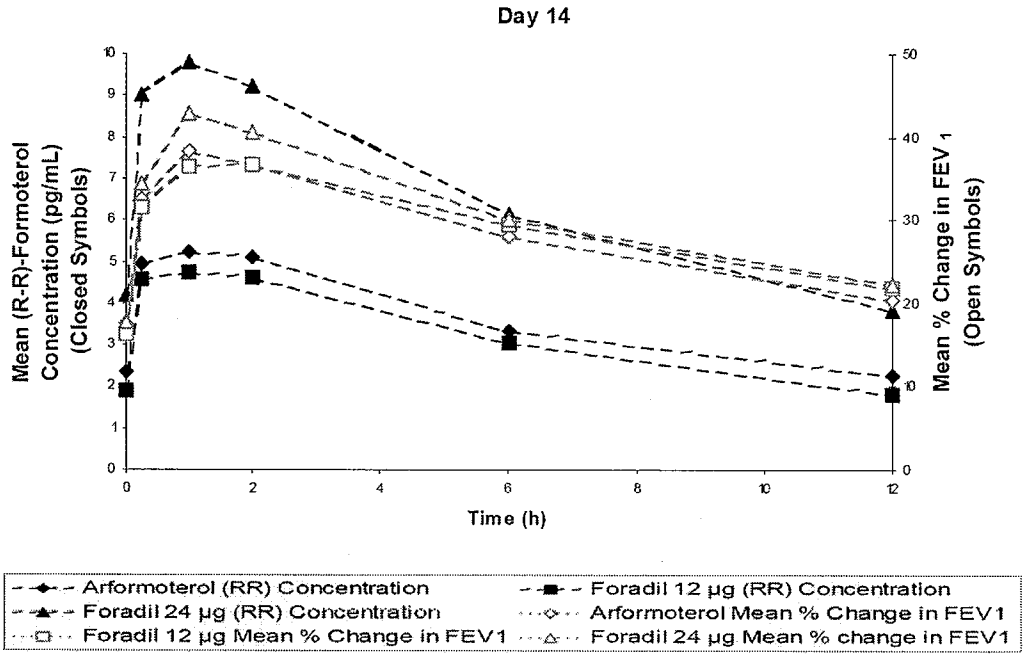


Figure 3: Mean % Change in FEV1 from Study Baseline and Mean (R,R)-Formoterol Plasma Concentrations Versus Time Following BID Administration of Arformoterol and Racemic Formoterol in COPD Subjects After 14 Days



It appears that there is a correlation between systemic exposure to (R,R)-formoterol and FEV_1 in patients with COPD (see review by Anthony Dumowicz, MD for detailed review for efficacy and safety).

Conclusions:

- After 14 days, arformoterol 15 μg BID produced similar (R,R)-formoterol plasma exposure (Cmax and AUC) to that from racemic formoterol 12 μg BID and lower than that with racemic formoterol 24 μg BID.
- Treatment with arformoterol 15 μg BID for 14 days provided similar accumulation of (R,R)-formoterol plasma concentrations (approximately 2.5 fold) compared with racemic formoterol 12 or 24 μg BID.
- There were insignificant differences in absorption rate across treatments after 14 days, with a median tmax of 0.92 hr in the arformoterol, 0.64 hr in the Foradil 12 μg, and 0.75 hr in the Foradil 24 μg, groups, respectively.
- The elimination rate (based on median $t_{1/2}$) of (R,R)-formoterol after arformoterol treatment for 14 days was similar to that obtained after racemic formoterol treatments (median $t_{1/2}$ range across treatments: 14 to 17 hrs).
- The amount of (R,R)-formoterol recovered in the urine (Ae) after 14 days was similar following treatment with arformoterol 15 μg and racemic formoterol 12 μg; these results are consistent with the exposures in plasma.
- There was an overall positive association between (R,R)-formoterol plasma concentration and percent change in FEV1.

Reviewer's Comment: Sponsor's analyses and conclusions are adequate.

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/s/

Shinja Kim
9/7/2006 04:10:15 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
9/7/2006 04:24:27 PM
BIOPHARMACEUTICS
I concur.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-912	Submission Date(s): 12/08/05, 01/03/06
Brand Name	[ ] b(4)
Generic Name	Arformoterol tartrate Inhalation Solution
Reviewer	Shinja Kim, Ph.D.
PM Reviewers	Bhattaaram Venkatesh A., Ph. D.
Team Leader	Emmanuel O. Fadiran, Ph.D.
OCPB Division	Division of Clinical Pharmacology – 2
ORM Division	Division of Pulmonary and allergy Drug Products
Sponsor	Sepracor Pharmaceuticals, Inc.
Relevant IND(s)	55,302
Submission Type; Code	NME, Standard Review; 3S
Formulation; Strength(s)	Oral Inhalation Solution, 15 mcg/2 mL Unit-Dose
Indication	Long term treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema

Table of Contents

1 Executive Summary

1.1 Recommendation

NDA 21-912 is acceptable from the Office of Clinical Pharmacology perspective provided that a mutually acceptable agreement is reached between the Agency and Sponsor regarding the language in the package insert.

1.2 Phase IV Commitments

None

1.3 Summary of CPB Findings

Arformoterol, (R,R)-enantiomer of formoterol, is a selective long-acting β_2-adrenergic bronchodilator. Racemic formoterol, a mixture of (R,R)- and (S,S)-isomers, is currently marketed in the United States (Foradil Aerolizer®) and Europe. The arformoterol clinical development program is comprised of 16 completed clinical studies. Pharmacokinetic including pharmacodynamic assessments were obtained from 11 of these studies, and 6 *in-vitro* studies. Clinical pharmacology is summarized based on these studies as follows:

Absorption: Arformoterol appeared rapidly in the systemic circulation following administration of nebulized doses of arformoterol tartrate inhalation solution in healthy subjects and patients with COPD. The median tmax was generally less than 1 hour.

Distribution:

- After oral administration of ^{3}H-arformoterol (35 μg free base), a blood-to-plasma concentration ratio of 0.6 [derived by dividing total radioactivity in blood by total radioactivity (parent drug and metabolites) in plasma at 30, 60, and 90 minutes] suggests minimal distribution of total radioactivity into red blood cells (Study 091-012).
- Over a wide range of plasma concentrations, arformoterol was not highly bound (52-65% bound) to plasma proteins.

Metabolism:

In vitro profiling studies in hepatocytes and liver microsomes have shown that arformoterol is primarily metabolized by direct conjugation (glucuronidation) and secondarily by O-demethylation. At least five human uridine diphosphoglucuronosyltransferase (UGT) isozymes catalyze arformoterol glucuronidation in vitro. O-demethylation of arformoterol was mediated by CYP2D6 and CYP2C19, in decreasing order of activity. Arformoterol did not inhibit common CYP enzymes.

Arformoterol was almost entirely metabolized following oral administration of 35 mcg of radiolabeled arformoterol in eight healthy subjects. Direct conjugation of arformoterol with glucuronic acid was the major metabolic pathway. Most of the drug-related material in plasma and urine was in the form of glucuronide or sulfate conjugates of arformoterol. O-Desmethylation and conjugates of the O-desmethyl metabolite were relatively minor metabolites accounting for less than 17% of the dose recovered in urine and feces. Desformoterol (desformylformoterol), another active metabolite, was not observed in plasma. Desformoterol was rarely found in human urine. Only trace amounts of desformylformoterol sulfate conjugates were observed.

No chiral inversion of arformoterol to its stereoisomers [(R,S)-, (S,R)-, or (S,S)-formoterol] were observed in plasma, however, trace amounts of (S,R)-formoterol were found in a few isolated (8/1000) urine samples from three (out of 23) asthmatic subjects. The levels of (S,R)-formoterol were very low as compared to (R,R)-formoterol levels [(S,R)-formoterol urine levels were less than 0.2% of (R,R)-formoterol urine levels].

Excretion:

After administration of a single oral dose of radiolabeled arformoterol to eight healthy male subjects, 63% of the total radioactive dose was recovered in urine and 11% in feces within 48 hours. A total of 89% of the total radioactive dose was recovered within 14 days, with 67% in urine and 22% in feces. Approximately 1% of the dose was recovered as unchanged arformoterol in urine over 14 days.

In COPD patients given 15 mcg inhaled arformoterol twice a day for 14 days, the mean terminal half-life of arformoterol was 26 hours.

Pharmacokinetics of Arformoterol in COPD Patients (Study 091-026)**:**

- Tmax was similar across all treatments and occurred at approximately 0.6-0.9 hours postdose.
- Systemic exposure, expressed in terms of Cmax and $AUC_{(0-24)}$, increased linearly with dose. Arformoterol $AUC_{(0-24)}$ after arformoterol tartrate inhalation solution doses of 25 μg BID and 50 μg QD was nearly identical.
- The plasma terminal phase half-life of arformoterol in COPD patients was 18 – 29 hours.
- Based upon mean concentrations at 0.75 hours post dose, the steady-state accumulation index following BID and QD administration was 1.7 to 1.8 and 1.1 to 1.3, respectively.

Population PK Analysis

- The population pharmacokinetics of arformoterol in patients with COPD (after nebulized administration) were linear and best described using a two-compartment model with a first-order absorption process.
- Body weight (kg) was found to be a significant positive predictor of both the apparent clearance and apparent central volume of distribution. The change in CL/F with body weight was not considered to be of clinical significance. Thus, dose adjustments according to body weight are not warranted.
- Other subject covariates (including age, gender, and race) had no additional predictive value once body weight was incorporated into the pharmacokinetic model for CL/F and Vc/F.
- Exposure to arformoterol was not significantly different based upon race, gender, or corticosteroid use.
- Examination of Bayesian estimates of AUC suggested that arformoterol pharmacokinetics were essentially dose-proportional over the range of doses and dosing regimens evaluated.

Population PK/PD Analysis

- Considerable inter-individual variability existed in both the single-dose and steady-state pharmacodynamics of arformoterol.
- Although a marked increase in EC50 between first dose and steady-state was observed, with EC50 increasing from 0.609 to 5.23 pg/mL, respectively, only a relatively modest decline in pulmonary outcome measures was seen clinically, suggesting that there can be a highly non-

linear relationship between concentration and response. This may suggest the development of some degree of tolerance following multiple dosing of arformoterol.

- The modeled estimate of keo (a rate constant describing lag time between arformoterol plasma concentration and $\%FEV_1$) was larger (3.78 hr^{-1}) at steady-state as compared to that observed following single-dose administration (1.49 hr_{-1}). This would suggest a diminution in the half-life delay for the onset of observed pharmacologic activity when compared to the drug concentration time course at steady-state and is consistent with a rapid onset of action following nebulized administration of arformoterol.
- Emax at steady-state was more difficult to model due to the lack of ample informative data at sufficiently high concentrations and a high degree of correlation with the EC50 parameter.
- There was no apparent impact of race, gender, or corticosteroid use upon model estimates of EC50 at steady-state.

Intrinsic Factors:

Body Weight: Body weight (kg) was found to be a significant predictor of both the apparent clearance and apparent central volume of distribution in the population pharmacokinetic model. However, the change in exposure with body weight was relatively modest. Therefore, adjustment in dose based upon body weight would not be necessary.

Age: No clinically relevant difference in systemic exposure was observed when healthy elderly subjects were compared to a control group of younger subjects, matched for demographic characteristics, following administration of a single nebulized dose of 50 µg arformoterol. No dosage adjustments are necessary for elderly subjects.

Race/Gender: Race and gender had no additional predictive value once body weight was incorporated into the population pharmacokinetic model for CL/F and Vc/F.

Renal Impairment: No clinically significant difference in systemic exposure was observed when subjects with varying degrees of renal impairment were compared to a control group of healthy subjects, matched for demographic characteristics, following administration of a single nebulized dose of 50 µg of arformoterol. No dosage adjustments are necessary for patients with impaired renal function.

Hepatic Impairment:

- Systemic exposure after a single nebulized dose of 50 µg arformoterol was about 1.5 to 2 times higher in subjects with mild, moderate-to-severe, or severe hepatic impairment as compared to healthy subjects.
- No apparent trend in exposure was observed with increasing degrees of hepatic impairment.
- Caution should be used in dosing subjects with hepatic impairment.

Genetic Polymorphism: Reduced CYP2D6 or UGT1A1 activity had no clinically significant impact on the exposure of arformoterol in healthy volunteers. Dosage adjustments are not necessary for patients with altered CYP2D6 or UGT1A1 activity.

Extrinsic Factors

Interaction with CYP2D6 Inhibitor: Steady-state arformoterol exposure was not affected by coadministration of multiple-dose paroxetine, a potent CYP2D6 inhibitor. Dosage adjustments of

arformoterol are not necessary when the drug is given concomitantly with potent CYP2D6 inhibitors, such as paroxetine.

Exposure-Safety Relationship

QTc: No systematic QTc prolongation was observed with arformoterol administration; no apparent correlation between QTc and arformoterol plasma concentration was evident.

$ß_2$-Mediated Side Effects

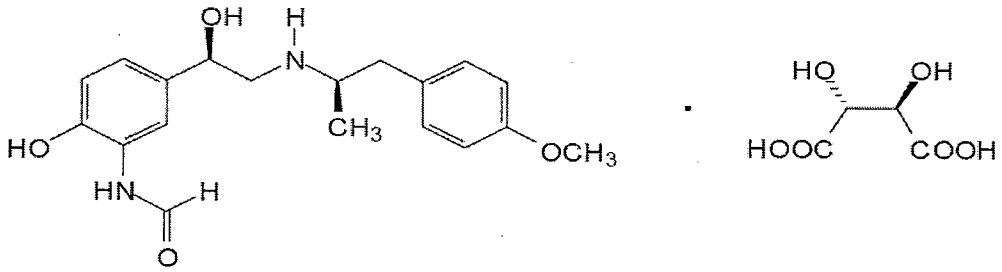
- Dose-related decreases in serum potassium and increases in serum glucose were observed at higher doses (50 µg QD), but there was no clear visual trend with plasma arformoterol concentrations. The lack of a relationship between concentration and these effects may be attributed, in part, to substantial intersubject variability associated with plasma concentrations and to a lesser extent in glucose and potassium measures.
- Heart rate showed a marginally increasing trend with plasma arformoterol concentrations.

2 QBR

2.1 General Attributes

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Arformoterol tartrate Inhalation Solution is a sterile, clear, colorless, preservative-free, aqueous solution of the tartrate salt of arformoterol, the (R,R)- enantiomer of formoterol. Arformoterol is a selective beta2-adrenergic bronchodilator. The chemical structure is shown below:



The molecular weight of arformoterol tartrate is 494.5 g/mol, and its empirical formula is $C_{19}H_{24}N_2O_4 \bullet C_4H_6O_6$ (1:1 salt). It is a white to off-white solid that is slightly soluble in water — b(4)
——— Arformoterol tartrate is supplied in 2-mL unit-dose vials. Each 2-mL unit-dose vial contains 15 mcg of arformoterol (22 mcg of the tartrate salt) in a sterile, isotonic saline solution, pH-adjusted to 5.0 with citric acid and sodium citrate. Arformoterol tartrate requires no dilution before administration by nebulization, and the amount delivered to the lungs will depend upon patient factors (like all other nebulized treatments), the nebulizer used, and compressor performance. Using the Pari LC Plus® nebulizer (with mouthpiece) connected to a Pari DURANEB® 3000 compressor under in vitro conditions, the mean delivered dose from the mouthpiece (% nominal) was approximately 4.1 mcg (27.6%) at a mean flow rate of 3.3 L/min. The mean nebulization time was 6 minutes or less.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action: Arformoterol is a selective long-acting β_2-adrenergic receptor agonist. β_2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and β_1-receptors are the predominant receptors in the heart, data indicate that there are also β_2-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors.
The pharmacologic effects of β_2-adrenoceptor agonist drugs, including arformoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased intracellular cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Indications and Usage: Arformoterol tartrate Inhalation Solution is indicated for twice daily long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

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

The recommended dosage of Arformoterol tartrate Inhalation Solution for COPD patients is 15 mcg administered twice a day (morning and evening) by nebulization. A total daily dose greater than 30 mcg (15 mcg twice daily) is not recommended. Arformoterol tartrate Inhalation Solution should only be administered by nebulizer by the inhalation route. Arformoterol tartrate Inhalation Solution should be stored refrigerated in individual unit dose, low-density polyethylene (LDPE) vials sealed in single foil pouches. Vials should be removed from the foil pouches and used immediately after opening.

No dose adjustment is required for patients with renal or hepatic impairment. However, patients with hepatic impairment should be monitored closely.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The arformoterol clinical development program is comprised of 16 studies. However, PK including PD assessments was obtained from 11 studies: Studies 091-001, 091-002, 091-003, 091-004, and 091-021 were initiated early in the development program (pilot formulation). [redacted] In addition six *in vitro* studies were conducted to support the NDA. b(4)

Phase 2 trial (091-021 and 091-026; dose-ranging studies) and two Phase 3 trials (Studies 091-050 and 091-051) conducted in patients with COPD support the dosing (or claims) of arformoterol. Also, Population PK and PK/PD analyses were performed using the data from these 3 (exclude Study 091-021) studies. Brief Overview of Completed Arformoterol Clinical Studies is shown in Table 1.

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

Yes. The parent drug, (R,R)-formoterol was measured in human plasma, urine and feces. *In vitro* pharmacology binding studies (Study 090-498) have shown that (R,R)-O-desmethylformoterol is an active metabolite. However, the concentration of this metabolite obtained samples from Studies 091-013 and 091-050 were not detected, therefore, the concentration of (R,R)-O-desmethylformoterol were considered less than 0.5 pg/mL, below the lower limit of quantitation (LOQ) of 0.5 pg/mL (LC/MS/MS method).

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response?

Clinical trials were conducted to evaluate the efficacy (and safety) of arformoterol: two Phase II studies (091-021, 091-026) and two pivotal (091-050, 091-051) and one long term (091-060) Phase III studies in patients with COPD. The brief summary of the studies (except Study 091-021) is provided below:

Study 091-021 (used pilot formulation): Placebo-and active-controlled single dose (QD) and single-day (BID) five way crossover study. The doses explored were between 9.6 μg and 96 μg. The primary endpoint was % change in FEV_1 whether measured at 24-hour or 12-hour post-dose time point.

Study 091-026: Placebo controlled, multiple-dose, dose-ranging study. The study consisted of both BID and QD dosing regimens. The first segment (Part A) compared bronchodilation outcomes for the 5, 15, and 25 μg BID doses of arformoterol versus placebo over a 2-week dosing period. The second segment (Part B) compared similar outcomes for subjects randomized to 15, 25, and 50 μg of arfomorterol dosed once daily. The primary endpoint was overall improvement in airway function in the 12 (BID) or 24 (QD doses) hours after dosing (FEV_1 $nAUC_{0\text{-}12\text{-}P}$ or FEV_1 $nAUC_{0\text{-}24\text{-}P}$).

Study 091-050, 091-051: Double-blind, double-dummy, randomized multi-center, parallel group, 12-week trial where arfomorterol 15 μg BID, 25 μg BID, and 50 μg QD were compared to placebo and salmeterol 42 μg BID as an active control.

Study 091-060 (Long term safety): Open-label, multicenter, randomized, active-controlled, parallel group, chronic safety study comparing arfomoterol 50 μg QD versus salmeterol 42 μg BID.

Study 091-026 showed that dose-response relationship as presented in Figures 1-2 and Tables 2-3 below:

Figure 1: Mean percent change in FEV_1 from Baseline Over 24 hrs after 14 Days of dosing (Part A)

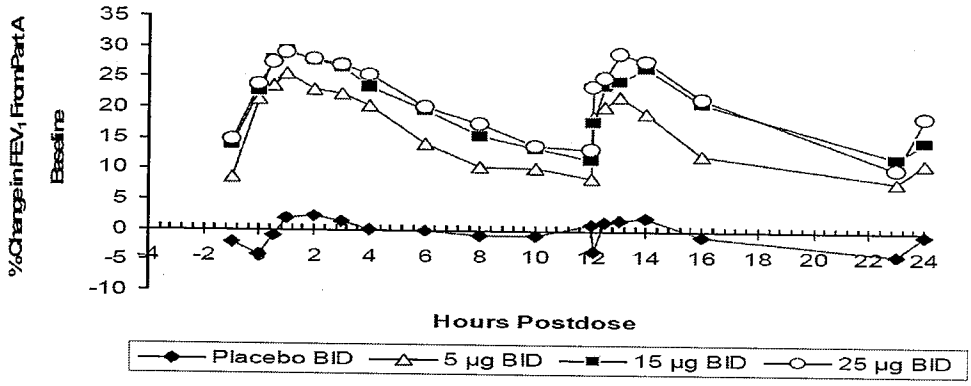


Table 2: Proportion of Subjects with ≥10% and ≥15% Improvement in FEV1 at Trough (24 Hours) after 14 Days of Double-blind Treatment (Part A)

% Improvement	Placebo BID N=54	ARF 5 µg BID N=54	ARF 15 µg BID N=54	ARF 25 µg BID N=53
≥10%	26.7% (8/30)	56.4% (22/39)	52.2% (21/40)	56.8% (21/37)
≥15%	16.7% (5/30)	35.9% (14/39)	45.0% (18/40)	54.1% (20/37)

Note: The 24-hour in FEV_1 values within 6 hours of prior supplemental/rescue medication use were excluded.

Figure 2: Mean percent change in FEV_1 from Baseline over 24 hrs after 14 days of dosing (Part B)

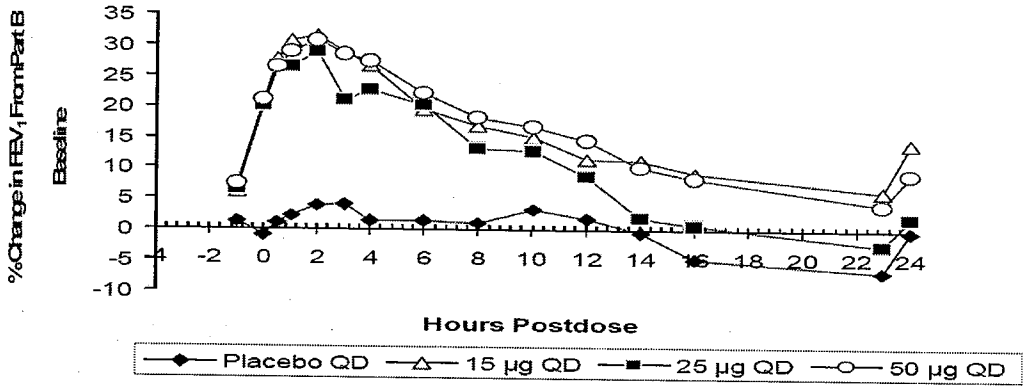


Table 3: Proportion of subjects with ≥10% and ≥15% Improvement in FEV_1 at trough (24 hrs) after 14 Days of Double-blind Treatment (Part B)

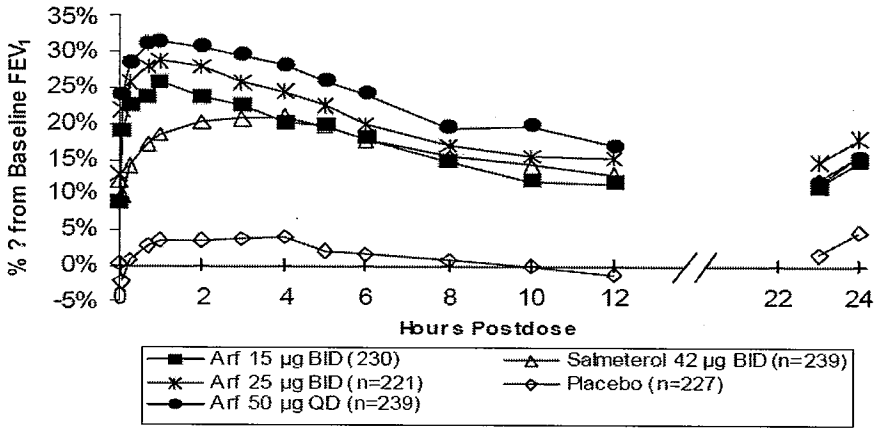
% Improvement	Placebo QD N=49	ARF 15 µg QD N=48	ARF 25 µg QD N=47	ARF 50 µg QD N-47
≥10%	23.5% (8/34)	52.8% (19/36)	41.2% (14/34)	27.6% (8/29)
≥15%	14.7% (5/34)	41.7% (15/36)	20.6% (7/34)	27.6% (8/29)

Note: The 24-hour in FEV_1 values within 6 hours of prior supplemental/rescue medication use were excluded.

All arformoterol doses were significantly more effective than placebo, and the dose-response was evident, with the 5 µg arformoterol BID dose demonstrating less improvement than the 15 µg BID or 25 µg BID doses, which were similar.

Based on the findings from Phase 2 studies (090-026), sponsor explored doses of 15, 25 mcg BID and 50 mcg QD arformoterol, and compared to placebo and salmeterol (42 mcg Bid) as a positive control in Phase III trials (Studies 091-050 and 091-051). In both studies, all arformoterol treatment groups significantly improved the percent change in trough FEV1 versus placebo over the 12-week double-blind period (primary endpoint) and when assessed at Weeks 0, 6, and 12. A dose-response relationship was evident for the 15 µg BID and 25 µg BID dose groups. The sponsor stated that 50 µg QD dose provided greater improvement in measures of pulmonary function improvement over the first 12 hours of the 24-hour QD treatment interval, but did not afford any additional improvement for the primary endpoint of trough FEV_1. The percent change in FEV1 is presented in Figure 3.

Figure 3: Percent Change from Study baseline FEV1 at Week 12 (Pooled Studies 091-050 and 091-051)



2.2.4.2 What are the characteristics of exposure-response relationships for safety?

Safety assessments, including standard safety evaluations (e.g., physical examinations, adverse events, vital signs, etc.), analyses of respiratory (assessment of tolerance by trough FEV_1 values over time, COPD exacerbation rates, and use of rescue and supplemental medication), cardiovascular safety (extensive ECG assessments, including QTC evaluations and Holter monitor) and beta-mediated effects have been performed throughout the arformoterol development program. Safety evaluations for the selected safety parameters (i.e., potassium and glucose levels in plasma and vital signs including change in heart rate and blood pressure) are summarized here.

Serum Potassium Levels: There were dose-related decreases in serum potassium across the single-dose and multiple-dose studies. There were consistently larger decreases in serum potassium with arformoterol treatment than with placebo; these decreases were often dose-related, with changes in the arformoterol 15 µg BID group similar to or slightly greater than that observed in the placebo group. However, the post-dose changes were transient. The effects on serum potassium did not increase over time in the 12-week pivotal or 12-month long-term

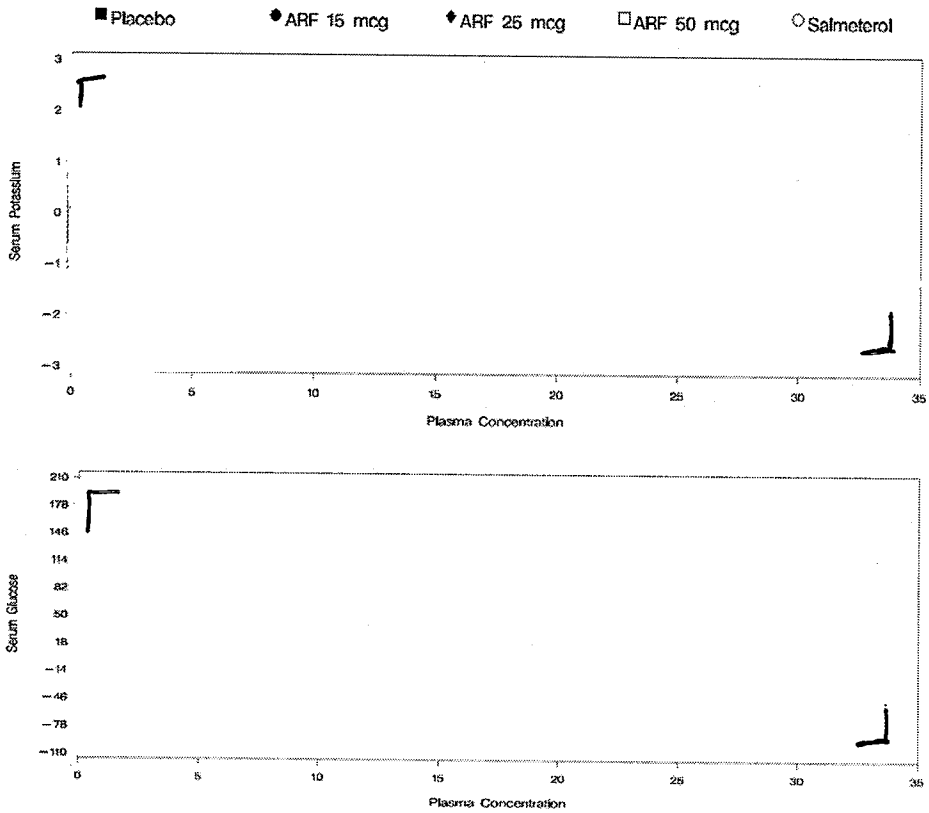
studies. In the long-term safety study, there were often larger decreases in serum potassium with arformoterol than with salmeterol.

Serum Glucose Levels: There were consistent, dose-related increases in serum glucose levels following arformoterol treatment both 2- and 6-hours post-dose across studies. Increases in the 15 µg BID group were slightly greater than observed in the placebo group. In the 12- week pivotal trials (pooled Studies 091-050 and 091-051), these increases did not change with prolonged treatment. In the 52-week long-term study (091-060), both arformoterol and salmeterol increased serum glucose levels, the increases were greater in the arformoterol group, and the increases did not change over time.

Vital signs: Heart rate is measured and plotted (plasma concentration *vs.* change in HR) as shown below.

Scatter plots of plasma concentration *vs.* serum potassium (upper panel), glucose (middle panel) and heart rate (lower panel) are shown in Figure 4.

Figure 4: Plasma Concentration 2 hrs post-dose *vs.* Potassium 2 hrs post-dose Change from Pre-dose for Studies 091 – 050 and 091 – 051 (ITT Population at Visit 5)



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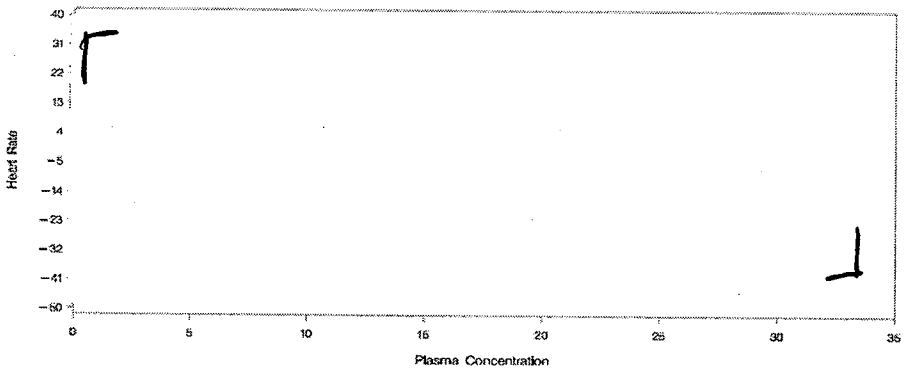
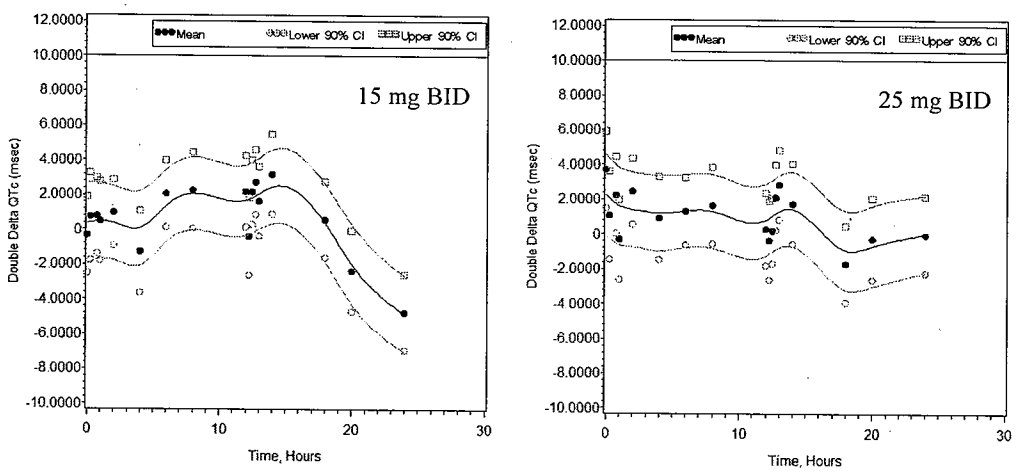


b(4)

2.2.4.3. Does this drug prolong the QT or QTc interval?

Pharmacometrics reviewer analyzed QT data as described in ICH E14 guidance. The results are shown in Figure 5. As can be seen in the figures below the upper 90% CI does not include 10 msec indicating that the arformoterol does not prolong QT after 5 mg BID (not shown here), 15 mg BID or 25 mg BID. Thus, it was concluded that the degree of QTc prolongation observed does not constitute a safety risk (see PM review on page 102 for detail).

Figure 5: Computation of 90% CI based on analysis using PROC MIXED in SAS



2.2.5 PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

As shown in Table 4, Cmax was similar after administration of single or multiple doses of 50 µg arformoterol between healthy subjects and patients with asthma or COPD across the studies. Steady state $AUC_{0\text{-}24hr}$ was higher in patients with COPD (110 pg•h/mL) compared to healthy subjects (74.3 pg•h/mL).

Table 4: Mean PK parameters after administration of 50 µg arformoterol from various studies

Parameter	Healthy volunteers						Patients	
	091-007	091-012	091-013	091-014	091-015	091-018	091-016	091-026
C_{max} (pg/mL)	11.7	10.48	10.7	10.7	7.8	12.3	11.8	11.7
$AUC_{0\text{-last}}$ (pg.h/mL)	42.2	44.3	46.8	51.7	28.8	74.3[a]	103.3[b]	110[a]
$AUC_{0\text{-}\infty}$ (pg.h/mL)	60.6	63.0	69.3	74.9	47.1	111	-	-
tmax (h)[c]	0.23	0.63	0.09	0.3	0.2	0.25	0.25	0.92
$t_{1/2}$ (h)	11.6	11.6	14.1	14.4	11.2	18.9	15.0	28.5

#091-007 = subjects with extensive CYP2D6/normal UGT1A1 #091-013 = elderly subjects
#091-018 = multiple dose, #091-016 = asthma (single dose) #091-026 = COPD (multiple-dose)
[a]$AUC_{0\text{-}24hr}$ [b]mean t_{last} = 42.1 hr [c]Median

2.2.5.2 What are the characteristics of drug absorption?

- After administration of 50 µg nebulized arformoterol to healthy subjects, drug absorption was rapid, with median t_{max} values of approximately 5 to 15 minutes (Studies 091-013, 091-014, 091-015). Mean Cmax ranged from 8 to 11 pg/mL (Studies 091-013, 091-014). Similar to healthy subjects, the mean Cmax of 11.8 pg/mL occurred within 15 minutes (median tmax) after dosing in subjects with asthma (Study 091-016).
- In patients with COPD, arformoterol appeared rapidly in the systemic circulation following drug administration; median tmax values ranged from 0.6 to 0.9 hours and peak concentrations after a 50 µg dose were 11.7 pg/mL. In COPD patients administered 15 µg BID arformoterol for 14 days, a mean steady-state peak arformoterol plasma concentration of 4.3 pg/mL was observed (Study 091-026).
- Absorption of an inhaled dose of arformoterol occurs by the pulmonary and GI tract routes. Although the extent of absorption is not known, the bioavailability of arformoterol and its metabolites from the GI tract is likely to be at least 64 to 67%, as this was the percentage of the administered radiolabeled dose recovered in urine following oral administration (Study 091-012).
- In subjects with asthma, co-administration of charcoal (blocking GI absorption) with a 50 µg inhaled dose of arformoterol decreased AUC by 30% (30.5 *vs.* 21.8 pg.h/mL) and Cmax by 26% (11.8 *vs.* 8.7 pg/mL) (Study 091-016). These results suggest that a substantial fraction of systemic exposure to arformoterol following administration of a nebulized dose is due to oral absorption.

2.2.5.3. What are the characteristics of drug distribution? (Include protein binding)

- When arformoterol was added to human whole blood, it was primarily found in red blood cells (Study 091-419).
- Following a single oral 35 µg (free base) dose of ^{3}H-arformoterol, the concentration-time profile of total radioactivity (primarily represents parent drug and metabolites) in blood was parallel to, but lower than plasma. A blood-to-plasma ratio of 0.6 (calculated during the first 2 hours of sample collection) suggested minimal distribution of total radioactivity into red blood cells (Study 091-012).
- The binding of arformoterol to human plasma protein was estimated to be between 52 to 65% and independent of concentration over a range of 250 to 1000 pg/mL (Report 091-419).

- The volume of distribution (V_d/F) after administration of arformoterol by inhalation was 6980 L, estimated by the Population PK analysis using the data from 3 studies (091-026, 091-050 and 091-051).

2.2.5.4 What are the characteristics of drug metabolism?

In vitro Metabolism: In vitro profiling studies were conducted using hepatocytes and liver microsomes to identify the major metabolites of arformoterol and support in vivo human ADME data. In vitro cytochrome P450 (CYP) and uridine 5'-phosphoglucuronosyltransferase (UGT) isoform phenotyping studies were also conducted in order to identify the enzymes responsible for the metabolism of arformoterol and assess the need for drug-drug interaction studies.

Glucuronosyltransferase Enzyme Activity

- Studies using human liver preparations have shown that arformoterol is primarily metabolized by direct glucuronidation at either the phenolic or to a lesser degree benzylic hydroxyl group. Arformoterol also undergoes Phase I, O-demethylation followed by glucuronide conjugation.
- Investigations were carried out to identify the principal UGT enzymes responsible for catalyzing the formation of glucuronide conjugates of [^{3}H]-arformoterol and [^{3}H]-(S,S)-formoterol (Reports 090-575A, 090-543). The primary UGT isozymes found to catalyze arformoterol glucuronidation were UGT2B17, UGT1A9, UGT2B7, UGT1A1, and UGT1A7 in decreasing order of activity.
- Since the typical amount of specific UGT isozymes expressed in human tissues is unknown, the relative in vivo contribution of individual UGT isozymes could not be estimated quantitatively.

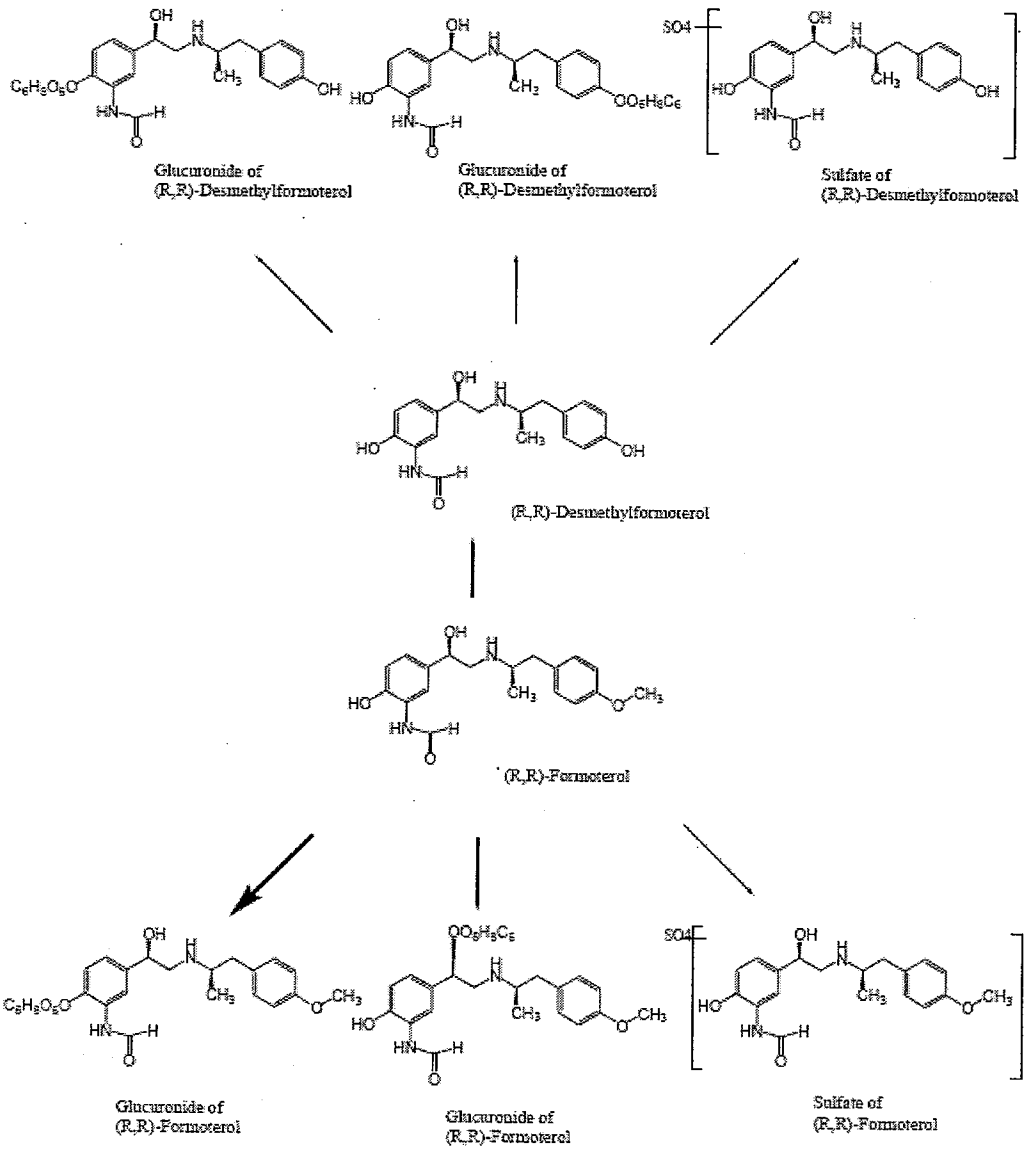
Cytochrome P450 Phenotyping: Incubations of both [^{3}H]-arformoterol and [^{3}H]-(S,S)-formoterol with human liver microsomes in the presence of NADPH yielded only one major Phase I metabolite (O-desmethylformoterol). To identify the cytochrome(s) P450 responsible for the formation of O-desmethylformoterol from both isomers, a combination of the techniques of correlation analysis, incubation with chemical inhibitors selective for various cytochromes P450, and incubation with single expressed P450s [ ] were used. Two CYP450 isozymes (CYP2D6 and, to a lesser extent, CYP2C19) catalyzed the formation of O-desmethylformoterol from arformoterol (Report 090-543A). b(4)

CYP450 Enzyme Inhibition Studies: An in vitro study to evaluate the inhibitory effects of arformoterol on human CYP450 enzyme activity showed that neither 100 nM arformoterol (typical plasma Cmax concentrations range from 2 - 50 pM) nor 200 nM racemic formoterol inhibited CYP450 activity. Hence, arformoterol and racemic formoterol are not expected to inhibit CYP450 isozyme activity at therapeutically relevant concentrations (Report 090-538).

In vivo Metabolism: Following oral administration of 35 µg of tritiated arformoterol (free-base), most of the drug-related material in plasma and urine was in the form of glucuronide or sulfate conjugates of arformoterol. Phase II metabolism was the major metabolic pathway of arformoterol in man. O-Demethylation, and subsequent conjugation was a relatively minor pathway, accounting for less than 17% of the dose recovered in urine (primarily) and to a lesser extent, in feces (Study 091-012). These results indicated that arformoterol was nearly completely metabolized following oral administration. In feces, no conjugates were found and unchanged drug represented a relatively high proportion of total drug-related material compared to plasma

and urine; both observations could be attributed to deconjugation reactions by endogenous intestinal microflora. Desformoterol was not observed in plasma; however, trace quantities of a desformoterol sulfate conjugate were found in human urine in all 8 subjects in study 091-012. It is also of interest to note that Rosenborg et al. reported that racemic formoterol is completely metabolized and that Phase II metabolism was considered the primary clearance pathway. The postulated metabolic pathways for arformoterol are shown in Figure 6.

Figure 6: Postulated Pathways of Metabolism of ^{3}H-Arformoterol L-Tartrate in Male Human Subjects



Note: The bold arrow indicates the postulated major metabolic pathway (Source: hpsum.pdf, pg.45)

Chiral Inversion: An investigation was conducted to assess the potential for ichiral inversion of arformoterol to its stereoisomers [(R,S)-formoterol, (S,R)-formoterol, and (S,S)- formoterol] in plasma samples from a single dose healthy subject study (Study 091-013) and a single and multiple dose COPD patient study (Study 091-050). The results indicated that no chiral inversion was observed in human plasma. However, in human urine, a trace amount (<0.2% of the corresponding arformoterol concentrations) of (S,R)-formoterol was observed in 3 out of 23 healthy subjects after an oral inhalation dose of 50 μg or 100 μg (Study 091-016). It should be noted that there were only one or two samples from 3 individual subjects (38 to 46 samples per subject) found to contain (S,R)-formoterol. In another investigation using human urine (Study 091-026, COPD patients were given various QD and BID dosing regimens for 2 weeks), selected urine samples were pooled and analyzed by LC/MS/MS methods. Under these experimental conditions, no evidence of chiral inversion from (R,R)-formoterol to (S,S)-, (R,S)-, or (S,R)-formoterol was found. The data indicated that chiral inversion of arformoterol was negligible in healthy subjects and COPD patients.

Impact of (S,S)-formoterol on Arformoterol PK when administered as a Racemic Mixture:

From Study 091-16, the observed terminal half-lives estimated from urine data were similar across all five treatments (11.7 to 13.2 hours) suggesting the presence of (S,S)-formoterol did not impact the elimination kinetics of arformoterol. Administration of 100 μg racemic formoterol resulted in modestly higher systemic exposure (23%) to (R,R)-formoterol as compared to treatment with 50 μg arformoterol (both treatments contained equivalent amounts of (R,R)-formoterol). Sponsor stated that one hypothesis that could explain these observations is transient inhibition of first pass metabolism by (S,S)-formoterol (Study 091-016).

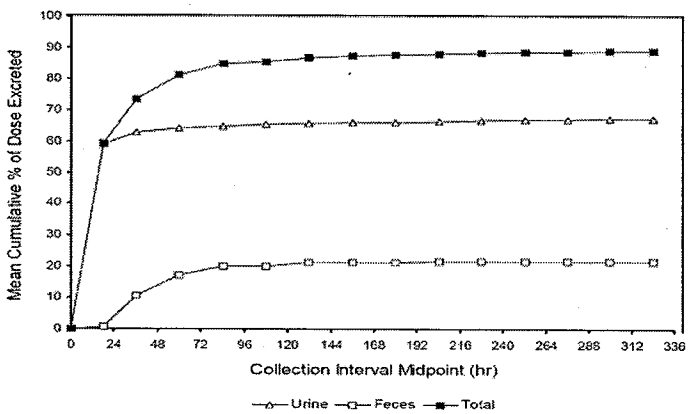
2.2.5.5. Does the mass balance study suggest renal or hepatic as major route of arformoterol elimination?

As shown above (*i.e.*, question under 2.2.5.4), arformoterol was nearly completely metabolized following oral administration, therefore, it is concluded that hepatic is the major route of elimination for arformoterol.

2.2.5.6 What are the characteristics of drug excretion?

Following oral administration of 35 μg of 2 mCi tritiated arformoterol (free-base), approximately 89% of the total radioactive dose was recovered (67% from urine and 22% from feces).

Figure 7: Mean Cumulative Percent of Dose Excreted in Urine and Feces as Total Radioactivity Following a Single Oral Dose of 50 μg/2 mCi 3H-Arformoterol Tartrate

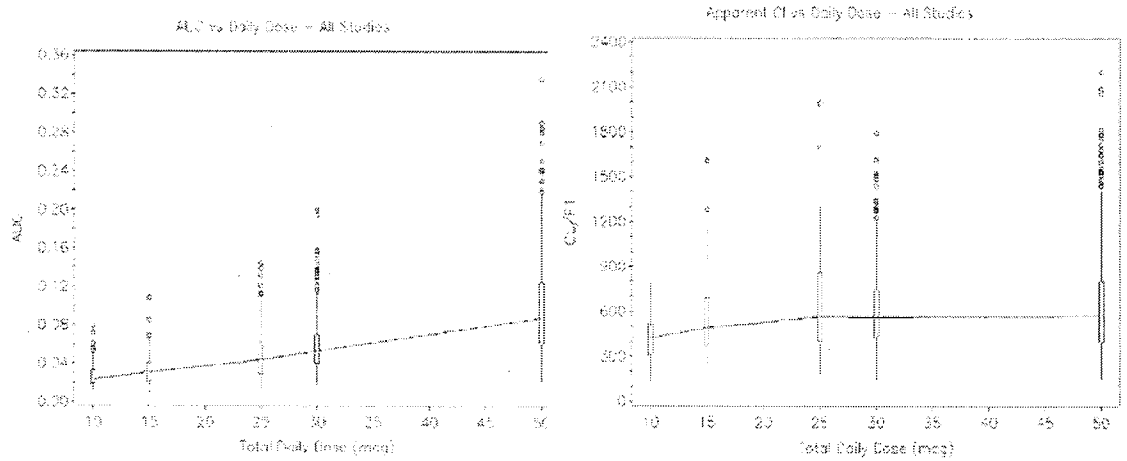


Of this, approximately 83% of the dose was excreted as nonvolatile radioactivity; 64% was recovered in urine and 19% was recovered in feces within 144 hours (Figure 7, Study 091-012). Approximately 1% of the dose was recovered in urine as unchanged arformoterol. This was similar to the amounts of unchanged drug recovered in the urine of healthy subjects receiving non-radiolabeled doses of the drug (Studies 091-013, 091-014, 091-015).

2.2.5.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Based on graphical assessment of arformoterol AUC and apparent clearance values versus dose, the PK of arformoterol appeared to be roughly dose-proportional (Figure 8). There was a very slight trend for lower drug clearance in the lowest dose group (5 μg twice daily).

Figure 8: Boxplots of Area under the Curve and Clearance *vs.* Total Daily Dose after Including Relative Bioavailability in the Pharmacokinetic Model



2.2.5.8 How do the PK parameters change with time following chronic dosing? (This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)

Blood samples for arformoterol concentrations were collected after single dose (up to 6 hrs post-dose) and multiple doses from the subjects only in Study 091-026. From other studies, blood samples were collected either after single dose or after multiple doses (i.e., steady-state). Therefore, the accumulation factor can't not be calculated accurately. Table 5 presents mean (± SD) plasma concentration after single and multiple doses up to 6 hrs post-dose from Study 091-026.

Table 5: Mean (SD) Arformoterol Plasma concentrations (pg/mL) after single or multiple-dose in Subjects with COPD in Part A of the Study (091-026)

Part A, Day 1, Single Dose			
Hours Post-first Dose	**5 µg BID**	**15 µg BID**	**25 µg BID**
0	BLQ	BLQ	BLQ
0.25	0.8 (0.7)	2.2 (2.1)	3.2 (2.1)
0.75	0.8 (0.6)	2.0 (1.5)	3.4 (3.0)
2	0.6 (0.6)	1.6 (1.1)	2.7 (1.2)
6	BLQ	1.0 (0.7)	1.7 (0.8)
Part A, Day 14, Multiple Dose (Steady-state)			
Hours Post AM Dose	**5 µg BID**	**15 µg BID**	**25 µg BID**
0	0.8 (0.7)	1.8 (1.3)	2.8 (1.7)
0.25	1.4 (0.9)	4.2 (2.7)	6.4 (3.9)
0.75	1.4 (0.9)	3.7 (2.3)	5.9 (3.1)
2	1.5 (1.2)	3.4 (2.2)	5.2 (2.6)
6	1.2 (1.4)	2.6 (1.8)	3.4 (2.0)

Steady-state concentration by the concentration after a single dose with BID (Part A) and QD (Part B, table not shown) doses were 1.7 to 1.8 and 1.1 to 1.3, respectively.

2.2.5.9 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Population PK analysis was conducted using data from Phase 2 (091-026) and two Phase 3 studies (091-50, 091-051). The analysis results showed that (a) the magnitude of interindividual variability in clearance, central volume of distribution, intercompartmental clearance, and absorption rate constant was 32%, 40%, 40%, and ~77%, respectively, (b) the interindividual and interoccasion (between-visit) variability in relative bioavailability for the 15 µg through 50 µg doses was 26% and 29%, respectively, and (c) residual variability was notably small at ~15% (see page xx, Pharmacometrics).

2.3. Intrinsic Factors

2.3.1 What intrinsic factors including specific populations (e.g., age, gender, race, weight, renal/hepatic impairment) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.1.1. Elderly subjects: Study 091-013 was a Phase 1, open-label, parallel group, single-dose study of 50 µg arformoterol by nebulization in healthy elderly (≥65 years) and younger (≥18 years and ≤45 years) adult subjects (24 subjects per group) to characterize the PK (and safety) of arformoterol in these subjects. Systemic exposure (AUC and Cmax) of arformoterol was similar in healthy elderly subjects compared to a control group of younger subjects, matched for body weight and gender (Table 6).

Table 6: Statistical Analysis of Age Effect on Key Plasma Pharmacokinetic Parameters

Parameter	Elderly (N=24)	Younger Adults (N=24)		
	Geometric LS Mean		Ratio	90% CI[a]
C_{max} (pg/mL)	9.69	8.40	1.15	0.914 – 1.46
$AUC_{(0\text{-last})}$ (pg·hr/mL)	40.8	40.1	1.02	0.743 – 1.393
$AUC_{(0\text{-}\infty)}$ (pg·hr/mL)	63.8	57.9	1.10	0.878 – 1.383
	Median			p-value
t_{max} (hr)	0.080	0.080	--	0.655[b]
	Mean			
$t_{1/2}$ (hr)	14.1	14.4	--	--

[a] Confidence intervals on the ratio elderly:younger adult was obtained by Linear Mixed Effect Modeling

[b] The p-value for t_{max} was determined by a two-sided Wilcoxon Rank-Sum test.

2.3.1.2. Pediatric patients: Pharmacokinetics of arformoterol have not been studied in pediatric subjects (indication of this drug is for patients with COPD).

2.3.1.3. Gender: A population PK analysis indicated that there was no effect of gender upon the pharmacokinetics of arformoterol.

2.3.1.4. Race: The influence of race on arformoterol pharmacokinetics was assessed using a population PK analysis and data from healthy subjects participating in Phase 1 studies of arformoterol. There was no clinically meaningful impact of race upon the pharmacokinetic profile of arformoterol.

2.3.1.5. Renal impairment: Study 091-014 was an open-label, single-dose PK study conducted at multiple clinical sites enrolling a total of 40 subjects in three groups of 8 subjects each with renal insufficiency (i.e., mild, moderate, severe) and 1 group of 16 healthy subjects with normal renal function. Objective was to describe and to compare the PK of a single 50-µg dose of arformoterol in subjects with impaired renal function and age-, gender-, BMI-, and weight-matched normal healthy subjects. Systemic exposure (AUC and Cmax) was similar in renally impaired patients compared with demographically matched healthy control subjects (Table 7).

Table 7: Statistical Comparison of Arformoterol Plasma Pharmacokinetic Parameters Between Subjects with Renal Impairment and Normal Subjects Following a Single, Nebulized 50-µg Dose of Arformoterol

Parameter	Renal Function	N	Geometric LS Mean	Ratio[a]	90% CI
$AUC_{(0\text{-}12)}$ (pg*hr/mL)	Normal	13	34.97	1	--
	Mild	8	40.72	1.16	0.84 to 1.61
	Moderate	8	35.26	1.01	0.73 to 1.39
	Severe	7	37.72	1.08	0.77 to 1.51
$AUC_{(0\text{-}24)}$ (pg*hr/mL)	Normal	8	56.92	1	--
	Mild	6	63.64	1.12	0.77 to 1.63
	Moderate	6	54.59	0.96	0.66 to 1.40
	Severe	6	57.26	1.01	0.69 to 1.46
$AUC_{(0\text{-}last)}$ (pg*hr/mL)	Normal	15	37.27	1	--
	Mild	8	65.73	1.76	0.94 to 3.30
	Moderate	8	49.76	1.34	0.71 to 2.50
	Severe	8	59.84	1.61	0.86 to 3.01
C_{max} (pg/mL)	Normal	15	9.30	1	--
	Mild	8	9.98	1.07	0.67 to 1.71
	Moderate	8	7.71	0.83	0.52 to 1.32
	Severe	8	7.95	0.85	0.54 to 1.36
$t_{½}$ (hr)	Normal	15	11.55	1	--
	Mild	7	15.39	1.33	0.81 to 2.18
	Moderate	8	14.48	1.25	0.78 to 2.01
	Severe	6	14.01	1.21	0.72 to 2.04

[a] Ratios were calculated using the normal renal function group as the reference in the denominator.

2.3.1.6. Hepatic impairment: Study 091-015 was an open-label, single-dose study enrolling three groups of hepatic-impaired subjects and one group of healthy normal subjects. Arformoterol 50 µg was administered by nebulization to 8 subjects with mild hepatic impairment, 8 subjects with moderate-to-severe hepatic impairment, 8 subjects with severe hepatic impairment, and 16 subjects with normal hepatic function. The 16 subjects with normal hepatic function were comparable to the 24 subjects with hepatic impairment in age, gender, BMI, and weight. The subject's degree of hepatic impairment was assessed based on the Child- Pugh classification system. The systemic exposure (Cmax and AUC) of arformoterol increased 1.3 to 2.4-fold in subjects with hepatic impairment compared to 16 demographically matched healthy control subjects (Table 8). However, no clear relationship between drug exposure and the severity of hepatic impairment was observed. Arformoterol tartrate Inhalation Solution should be used cautiously in patients with hepatic impairment.

Table 8: Statistical Treatment Comparison of Plasma PK Parameters between Subjects with Normal Hepatic Function and Subjects with Hepatic Impairment after a Single Inhaled 50-µg Dose of Arformoterol

Parameter	Hepatic Impairment	N	Geometric LS Mean	Ratio[a]	90% CI
$AUC_{(0\text{-}last)}$ (pg*hr/mL)	Normal	15	24.6	1	--
	Mild	8	57.7	2.35	1.39 to 3.98
	Moderate-to-Severe	7	48.9	1.99	1.15 to 3.45
	Severe	8	53.7	2.19	1.29 to 3.70
C_{max} (pg/mL)	Normal	15	6.42	1	--
	Mild	8	8.92	1.39	0.80 to 2.41
	Moderate-to-Severe	7	9.35	1.46	0.82 to 2.59
	Severe	8	8.03	1.25	0.72 to 2.17
$t_{½}$ (hr)	Normal	8	10.7	1	--
	Mild	6	10.4	0.98	0.67 to 1.42
	Moderate-to-Severe	4	15.0	1.41	0.92 to 2.16
	Severe	7	15.3	1.43	1.00 to 2.06
t_{max}[b] (hr)	Normal	15	0.22[b]	--	--
	Mild	8	0.25[b]	--	--
	Moderate-to-Severe	7	0.17[b]	--	--
	Severe	8	0.23[b]	--	--

[a] Ratios were calculated using the normal hepatic function group as the reference in the denominator.

[b] Values for t_{max} shown are median values, p values for comparisons to normal were >0.05.

2.3.1.7. Pharmacogenetics: Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Desmethylation is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP2C19. Effects of Polymorphic enzymes/isozymes on PK of arformoterol were evaluated in Study 091-007.

Study 091-007: This was an open-label, parallel-group, single-dose study to evaluate the metabolic impact of poor and extensive cytochrome CYP2D6 metabolizers and reduced and normal UGT1A1 metabolizers on the PK of arformoterol. Analyses were conducted with a reference group that consisted of subjects with extensive CYP2D6 and normal UGT1A1 metabolism. Each subject received one 50 µg nebulized dose of arformoterol tartrate inhalation solution on the morning of Day 1 after fasting overnight. The results are presented in Tables 9-10.

There was no significant impact of UGT1A1 metabolizer status upon systemic exposure to arformoterol nor was there any significant change in the terminal phase half-life. The median tmax was also similar in all subjects, regardless of the status of their metabolic activity. Although the exposure to arformoterol (mean Cmax and $AUC_{0-\infty}$) was slightly lower in poor CYP2D6/normal UGT1A1 metabolizers as compared with extensive CYP2D6/normal UGT1A1 metabolizers, these differences were not considered to be clinically relevant. Additionally, the mean arformoterol $t_{1/2}$ was longer for subjects with poor CYP2D6 activity; however, the longer half-life did not cause an obvious increase in AUC to arformoterol. These observations indicate that the prolongation of half-life with poor CYP2D6 activity is unlikely to be clinically

significant, because exposure did not increase. There were only three subjects with poor CYP2D6 and reduced UGT1A1 activity; therefore, conclusive comparisons could not be made with the other metabolizer groups.

Table 9. Mean (SD) Plasma Arformoterol PK parameters after a Single Inhalation dose of 50 µg Arformoterol by metabolizer group

Parameter	Extensive CYP2D6/ Normal UGT1A1 Metabolizer (N = 18)	Poor CYP2D6/ Normal UGT1A1 Metabolizer (N = 13)	Extensive CYP2D6/ Reduced UGT1A1 Metabolizer (N= 6)	Poor CYP2D6/ Reduced UGT1A1 Metabolizer# (N = 3)
C_{max} (pg/mL)	n=18 11.7 (6.0)	n=13 9.5 (5.4)	n=6 10.4 (2.5)	n=3 7.8, 8.4, 3.6
$AUC_{(0-\infty)}$ (hour*pg/mL)	n=11 60.6 (14.3)	n=9 56.1 (23.8)	n=5 54.8 (12.1)	n=1 NC, 69.0, NC
$AUC_{(0\text{-last})}$ (hour*pg/mL)	n=18 42.2 (19.4)	n=13 41.7 (18.9)	n=6 44.8 (10.6)	n=3 24.3, 51.3, 2.56
t_{max}## (hour)	n=18 0.23 (0.20 - 0.33)	n=13 0.22 (0.17 - 0.27)	n=6 0.23 (0.17 - 0.25)	n=3 0.20, 0.22, 0.18
$t_{1/2}$ (hour)	n=17 11.6 (4.49)	n=13 16.4 (10.7)	n=6 13.9 (6.86)	n=2 35.2, 24.4, NC

NC=not calculated.

#For the Poor CYP2D6/Reduced UGT1A1 group, individual values have been reported.

##t_{max} is reported as median (minimum - maximum).

Table 10. Statistical Analysis of Arformoterol plasma PK parameters in Subjects classified as Extensive *vs.* Poor CYP2D6 Metabolizers with Normal UGT1A1 Activity

Parameter	Group	n	Geometric LS Means	B:A Ratio#	(90% CI)
C_{max} (pg/mL)	Extensive CYP2D6/Normal UGT1A1 Metabolizer (A)	18	10.6	0.79	(0.59, 1.07)
	Poor CYP2D6/Normal UGT1A1 Metabolizer (B)	13	8.4		
$AUC_{(0-\infty)}$ (pg*hr/mL)	Extensive CYP2D6/Normal UGT1A1 Metabolizer (A)	11	58.88	0.88	(0.68, 1.15)
	Poor CYP2D6/Normal UGT1A1 Metabolizer (B)	9	52.03		

#Ratios were calculated using the extensive CYP2D6/normal UGT1A1 activity group as the reference in the denominator.

Overall, the PK observations in this study, although based on a small number of subjects in one of the four metabolizer groups, suggest that the metabolic clearance of arformoterol is unlikely to be clinically meaningfully prolonged for subjects with no or reduced expression of CYP2D6 or UGT1A1.

2.4. Extrinsic Factors

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

Cigarette smoking is the most important risk factor for developing COPD. In approximately 80% to 90% of COPD cases, cigarette smoking is a causal factor (other factors play a role as well, such as age, heredity, exposure to air pollution, and a history of childhood respiratory problems). However, whether smoking has any effect on PK or PD of arformoterol has not been evaluated.

2.4.2 Drug-drug interactions

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

Yes. In vitro studies have indicated that the clearance of arformoterol is mediated by several metabolic pathways, namely UGT and CYP2D6. Study 091-018 evaluated effects of paroxetine, a potent inhibitor of CYP2D6, on the PK of arformoterol.

Study 091-018: This was an open-label, nonrandomized, multiple-dose study in healthy adult subjects classified as extensive CYP2D6 and normal UGT1A1 metabolizers. Eligible subjects received arformoterol 50 µg QD inhalation solution alone for 7 consecutive days followed by a 7-day wash-out period, paroxetine 20 mg QD tablets alone for 10 consecutive days, and arformoterol 50 µg QD in combination with paroxetine 20 mg QD for 7 consecutive days followed by a 7-day wash-out period. In this study design, the PK profiles obtained from administering arformoterol and paroxetine alone each served as reference points for the analysis of the PK parameters from the combination treatment. The results are presented in Tables xx.

Table 11: Statistical Analysis of Drug Interaction Effect on Plasma PK Parameters of Arformoterol at steady state

Parameter	Treatment Group	n	Mean	With Paroxetine versus Arformoterol Alone	
				Ratio (%)	90% CI
$AUC_{(0-\tau)}$ (hour*pg/mL)	ARF 50 µg	28	74.3	100.7	86.6 – 117.1
	ARF 50 µg + PAR 20 mg	30	70.5		
C_{max} (pg/mL)	ARF 50 µg	29	12.3	100.8	84.5 – 120.4
	ARF 50 µg + PAR 20 mg	30	12.7		

ARF=arformoterol; PAR=paroxetine.

Table 12: Plasma Paroxetine PK Parameters after 10 Daily Doses of 20 mg Paroxetine Alone and after Coadministration for 7 days

Parameter	Paroxetine 20 mg QD (N=31)	Paroxetine 20 mg + Arformoterol 50 µg QD (N=31)
C_{max} (ng/mL)	n=31 42.2 (22.5)	n=30 46.6 (24.9)
$AUC_{(0-\tau)}$ (hour*ng/mL)	n=30 718 (418)	n=30 812 (464)
t_{max}* (hour)	n=31 6.00 (4.0, 12.0)	n=30 6.18 (1.2, 10.1)
$t_{1/2}$ (hour)	--	n=30 19.7 (9.68)

-- indicates value was not calculated. $t_{1/2}$ was not determined for paroxetine alone, because the sampling period (24 hours) was too short and did not cover the terminal phase.
*t_{max} is reported as median (minimum, maximum).

Arformoterol $AUC_{(0-\tau)}$ and Cmax were similar when arformoterol was administered in combination with paroxetine, compared to arformoterol given alone. Coadministration of paroxetine with arformoterol caused a slight increase in exposure to paroxetine; the mean ratios for Cmax and AUC(0-t) were 110.3 and 115.7%, respectively. However, there was no meaningful change in the tmax of paroxetine. Collectively, these observations suggest that a dose adjustment of 50 µg QD arformoterol is not required when coadministered with therapeutic agents that are potent inhibitors of CYP2D6, such as paroxetine.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes. Arformoterol is eliminated via multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Desmethylation is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP2C19. Effects of Polymorphic enzymes/isozymes on PK of arformoterol were evaluated in Study 091-007. The results from this study showed that there was no significant impact of UGT1A1 metabolizer status upon systemic exposure to arformoterol nor was there any significant change in the terminal phase half-life. Although the exposure to arformoterol (mean Cmax and $AUC_{0-\infty}$) was slightly lower in poor CYP2D6/normal UGT1A1 metabolizers as compared with extensive CYP2D6/normal UGT1A1 metabolizers, these differences were not considered to be clinically relevant. Additionally, the mean arformoterol $t_{1/2}$ was longer for subjects with poor CYP2D6 activity; however, the longer half-life did not cause an obvious increase in AUC to arformoterol. These observations indicate that the prolongation of half-life with poor CYP2D6 activity is unlikely to be clinically significant, because exposure did not increase. There were only three subjects with poor CYP2D6 and reduced UGT1A1 activity; therefore, conclusive comparisons could not be made with the other metabolizer groups.

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

No. *In vitro* study showed that CYP2E1, CYP3A4/5, or CYP4A9/11 enzymes even at >1,000-fold higher concentrations than the expected peak plasma concentrations following a therapeutic dose.

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

This subject was not studied in this NDA.

2.5. General Biopharmaceutics

2.5.1. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Relative or absolute bioavailability of the proposed to-be-marketed formulation was not evaluated in this NDA.

2.6 Analytical section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The bioanalytical methods used to support specific clinical pharmacology studies are presented in Table 13. Validation and sample analysis results were acceptable.

Table 13: Analytical methods used in Clinical pharmacology studies

Method (No.)	Studies	Matrix	Validation summary
Validation of LC/MS/MS assay for the determination of (R,R)-formoterol in human Plasma with a Lowered Limit of quantitation (091-000-V01)	091-012 to 091-016, 091-026, 091-050, 091-051, 091-060	Plasma	The assay was linear ($r \geq 0.999$) over a range of 0.5 to 200 pg/mL. Intra and inter-assay precision values were within 15%. Intra and inter-assay accuracy (% bias) values ranged from -2.3% to 7.3%. The recovery values ranged from 47.7% to 51.5% for (R,R)-formoterol and [ ] (isotopically labeled internal standard). b(4)
Method validation of an improved LC/MS/MS Assay for the Determination of (R,R)-, and (S,S)-formoterol (091-000-V02)	091-016	Plasma	The assay was linear over a range of 2-200 pg/mL for (R,R)-formoterol ($r \geq 0.999$) and (S,S)-formoterol ($r \geq 0.998$) Intra and inter-assay precision values were within 15%. Intra and inter-assay accuracy values ranged -8.8-10.7% for R,R- and -6.3-10% for S,S-formoterol. The recovery values ranged 78-90.7% for R,R- and 68.7-70.6% for S,S-formoterol
Validation of an LC/MS/MS assay for determination of (R,R)-formoterol (091-000-V04)	091-012 to 091-015	Urine	Linear ($r \geq 0.999$) over a range of 2.5-500 pg/mL. Intra and inter-assay precision values were within 15%, and accuracy values ranged -12.2 - 9%. The recovery values ranged 31.8-40.2% for (R,R)-formoterol and 33.7-40% for [ ] b(4)
Validation of an LC/MS/MS assay for determination of the sterioisomers (091-000-V10)	091-016	Urine	Chiral assay for the determination of (R,R)-, (R,S)-, (S,R)-, and (S,S)-formoterol in human urine using 4 mL sample volume. The assay was linear over a range of 5-1250 pg/mL. The precision, accuracy and recovery were satisfactory.
UGT1A1*28 PCR assay Validation summary (091-000-V11)	091-007, 091-018	Blood	A polymerase chain reaction (PCR) method to test for the presence of the UGT1A1*28 polymorphism. The final genotypes from each sample, run in triplicate, in tests performed by 3 scientists were identical. Assay results were considered acceptable.
Validation Summary Report of the Identification of the CYP2D6 Alleles *3, *4, *6, *7, and *8 by Multiplex Polymerase Chain Reaction (091-000-V12)	091-007, 091-012, 091-015, 091-018, 091-050, 091-051	Blood	This assay consists of the amplification of a first round fragment from the 2D6 gene, which contains the five CYP2D6 alleles followed by a second round of amplification using allele specific primers. The performance of the CYP2D6 multiplex assay during the course of the validation testing activities met all pre-determined acceptance criteria.
Validation Summary Report of the Identification of the CYP2D6 Alleles *5, *10, *17, and *2XN (091-000-V22)	091-007, 091-012, 091-015, 091-018, 091-050, 091-051	Blood	Four different PCR methods were used to detect 4 CYP2D6 Alleles. The intra-assay precision foe each assay was performed on 12-16 samples tested in triplicate by 3 scientists. Assay results were considered acceptable.
Method validation of an LC/MS/MS Assay for the Determination of Paroxene (091-000-V23)	091-018	Plasma	The assay was linear ($r \geq 0.996$) over a range of 0.1-50 ng/mL using 0.2 mL sample volume for paroxetine. Intra and inter-assay precision values were within 15%, and accuracy values ranged -11.3-11.8%. The recovery values for paroxetine and [ ] (internal standard) ranged 81.5-92.6%. b(4)
LC/MS/MS method for the determination of active metabolite, (R,R)-O-desmethylformoterol (091-000-B03)	091-013, 091-050	Plasma	Assay LLOQ was 0.5 pg/mL. The precision (%CV) were 4.02% for (R,R)- O-desmethylformoterol, 4.39% for [ ] (internal standard), and 7.23% for the ratio (analyte/IS). b(4)

20 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

4.2. Individual Study Reviews

Protocol 091-007

Study Type: Single-dose PK study in healthy subjects with polymorphic enzymes.

Title: An Evaluation of the Impact of Cytochrome P450 (CYP) 2D6 and UGT1A1 Metabolism on the Pharmacokinetics of Arformoterol Inhalation Solution.

Objectives:

Primary: To characterize the PK of arformoterol inhalation solution in subjects classified as poor versus extensive CYP2D6 metabolizers or with reduced uridine diphosphate glycosyl transferase 1 polypeptide A1 (UGT1A1) activity.

Secondary: To describe the safety and tolerability of a single 50 µg dose of arformoterol in subjects considered to be poor or extensive CYP2D6 metabolizers, in subjects considered to be reduced UGT1A1 metabolizers, and in subjects considered to be both reduced UGT1A1 and poor CYP2D6 metabolizers.

Methodology: This was an open-label, multicenter, parallel-group, in- and out-patient, single-dose study of 48 healthy adult subjects, aged between 18 and 55 years, classified as one of the following: a) extensive CYP2D6 and normal UGT1A1 metabolizers (12-18 subjects), b) poor CYP2D6 and normal UGT1A1 metabolizers (12-18 subjects), c) extensive CYP2D6 and reduced UGT1A1 metabolizers (up to 6 subjects), or d) poor CYP2D6 and reduced UGT1A1 metabolizers (up to 6 subjects).

CYP2D6 Genotype: The CYP2D6 alleles tested were *3, *4, *5, *6, *7, *8, *10, *17, and *2XN. The classification of CYP2D6 metabolizer status was as follows:

- **Poor** CYP2D6 metabolizers were predicted by genotypes of *3, *4, *5, *6, *7, or *8 with **4, *5, *6, *7, or *8 in any combination (e.g., *4/*6 or *4/*4, etc.).
- **Extensive** CYP2D6 metabolizers were predicted by:
  - Genotypes of wild type/wild type (wt/wt) or normal.
  - Genotypes of wt/* with a polymorphism of *3, *4, *5, *6, *7, *8, *10, or *17 (e.g., wt/*5).
  - Genotypes of wt/* with a polymorphism of *3, *4, *5, *6, *7, or *8 and gene
- **Ultra-rapid** metabolizers were predicted by genotypes of wt/wt or wt/*17 with gene duplication *2XN.

Subjects classified as "ultra-rapid" CYP2D6 metabolizers were considered as "extensive". Intermediate metabolizers (about 14% of the population) were not enrolled.

UGT1A1 Genotype: The UGT1A1 enzyme catalyzes the glucuronidation of bilirubin and other compounds; thus, affecting several important clinical disorders. The UGT1A1 *28 mutation reduces levels of expression of the UGT1A1 gene, resulting in mild hyperbilirubinemia consistent with Gilbert's syndrome. The UGT1A1 genotype was classified according to Table 1.

Table 1: UGT1A1 Genotype Classification

Genotype	# of TA Repeats	Phenotype
Wild type	TA6	Normal activity/expression
*28	TA7	Reduced activity/expression
Other	TA5	Altered/increased activity/expression
Other	TA8	Altered/reduced activity/expression

Normal UGT1A1 expression was determined by the presence of the TA6 and/or TA5 allele(s) in the homozygous and heterozygous state.
Reduced UGT1A1 expression was determined by the presence of the TA7 and/or TA8 allele(s) in the homozygous state.

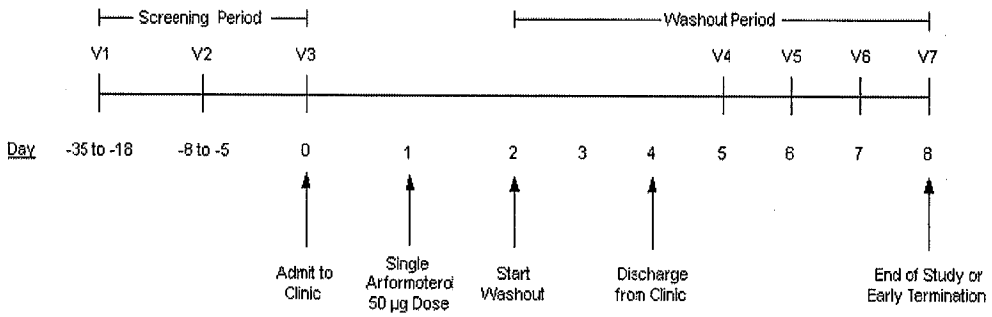
Test Product: 50 µg (in 2 mL) Arformoterol tartrate inhalation solution. Lot #02403C

Criteria for Evaluation:

Pharmacokinetic: $AUC_{(0-\infty)}$, Cmax, tmax, $t_{1/2}$, and $AUC_{(0\text{-last})}$.

Safety: Adverse events, laboratory parameters (hematology; serum chemistry, including glucose and potassium; urinalysis), vital signs, electrocardiogram (ECG), 24-hour Holter monitoring, and physical examination.

Sampling Times: A study schematic is shown in Figure below:



PK: Blood samples were drawn for arformoterol PK predose and at 5, 15, 30, 60, 90 minutes postdose and 2, 4, 6, 8, 12, and 18 hours postdose on Day 1 and at 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose on Days 2 to 8.

Safety: Pre-dose and several time points post-dose for safety evaluation criteria, e.g., ECG at screening, and predose and 5, 15, 30, 60, 90 min postdose and 2, 4, 6, 8, 12, 18 hrs postdose on Day 1; and at 24, 36, 48, 72, 96, and 168 hrs postdose during Days 2 to 5 and Day 8.

Statistical Methods: The PK population was defined as all subjects who received arformoterol and provided any evaluable PK data (used for PK analyses). The ITT population was defined as all subjects who received the single dose of study drug (safety analyses).

Pharmacokinetic: Noncompartmental methods and WinNonlin® were utilized to obtain estimates of relevant PK parameters. The primary analyses compared subjects with poor CYP2D6 and normal UGT1A1 metabolism to subjects with extensive CYP2D6 and normal UGT1A1 metabolism, with the latter group as the reference group. The effect of metabolizer group was assessed using a linear model and SAS. PROC MIXED, with metabolizer group as the single fixed effect. The AUC and Cmax data were natural log (ln)-transformed before analysis. PK parameters also were summarized descriptively by metabolizer group (secondary analyses).

Safety: Data were summarized using descriptive statistics.

RESULTS

No. of Subjects: PK and safety were analyzed from 40 subjects.

Pharmacokinetics: Mean (SD) arformoterol plasma concentrations over time resulting from a single dose of arformoterol are presented in Figure 1 and Table 1. Results of statistical analysis of Cmax and $AUC_{0-\infty}$ are shown in Table 2.

Figure 1. Mean Arformoterol Plasma Concentrations Following a Single Inhaled 50 µg Arformoterol Dose in Subjects Classified as Poor *vs.* Extensive CYP2D6 Metabolizers with Normal *vs.* Reduced UGT1A1 Activity

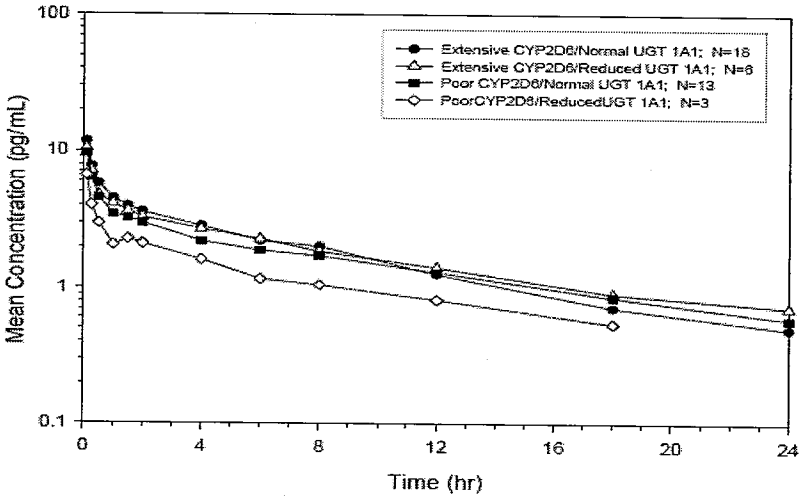


Table 1. Mean (SD) Plasma Arformoterol PK parameters after a Single Inhalation dose of 50 µg Arformoterol by metabolizer group

Parameter	Extensive CYP2D6/ Normal UGT1A1 Metabolizer (N = 18)	Poor CYP2D6/ Normal UGT1A1 Metabolizer (N = 13)	Extensive CYP2D6/ Reduced UGT1A1 Metabolizer (N= 6)	Poor CYP2D6/ Reduced UGT1A1 Metabolizer# (N = 3)
C_{max} (pg/mL)	n=18 11.7 (6.0)	n=13 9.5 (5.4)	n=6 10.4 (2.5)	n=3 7.8, 8.4, 3.6
$AUC_{(0-\infty)}$ (hour*pg/mL)	n=11 60.6 (14.3)	n=9 56.1 (23.8)	n=5 54.8 (12.1)	n=1 NC, 69.0, NC
$AUC_{(0-last)}$ (hour*pg/mL)	n=18 42.2 (19.4)	n=13 41.7 (18.9)	n=6 44.8 (10.6)	n=3 24.3, 51.3, 2.56
t_{max}## (hour)	n=18 0.23 (0.20 - 0.33)	n=13 0.22 (0.17 - 0.27)	n=6 0.23 (0.17 - 0.25)	n=3 0.20, 0.22, 0.18
$t_{1/2}$ (hour)	n=17 11.6 (4.49)	n=13 16.4 (10.7)	n=6 13.9 (6.86)	n=2 35.2, 24.4, NC

NC=not calculated.

#For the Poor CYP2D6/Reduced UGT1A1 group, individual values have been reported.

##t_{max} is reported as median (minimum - maximum).

Table 2. Statistical Analysis of Arformoterol plasma PK parameters in Subjects classified as Extensive *vs.* Poor CYP2D6 Metabolizers with Normal UGT1A1 Activity

Parameter	Group	n	Geometric LS Means	B:A Ratio[#]	(90% CI)
C_{max} (pg/mL)	Extensive CYP2D6/Normal UGT1A1 Metabolizer (A)	18	10.6	0.79	(0.59, 1.07)
	Poor CYP2D6/Normal UGT1A1 Metabolizer (B)	13	8.4		
$AUC_{(0-\infty)}$ (pg*hr/mL)	Extensive CYP2D6/Normal UGT1A1 Metabolizer (A)	11	58.88	0.88	(0.68, 1.15)
	Poor CYP2D6/Normal UGT1A1 Metabolizer (B)	9	52.03		

[#]Ratios were calculated using the extensive CYP2D6/normal UGT1A1 activity group as the reference in the denominator.

Conclusions:

Pharmacokinetics:

- The exposure to arformoterol (mean Cmax and $AUC_{0-\infty}$) was slightly lower in poor CYP2D6/normal UGT1A1 metabolizers as compared with extensive CYP2D6/normal UGT1A1 metabolizers ; these differences were not considered to be clinically relevant. These data suggest that CYP2D6 does not play an important role in the metabolism of arformoterol (Table 2).
- In comparing groups with normal and reduced UGT1A1 activity with extensive CYP2D6 metabolizer status, arformoterol systemic exposure, median tmax, and mean $t_{1/2}$ were similar. These data suggest that UGT1A1 does not play an important role in the metabolism of arformoterol (Table 1).
- Conclusive statements could not be made about the poor CYP2D6/reduced UGT1A1 group, because it only included 3 subjects with limited pharmacokinetic data.

Comment: Overall, the sponsor's conclusions are acceptable. However, in vitro study found that the primary UGT isozymes found to catalyze arformoterol glucuronidation were UGT2B17, UGT1A9, UGT2B7, UGT1A1, and UGT1A7 in decreasing order of activity.

Protocol 091-012

Study Type: Single-dose, characterize ADME of aformoterol in healthy subjects.

Title: An Open Label, Single Dose, Radio-label Study to Characterize the Disposition of 50 μg Arformoterol in Healthy Adult Male Subjects.

b(4)

Clinical Investigators: [redacted]

Objectives:

Primary Objective: To characterize the disposition of radiolabeled arformoterol and its metabolites by determining the total radioactive dose recovery (mass balance) and relative excretion of total radioactivity in urine and feces.

Secondary Objectives:

- To characterize the disposition of radiolabeled arformoterol and its metabolites by determining the PK of total radioactivity in blood, plasma, urine, and feces as well as the unchanged drug in plasma, urine, and feces.
- Identify and profile, where possible, arformoterol metabolites in selected samples of plasma, urine, and feces.
- To monitor the safety of a single dose of 2 mCi tritium-labeled 50 μg arformoterol.

Methodology: Open label, single dose, radiolabeled absorption, distribution, metabolism, and excretion (ADME) study in 8 healthy adult male subjects (18-35 yrs of age). Following a screening period (maximum of 14 days), eligible subjects returned to the clinic for a maximum 21-day stay. After fasting at least 8 hours, subjects received a single, 50 μg oral dose of 2 mCi ^{3}H-arformoterol. Blood, urine, and fecal samples were obtained prior to dosing. Subjects fasted for an additional 4 hours following dosing. Blood samples were collected serially for 21 days postdose. Feces and urine were collected in intervals for 21 days postdose. In addition, all subjects underwent genotyping of cytochrome P450 isoenzyme 2D6 (CYP2D6).

Investigated product: ^{3}H-arformoterol oral solution. Subjects received a single 50 μg dose (2 mCi) ^{3}H-arformoterol tartrate (equivalent to 34.8 μg free base) Lot 3490-097.

Sampling times:
Blood samples: Predose and at the following postdose time points: 10, 20, 30, 45, 60 and 90 min, and 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, and 504 hours.
Others: Urine was collected 0-2, 2-4, 4-8, 8-12 and 12-24 hours on Day 1. Feces were collected in a pooled 0-24 hour collection on Day 1. All other urine and fecal samples during the 21-day period were collected and pooled into 24-hour samples, e.g., 24-48 hrs, 48-72 hrs, etc. Radioactivity levels in the urine were measured daily beginning on Day 10 to assess whether or not background levels were achieved. Once achieved, no further collection of blood, urine, and feces was required.

Criteria for Evaluation:

Pharmacokinetics: Primary PK parameters of arformoterol were determined from concentrations in plasma and urine of each subject and for nonvolatile radioactivity in plasma, urine, and feces of

each subject. In addition, PK parameters were estimated for total radioactivity in whole blood. Urine and plasma data were used to calculate renal clearance of arformoterol.

Safety: Adverse events, laboratory parameters (hematology, serum chemistry including glucose and potassium, and urinalysis), vital signs, electrocardiogram (ECG) findings, and physical examination findings.

PK Analysis: Descriptive statistics included number of subjects (n), mean, median, minimum, maximum, standard deviation, and coefficient of variation. Only median, minimum, and maximum were to be presented for parameters with ≤3 subjects.

Safety Analysis: Adverse events were summarized using counts and percentages. Changes in vital signs and ECG parameters from baseline were presented descriptively for each treatment.

RESULTS

Assay Report: Radioactivity was measured by liquid scintillation spectrometry using ⊂ ⊐ scintillation counters, and HPLC was used for the separation of metabolites. The assay results from this study as summarized by sponsor (acceptable by this reviewer) are as follows: b(4)

In this ⊂ ⊐ study, plasma, whole-blood, urine and faeces samples collected from eight healthy male human subjects during a preceding clinical trial (Sepracor study 091-012, conducted by ⊂ ⊐ were analysed. These subjects each received single oral doses of 50 µg (74 MBq) of [^{3}H]-(R,R)-formoterol L-tartrate, equivalent to 34.8 µg free base. Concentrations of radioactivity in plasma (before and after lyophilisation), whole-blood, urine and faeces were measured to provide information in radioactivity concentrations in blood fractions and on the rates and routes of excretion of radioactivity. Selected samples of urine and extracts of plasma and faeces were analysed by High Performance Liquid Radiochromatography to determine the number and proportions of metabolites and Single Reaction Monitoring was used as the mass spectrometry approach to provide structural information on the metabolites formed. b(4)

[^{3}H]-(R,R)-formoterol was rapidly absorbed, because radioactivity was present in all plasma (mean of 0.059 ng equivalents free base/mL) and whole-blood (mean of 0.043 ng equivalents/mL) samples collected 10 minutes after dosing (the first sampling time). Highest mean radioactivity concentrations in both plasma and whole-blood were measured 1 hour after dosing (0.411 and 0.254 ng equivalents/mL, respectively). In plasma collected within 2 hours of dosing, less than 10% of sample radioactivity was volatile but, despite the relatively small overall extent of tritium exchange (about 7%), the proportion of non-volatile radioactivity in plasma declined to about 30% at 24 hours and further to only 13 – 16% during 96 – 336 hours. The decline in total plasma radioactivity concentration was slow, but since at later times, most plasma radioactivity was present as tritiated water, the decline would be predicted to be similar to that for tritiated water in man (half-life 9.5 days). Because of the great influence of the kinetics of ^3H_2O on those of total plasma radioactivity, it is probable that, at later sampling times, the plasma radioactivity kinetics are not clinically relevant. Within 2 hours of dosing (when most whole-blood radioactivity was not volatile and fully representative of (R,R)-formoterol and it's metabolites of close structural relationship), the association of radioactivity with blood cells was small (7% or less) and most radioactivity remained in the plasma fraction.

In the excretion phase of the study, the mean total recovery of radioactivity in urine and faeces was 88.91% dose in the 336 hours after dosing. In view of the tritium exchange which occurred, some radioactivity would have been respired and lost and the overall recovery is, in these circumstances, considered acceptable. Most radioactivity (a mean of 67.23% dose) was excreted in urine during 336 hours with a lesser proportion (mean of 21.68% dose) excreted in faeces. Most of this (62.80 and 10.61% dose; urine and faeces, respectively) was excreted within 48 hours of dosing, but the excretion of radioactivity was subsequently protracted, mainly as a consequence of the elimination of ^3H_2O which, at later times, accounted for large proportions of excreta sample radioactivity.

In all subjects, most systemic exposure and excretion was due to (R,R)-formoterol and its glucuronide conjugates. The major glucuronide conjugate co-chromatographed with a metabolite in mouse urine in which a more comprehensive structural elucidation of this metabolite was obtained showing it to be the 'phenolic' glucuronide. A second, possibly benzylic, glucuronide was also formed, as was a single sulphate conjugate of formoterol. *O*-Demethylation (to desmethylformoterol) was a lesser pathway of metabolism, although glucuronide and sulphate conjugates of desmethylformoterol were seen in urine and plasma and desmethylformoterol was also present in extracts of faeces, presumably as a consequence of the hydrolysis of such conjugates by the intestinal microflora after biliary excretion. There was little evidence for the deformylation of (R,R)-formoterol except in one subject, in which the production of the major glucuronide of formoterol was relatively small and a metabolite believed to be a sulphate conjugate of desformylformoterol was present in the urine of this subject.

PK RESULTS

Plasma concentration-time data: Mean plasma concentrations for arformoterol, nonvolatile radioactivity, and total radioactivity for 0-24 hours (left graph) and for the entire sampling period (right graph) are presented in Figure 1. Plasma PK Parameters are presented in Table 1.

Figure 1: Mean Plasma Arformoterol, Nonvolatile Radioactivity, and Total Radioactivity *vs.* Time Following a Single Oral Dose of 50 µg/2 mCi ^{3}H-Arformoterol Tartrate

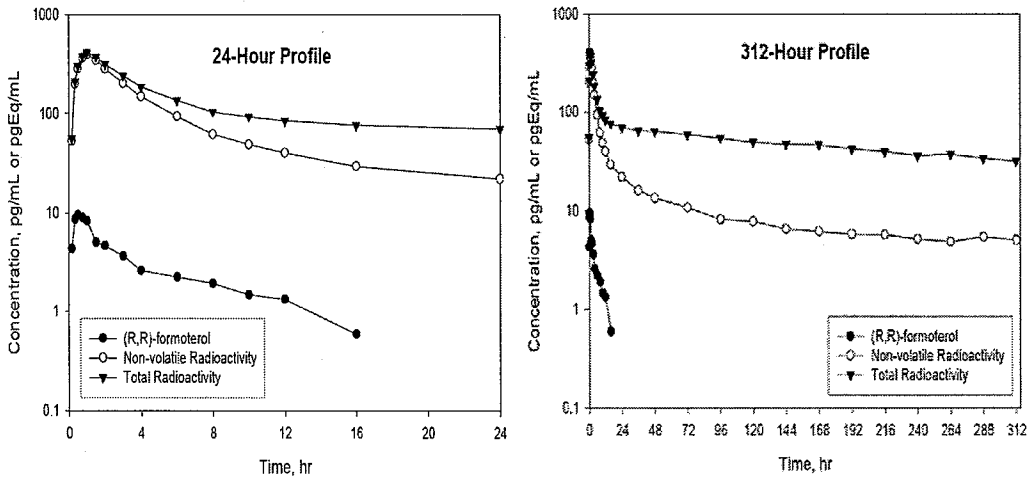


Table 1: Plasma PK Parameters of Arformoterol and Nonvolatile Radioactivity Following a Single Oral Dose of 50 µg/2 mCi ^{3}H-Arformoterol Tartrate

Parameter	Units	Arformoterol			Nonvolatile Radioactivity		
		n	Mean	SD	n	Mean	SD
C_{max}	pg/mL	8	10.48	5.47			
	pgEq/mL				8	420.50	90.80
$AUC_{(0\text{-last})}$	pg*hr/mL	8	44.25	29.54			
	pgEq*hr/mL				8	4002.66	940.71
$AUC_{(0\text{-}\infty)}$	pg*hr/mL	5	63.04	38.39			
$t_{1/2}$	hr	7	11.58	6.11	*	*	*
$R_{C_{max}}$(drug/nonvolatile radioactivity)	N/A	8	0.03	0.01			
R_{AUC}(drug/nonvolatile radioactivity)	N/A	8	0.02	0.01			
			Median			Median	
t_{max}	hr	8	0.63		8	1.00	

Note: N/A = Not applicable.

Note: The units of measure, pg/mL and pgEq/mL, were used for the concentration of plasma and the concentration based on nonvolatile radioactivity, respectively.

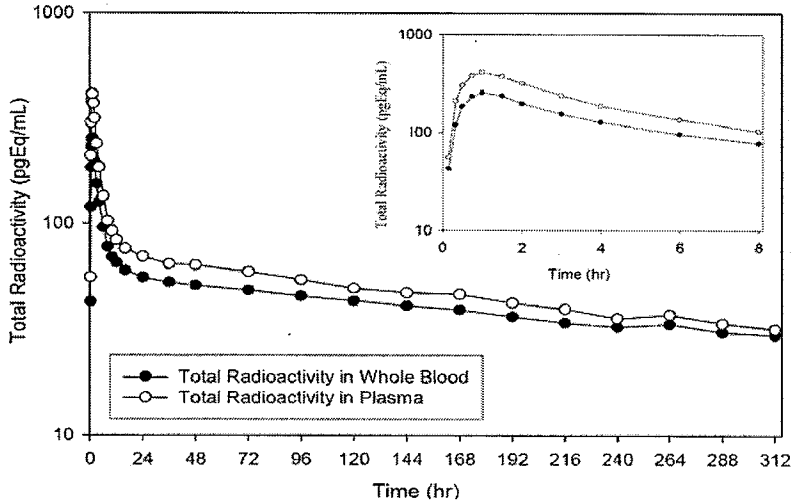
*Note: The half-life of nonvolatile radioactivity in plasma could not be estimated with certainty.

Reference: Table 14.2.2.1

The ratio of parent drug (arformoterol) to nonvolatile radioactivity was between 2-3%. This indicates that in the systemic circulation, 97% of the exposure can be attributed to metabolites.

Total Radioactivity in Whole Blood: Total radioactivity concentrations represented drug-related labeled species and minimal amounts of tritiated water had been produced. A comparison of the mean total radioactivity profiles in blood and plasma are shown in Figure 2.

Figure 2: Mean Total Radioactivity in Whole Blood and Plasma Following a Single Oral Dose of 50 µg/2 mCi ^{3}H-Arformoterol Tartrate



Concentrations of total radioactivity in whole blood were slightly lower than those in plasma, but the concentration-time profiles were parallel.

Whole Blood PK Parameters: PK parameters for total radioactivity in whole blood are summarized in Table 2.

Table 2: PK Parameters of Total Radioactivity in Whole Blood Following a Single Oral Dose of 50 µg/2 mCi 3H-Arformoterol Tartrate

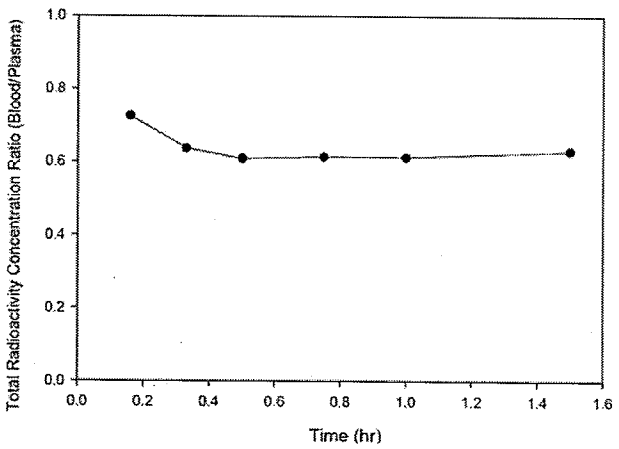
Parameter	Units	N	Mean	SD
C_{max}	pgEq/mL	8	266.88	59.31
$AUC_{(0\text{-last})}$	pgEq*hr/mL	8	12681.84	3205.36
$t_{1/2}$	hr	8	318.51	134.03
			Median	
t_{max}	hr	8	1.00	

Reference: Table 14.2.2.2

The mean concentrations of total radioactivity in whole blood declined very slowly over the 312-hour post-dose time period (due to a large proportion of tritiated water was present in blood).

Blood to plasma ratios for total radioactivity concentrations were calculated and plotted versus time from 1 to 1.5 hours postdose, and are presented in Figure 3.

Figure 3: Blood to Plasma Ratios of Total Radioactivity Following a Single Oral Dose of 50 µg/2 mCi 3H-Arformoterol Tartrate



Blood to plasma concentration ratios indicate the extent of drug distribution into or binding to red blood cells. The ratio was slightly higher at the 10- and 20-minute postdose time points, but then appeared to equilibrate to a value of about 0.6 thereafter.

Arformoterol and Nonvolatile Radioactivity in Urine and Feces:

The sponsor stated that the concentration and amount of arformoterol excreted in the feces were not provided due to the lack of an analytical method for the determination of arformoterol in feces. Instead, these parameters were derived and summarized for total and nonvolatile radioactivity based on percent of dose excreted.

a. *Cumulative Amount Excreted and Excretion Rates:*

The cumulative amounts and percent of dose excreted in urine and feces are graphically displayed in Figures 4 and 5, respectively.

As shown in Figure 4, the amounts of arformoterol excreted in urine after 72 hours were negligible. Most of the radioactivity was recovered within 144 hours after dosing. Approximately 1% (see insert) of the dose was excreted in urine as unchanged arformoterol, and approximately 64% as nonvolatile and 67% as total radioactivity.

Figure 4: Cumulative Amounts and Percent of Dose of Arformoterol and Radioactivity (Nonvolatile and Total) Excreted in Urine Following a Single Oral Dose of 50 µg/2 mCi ^{3}H-Arformoterol Tartrate

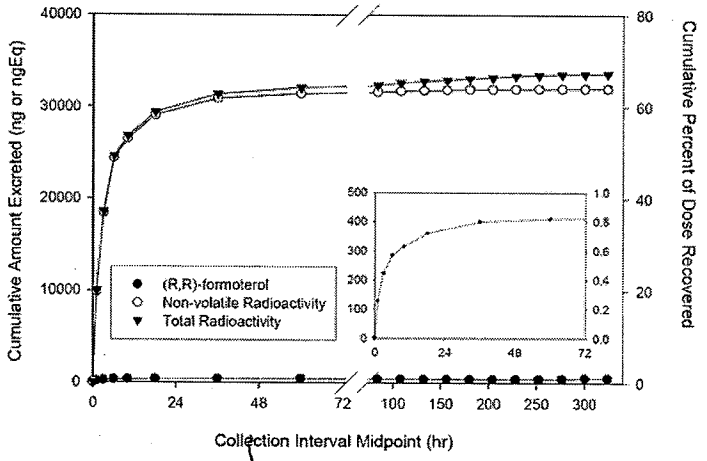
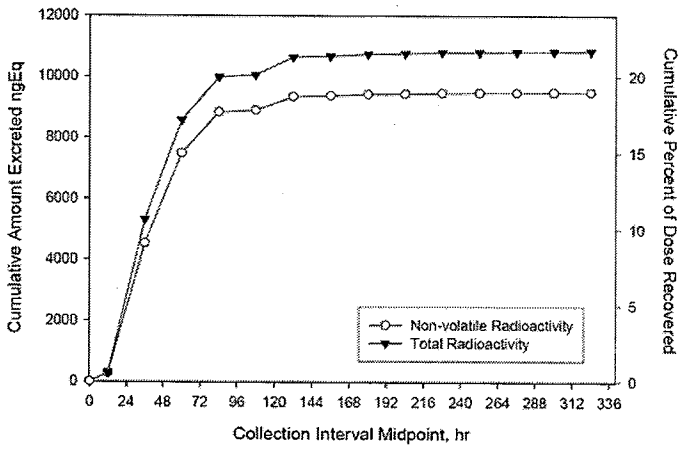


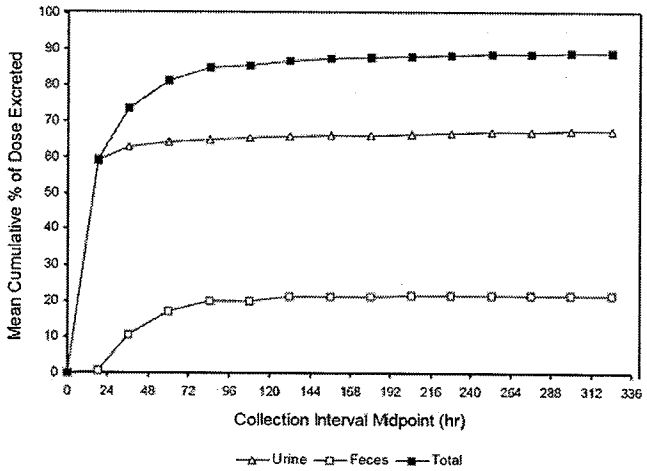
Figure 5: Cumulative Amounts and Percent of Dose Excreted in Feces as Nonvolatile and Total Radioactivity Following a Single Oral Dose of 50 µg/2 mCi 3H-Arformoterol Tartrate



As with urine, most of the radioactivity was recovered from feces within 144 hours after dosing. Figure 5 illustrates that approximately 19% and 22% of the dose was ultimately recovered in feces as nonvolatile and total radioactivity, respectively.

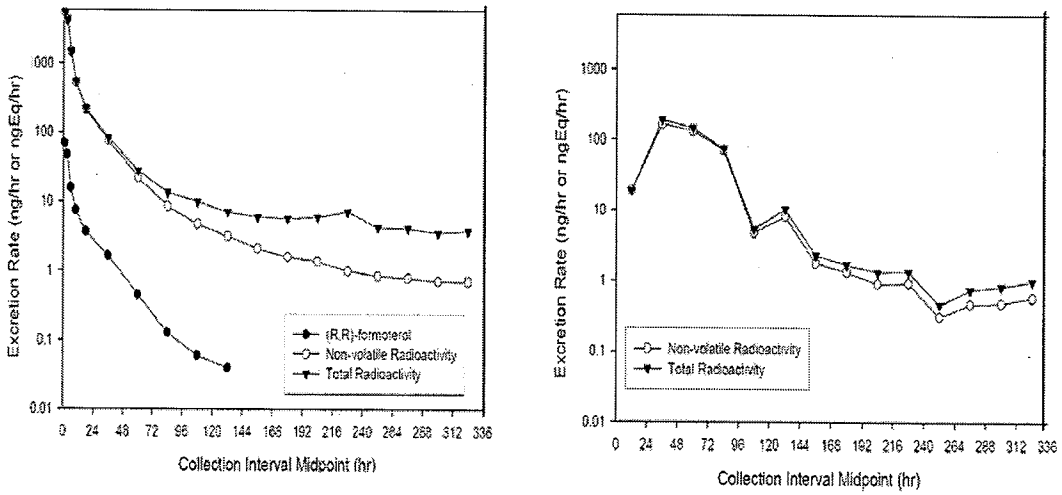
Figure 6 shows that approximately 89% of the dose was excreted as total radioactivity; 67% was recovered in urine and 22% was recovered in feces. Most of this was recovered within 144 hours post-dose.

Figure 6: Mean Cumulative Percent of Dose Excreted in Urine and Feces as Total Radioactivity Following a Single Oral Dose of 50 µg/2 mCi 3H-Arformoterol Tartrate



Mean urinary excretion rates versus collection interval midpoints for arformoterol, nonvolatile radioactivity, and total radioactivity are displayed in Figure 7 (left panel), and mean fecal excretion rates of nonvolatile radioactivity and total radioactivity are shown in Figure 7 (right panel).

Figure 7: Mean Urinary Excretion Rates of Arformoterol, Nonvolatile Radioactivity, and Total Radioactivity Following a Single Oral Dose of 50 µg/2 mCi 3H-Arformoterol Tartrate



The mean excretion rate figures illustrate the trends in the data from which the elimination half-live in urine ($t_{1/2}$, ur) and feces ($t_{1/2}$, fc) were derived. Fecal excretion rates were the highest during the 24-72 hour postdose period and slowed considerably after 144 hours.

b. Urine and Feces Pharmacokinetic Parameters (Tables 3-4):

Table 3: Urine PK Parameters of Arformoterol and Nonvolatile Radioactivity Following a Single Oral Dose of 50 µg/2 mCi 3H-Arformoterol Tartrate

Parameter	Units	Arformoterol			Nonvolatile Radioactivity		
		N	Mean	SD	N	Mean	SD
$Ae_{ur(0-\infty)}$	ng	8	425.88	272.60			
	ngEq				8	32083.06	2040.35
$Ae_{ur(0-last)}$	ng	8	414.82	270.39			
	ngEq				8	31997.69	2063.20
Cl_{ur}	L/hr	8	8.88	3.00	8	8.79	1.83
$Fe_{ur(0-\infty)}$	%	8	0.85	0.54	8	64.17	4.08
$Fe_{ur(0-last)}$	%	8	0.83	0.54	8	64.00	4.13
$t_{1/2,\ ur}$	hr	8	20.04	8.29	8	86.38	25.72

Note: The lower limit of quantification was set at 2.5 pg/mL for arformoterol.
Note: Nonvolatile radioactivity was based on arformoterol tartrate.
Note: Nonvolatile radioactivity represents the radioactivity measurement of the urine samples excluding the volatile radioactivity ($^3H_20$, etc.).
Reference: Table 14.2.2.3.1

The mean $Fe_{ur\ (0-\infty)}$ values for unchanged arformoterol and for nonvolatile radioactivity were 0.85% and 64.17%, respectively. The mean $Fe_{ur\ (0-\infty)}$ was nearly equal to the mean $Fe_{ur\ (0-last)}$, indicating that the excretion of radioactivity in urine was virtually complete during the 336-hour collection interval. The mean urinary elimination half-life of arformoterol (20.04 ± 8.29 hr) was longer than the half-life derived from the plasma concentration data (11.58 ± 6.11 hr), possibly due to differences in tlast (20 hours [plasma] and 290 hours [urine]). The mean elimination half-life for nonvolatile radioactivity was 86.38 ± 25.72 hr. Renal clearance was approximately 9.0 L/hr for both unchanged arformoterol and nonvolatile radioactivity.

Table 4: PK Parameters in Feces for Nonvolatile Radioactivity Following a Single Oral Dose of 50 µg/2 mCi 3H-Arformoterol Tartrate

Parameter	Nonvolatile Radioactivity			
	Units	N	Mean	SD
$Ae_{fc(0-\infty)}$	ngEq	8	9528.95	1966.14
$Ae_{fc(0-last)}$	ngEq	8	9493.82	1955.68
$Fe_{fc(0-\infty)}$	%	8	19.06	3.93
$Fe_{fc(0-last)}$	%	8	18.99	3.91
$t_{1/2,\ fc}$	hr	8	44.79	21.05
$\lambda_{z,\ fc}$	hr^{-1}	8	0.02	0.01

Note: Nonvolatile radioactivity represents the radioactivity measurement of the feces samples excluding the volatile radioactivity ($^3H_20$, etc.).

$Fe_{fc\ (0-last)}$ was 18.99% and was nearly equal to $Fe_{fc\ (0-\infty)}$, indicating that the fecal elimination was nearly complete during the 336-hour collection period. The elimination half-life for nonvolatile

radioactivity excreted in feces was 44.79 ± 21.05 hours. The elimination half-life of nonvolatile radioactivity excreted in feces was approximately 50% less than that of urine, possibly due to the difference in the metabolic profile of urine and feces.

c. Metabolites of Arformoterol

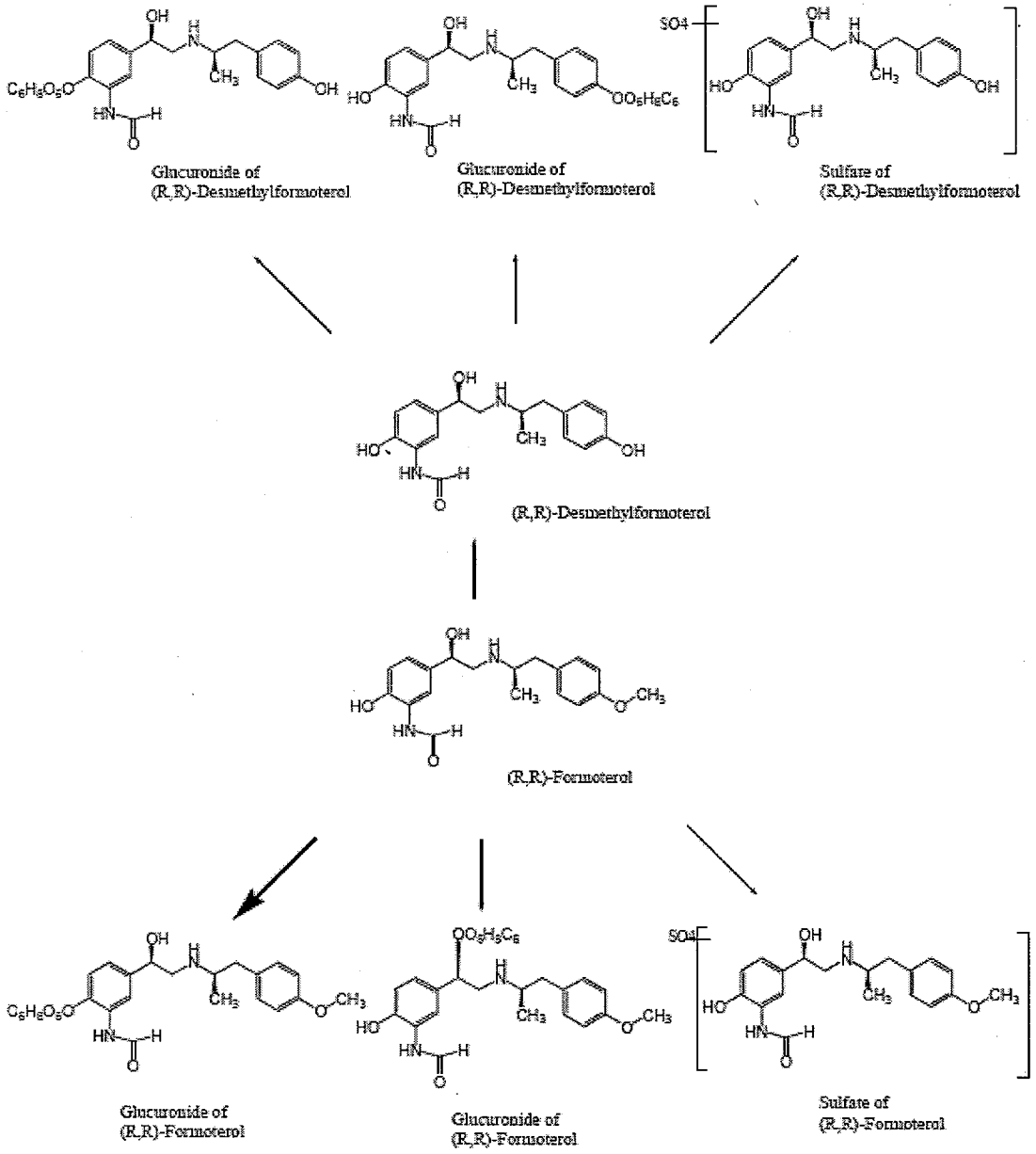
Metabolite profiling of arformoterol was performed using plasma, urine, and fecal samples collected during the study (Figure 8).

Most of the systemic exposure in plasma was attributed to the conjugated metabolites of arformoterol. Only trace levels of O-desmethylformoterol were found in plasma. No evidence for the presence of desformoterol in plasma was found; however, trace quantities of a desformoterol sulfate conjugate may exist in human urine. Sulphate and glucuronide conjugates were also the dominant moieties found in urine. Relatively high amounts of arformoterol were found in feces, which differed from the metabolic profile found in plasma and urine. It is suspected that bacterial hydrolysis of arformoterol conjugates may have occurred; however, biliary excretion of parent drug and/or incomplete absorption of the administered oral dose cannot be ruled out. O-demethylation of arformoterol and conjugation of the O-desmethyl metabolite were relatively minor pathways, accounting for less than 17% of the dose recovered in urine and feces (primarily the urine).

Pharmacokinetic Conclusions:

- Urine and feces were collected for a sufficient length of time and excretion of radioactivity was nearly complete; most of the radioactivity was recovered by 144 hours postdose.
- The total radioactivity recovered was approximately 89%, including 67% from urine and 22% from feces. Of this, approximately 83% of the dose was excreted as nonvolatile radioactivity; 64% was recovered in urine and 19% was recovered in feces within 144 hours after dosing.
- During the first 1.5 hours postdose, the mean total radioactivity concentration-time profile in blood was parallel to, but lower than, the concentration-time profile in plasma. A blood-to-plasma ratio of 0.63 indicated that there is no preferential distribution of radioactivity into red blood cells.
- The ratio of parent drug (arformoterol) to nonvolatile radioactivity was between 2-3%. This indicates that in the systemic circulation, 97% of the exposure can be attributed to metabolites.
- The amount of radioactivity recovered as nonvolatile radioactivity in urine indicates that the fraction of the oral 3H-arformoterol dose absorbed was at least 64%. Unchanged arformoterol in urine accounted for approximately 1% of the dose, indicating that urinary excretion of the parent compound is a minor elimination pathway.
- The mean elimination half-life estimated for arformoterol from urine excretion data (20.04 ± 8.29 hours) was longer than the half-life derived from the plasma concentration data (11.58 ± 6.11 hours), possibly due to differences in tlast (20 hours [plasma] and 290 hours [urine]). The mean elimination half-life for nonvolatile radioactivity derived from urine data was 86.38 ± 25.72 hours.
- Most of the systemic exposure in plasma was attributed to the conjugated metabolites of arformoterol. Glucuronidation and sulfation of arformoterol were the primary metabolic pathways; phase I metabolism (demethylation of arformoterol) was a minor pathway of metabolism. No evidence for the presence of desformoterol in plasma was found. Only trace levels of O-desmethylformoterol were found in plasma. Sulphate and glucuronide conjugates were also the dominant moieties found in urine.

Figure 8: Postulated Major Pathways of Metabolism of Arformoterol in Male Human Subjects



Comment: Conclusions made by the sponsor are acceptable.

Protocol 091-013

Study Type: Single-dose, PK in elderly subjects.

Title: The Pharmacokinetics and Safety of a Single Dose of 50 µg Arformoterol in Healthy Elderly Subjects

Investigator: [redacted] b(4)

Objective: To evaluate the safety and pharmacokinetics of a single inhaled dose of 50 µg arformoterol in healthy elderly subjects and younger adults.

Methodology: This was an open-label, single-dose, single-center, parallel-group study in healthy elderly and younger adult subjects.

No. of Subjects: Planned: 48. Analyzed: 48. Twenty-four healthy elderly males and females, aged ≥65 years and 24 gender-, BMI-, and weight-matched healthy adult males and females, ≥ 18 years and ≤ 45 years were enrolled.

Diagnosis and Main Criteria for Inclusion: Healthy non-smoking males and females (18 to 45 years of age or 65 years old or older) with a BMI between 16 kg/m2 - 40 kg/m2.

Test Product/dosage/rout of administration: 50 µg arformoterol inhalation solution (lot 03501C) by Oral inhalation via nebulization.

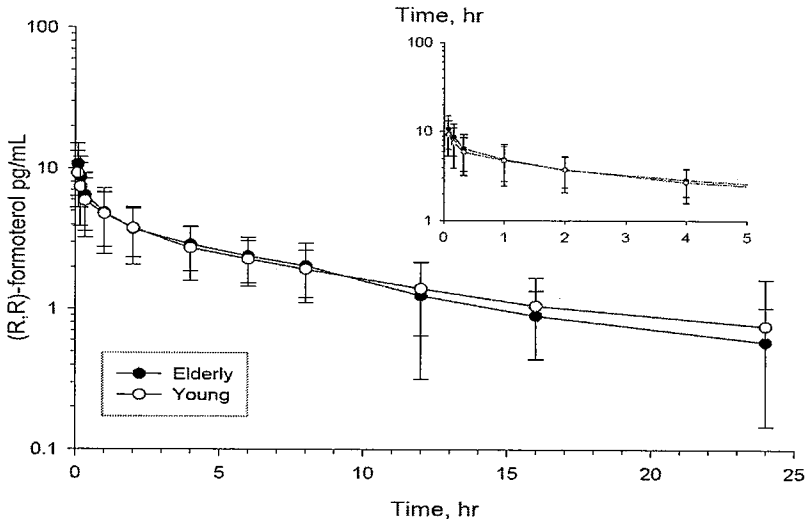
Meal Relationship: All study medication was administered in the morning on Day 1. Study medication was administered after an 8 hour fast prior to scheduled first dose. With the exception of water, subjects continued to fast until 4 hours post dosing. Caffeinated food and beverages were prohibited during the study.

Blood samples: Collected for PK analysis 15 minutes predose, and postdose at 5, 10, and 20 minutes and 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours. Urine samples for PK analysis were collected 15 minutes predose and from 0 to 6 and 6 to 24 hours postdose.

PK Analyses: The PK parameters were calculated using WinNonlin. Statistical analysis of PK parameters was performed using a linear model and descriptive statistics. The primary analyses were conducted using the arformoterol PK parameters $AUC_{(0\text{-last})}$ and Cmax. The effect of age was assessed using a linear model, via SAS. PROC MIXED, with age group as the single fixed effect. The PK parameter data were natural log-transformed before analysis. The least squares means for each age group, estimated group differences, and 90% confidence intervals (CI) for group differences were calculated. These log-transformed results were transformed to the original scale by exponentiation to obtain adjusted means, group ratios, and 90% CIs for these ratios. The elderly group was compared to the younger adult group, with the younger adult group as the reference. Age group differences were tested using a two-sided Wilcoxon Rank-Sum test. Each of the primary PK parameters was summarized by age group and by race (Black, Caucasian, or other) within age group using descriptive statistics.

RESULTS: Mean plasma concentration-time profiles and statistical analysis on key PK parameters are presented in Figure 1 and Table 1, respectively.

Figure 1: Mean Arformoterol Plasma Concentration-Time Profiles Following a Single, Inhaled 50 µg Dose in Elderly and Younger Adults



Note: (R,R)-formoterol = arformoterol. Concentrations at 36, 48, 60, and 72 hrs postdose were BLQ and are not shown. Insets show 0-4 hour postdose data.

Mean plasma concentrations were similar in both the elderly and younger adults groups. Arformoterol was detected at the first postdose sampling time, 5 minutes after the nebulization ended, which was also the time of the maximum concentration for most subjects. Sponsor reported two subjects (036 and 056) in the younger adult group had plasma concentrations that were near, but above LOQ in their predose samples (0.933 and 0.554 pg/mL, respectively). There is no evidence that these samples were obtained postdose rather than predose.

The drug was generally detectable through 24 hours postdose. Plasma concentrations at 24 hours postdose were near the LLOQ (0.5 pg/mL) and were highly variable. Mean concentrations at 36, 48, 60, and 72 hours postdose were BLQ. The mean plasma concentration-time profiles from the two age groups appear similar.

Table 1: Statistical Analysis of Age Effect on Key Plasma Pharmacokinetic Parameters

Parameter	Elderly (N=24)	Younger Adults (N=24)		
	Geometric LS Mean		Ratio	90% CI[a]
C_{max} (pg/mL)	9.69	8.40	1.15	0.914 – 1.46
$AUC_{(0\text{-}last)}$ (pg·hr/mL)	40.8	40.1	1.02	0.743 – 1.393
$AUC_{(0\text{-}\infty)}$ (pg·hr/mL)	63.8	57.9	1.10	0.878 – 1.383
	Median			p-value
t_{max} (hr)	0.080	0.080	--	0.655[b]
	Mean			
$t_{1/2}$ (hr)	14.1	14.4	--	--

[a] Confidence intervals on the ratio elderly:younger adult was obtained by Linear Mixed Effect Modeling

[b] The p-value for t_{max} was determined by a two-sided Wilcoxon Rank-Sum test.

The estimated urine-derived pharmacokinetic parameters are presented in Table 2.

Table 2: Urine PK Parameters by Age Group Following a Single, Arformoterol

Parameter	Ae_{0-24} (ng)	fe (%)	CLr (L/hr)
	Elderly		
n	22	22	14
Mean±SD	322 ± 150	0.644 ± 0.3	7.29 ± 3.22
Median	291	0.581	7.31
Range	85 – 623	0.17 – 1.25	3.63 – 15.8
CV (%)	47	47	44
	Younger Adults		
n	22	22	15
Mean±SD	521 ± 251	1.041 ± 0.502	12.09 ± 5.68
Median	446	0.891	12.08
Range	111 – 1010	0.221 – 2.02	1.75 – 21.09
CV (%)	48	48	47

Approximately 1% of parent drug administrated dose was revered. There were age-related differences in urinary elimination of the parent compound, i.e., in young adults an average of 521 ng was recovered while in elderly adults only 322 ng was recovered. However, no impact upon systemic exposure to arformoterol would be expected because unchanged arformoterol is a minor excretion pathway, with approximately 1% of the administered dose excreted as unchanged arformoterol in urine.

Conclusions:

- There was a modest increase in Cmax (15%) and no meaningful change in $AUC_{(0\text{-last})}$ (2%) or in $AUC_{(0\text{-}8)}$ (10%) in the elderly group as compared to the younger adult group. The CIs for the mean ratios exceeded the equivalence criterion. This was most likely due to the high degree of variability observed within each treatment group (per the sponsor). The modest increase in Cmax is not expected to be clinically meaningful.
- Tmax was not significantly different between age groups as indicated ($p = 0.655$).
- $t_{1/2}$ averaged about 14 hours in both the younger adult and elderly groups.
- Approximately 1% of the dose was recovered in urine, as unchanged drug. In young adults an average of 521 ng was recovered while in elderly adults only 322 ng was recovered. However, any change in renal clearance as a function of age will not likely impact the systemic exposure to arformoterol.

Protocol 091-014

Study Type: Single-dose, PK in subjects with renal insufficiency.

Title: Pharmacokinetics of arformoterol tartrate inhalation solution in subjects with renal insufficiency.

Investigators: Multi-center

Objectives:

Primary Objective: To describe and to compare the PK of a single 50-μg dose of arformoterol in subjects with impaired renal function and age-, gender-, BMI-, and weight-matched normal healthy subjects.

Secondary Objective: To describe and to compare the safety and tolerability of a single 50-μg dose of arformoterol in subjects with impaired renal function and age-, gender-, BMI-, and weight-matched normal healthy subjects.

Methodology: An open-label, single-dose efficacy and safety study conducted at multiple inpatient clinical sites enrolling a total of 40 subjects in three groups of 8 subjects each with renal insufficiency (i.e., mild, moderate, severe) and 1 group of 16 healthy subjects with normal renal function.

Diagnosis and Main Criteria for Inclusion. Male or female subjects between the ages of 18 and 75 (inclusive) were enrolled. Subjects with normal renal function were required to have both normal renal and liver functions tests. Subjects with renal impairment must have documented stable renal disease. Subjects requiring dialysis were allowed but the time interval between dialysis and screening must have been the same as the time interval between dialysis and dosing. Dialysis was not allowed during Days 0-4.

Test Product. Arformoterol tartrate inhalation solution, 50 μg (Lot #03501C) by Nebulization.

Meal Relationship. Subjects fasted overnight (or for at least 8 hours) prior to dosing.

Treatment Visit: The study consisted of two screening visits, Visit 1 (Days -14 to -6), and Visit 2 (Day -5 to -4). Subjects who met the eligibility requirements at Screen Visit 1 were admitted to the clinic for 24 hours on Screen Visit 2 for a 24-hour urine creatinine collection in order to assess the degree of renal insufficiency. Eligible subjects were readmitted to the clinical study unit on Day 0 prior to administration of study medication on Day 1 and remained at the unit for at least 48 hours after treatment. At the discretion of the Investigator, subjects were allowed to leave the clinic after the scheduled study procedures. Subjects returned to the clinic for blood draws for PK during follow-up Visit 4 at 60-hours postdose and follow-up Visit 5 at 72 hours postdose.

Serial blood collection for PK: at predose, and postdose at 5, 10, 20 minutes and 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours. Urine samples were collected at predose, 0 to 6 and 6 to 24 hours postdose (or early termination).

Criteria for Evaluation:

Pharmacokinetics: The primary PK parameters were $AUC_{(0\text{-last})}$ and Cmax. The secondary PK parameters were tmax, $t_{1/2}$, $Ae_{(0\text{-}24)}$, fe, Clr, $AUC_{(0\text{-}12)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}\infty)}$, tlast, and Clast.

Safety: Adverse events, clinical laboratory testing, vital signs, 12-lead ECGs, Holter monitoring, and physical examinations.

PK analysis: The PK parameters were determined by non-compartmental methods using WinNonlin® based on the individual plasma concentration-time data for each renal function group and analyte. The primary analyses were conducted using the arformoterol PK parameters $AUC_{(0\text{-last})}$ and Cmax. The effect of renal impairment was assessed using a one-way analysis of variance (ANOVA) with renal impairment group as the single factor. The PK parameter data were natural log transformed before analysis. From this ANOVA, least squares means for each group, estimated group differences, and 90% confidence intervals for group differences were calculated. These log transformed results were transformed back to the original scale by exponentiation to obtain adjusted means, group ratios, and 90% CIs for these ratios. Each of the three renal impairment groups was compared to the normal healthy subject group, with the normal healthy subject group as the reference.

RESULTS

Mean arformoterol plasma concentration-time profiles following a single, nebulized 50-µg dose of arformoterol are presented in Figure 1. The plasma PK parameters and the statistical analysis are presented in Table 1 and 2, respectively. Comparative plots of individual, mean, and median Cmax, AUC(0-last), and AUC(0-12) across renal function groups are presented in Figures 2-4.

Figure 1: Mean Arformoterol Plasma Concentration-Time Profiles Following a single, Nebulized 50-µg Dose in Normal and Renal Insufficiency Subjects

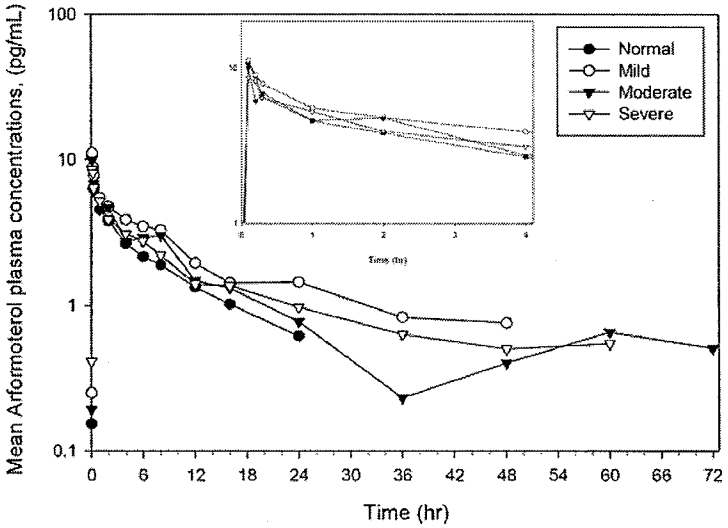


Table 1: Plasma PK parameters Following a Single, Nebulized 50-µg Dose of Arformoterol in Normal and Subjects with Renal Impairment

Parameter	Value	Renal Function Group			
		Normal (N=16)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
C_{max} (pg/mL)	n	15	8	8	8
	Mean (SD)	10.7 (5.3)	11.2 (4.9)	10.2 (9.4)	9.1 (5.3)
$AUC_{(0\text{-last})}$ (pg·hr/mL)	n	15	8	8	8
	Mean (SD)	51.7 (42.3)	84.9 (58.5)	64.8 (65.0)	76.7 (50.7)
$AUC_{(0\text{-}\infty)}$ (pg·hr/mL)	n	12	4	6	5
	Mean (SD)	74.9 (57.4)	117.3 (79.1)	97.9 (107.8)	88.6 (44.1)
$AUC_{(0\text{-}24)}$ (pg·hr/mL)	n	8	6	6	6
	Mean (SD)	59.3 (18.4)	70.3 (32.5)	60.6 (33.2)	59.7 (18.0)
$AUC_{(0\text{-}12)}$ (pg·hr/mL)	n	13	8	8	7
	Mean (SD)	36.6 (11.7)	46.1 (22.1)	39.2 (20.8)	39.6 (13.0)
$AUC_{(0\text{-}6)}$ (pg·hr/mL)	n	14	8	8	8
	Mean (SD)	23.7 (7.5)	28.9 (14.1)	24.2 (14.7)	24.1 (10.0)
C_{last} (pg/mL)	n	15	8	8	8
	Mean (SD)	0.8 (0.2)	1.3 (0.7)	0.9 (0.3)	1.0 (0.4)
t_{max} (hr)	n	15	8	8	8
	Mean (SD)	0.3 (0.3)	0.2 (0.1)	1.5 (2.8)	0.2 (0.0)
t_{last} (hr)	n	15	8	8	8
	Mean (SD)	26.5 (20.6)	32.1 (15.0)	28.1 (18.2)	40.4 (27.6)
$t_{½}$ (hr)	n	15	7	8	6
	Mean (SD)	14.4 (11.5)	18.3 (12.5)	17.4 (11.9)	16.4 (10.6)

Reference: Table 14.2.2.1

Figure 2: Individual, Mean, and Median Cmax parameters for Arformoterol Following nebulization of a Single 50-µg Dose in Normal and Renal Insufficiency Subjects

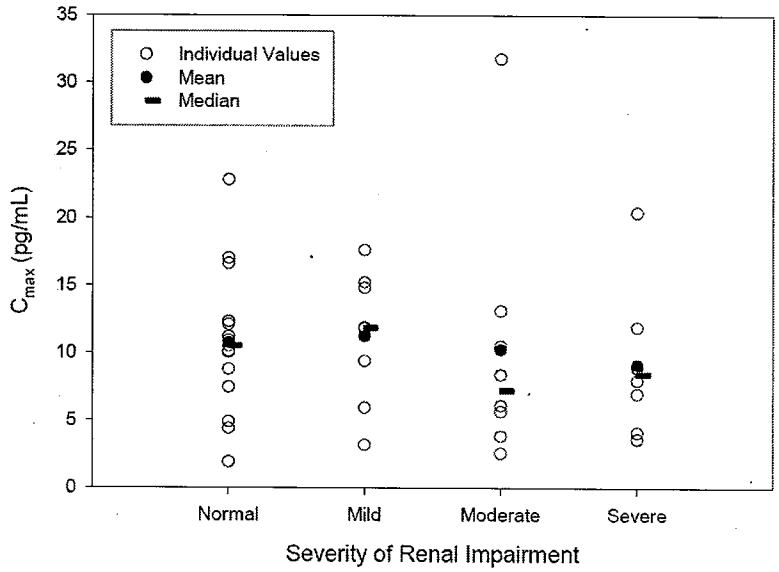


Figure 3: Individual, Mean, and Median AUC parameters for Arformoterol Following nebulization of a Single 50-µg Dose in Normal and Renal Insufficiency Subjects

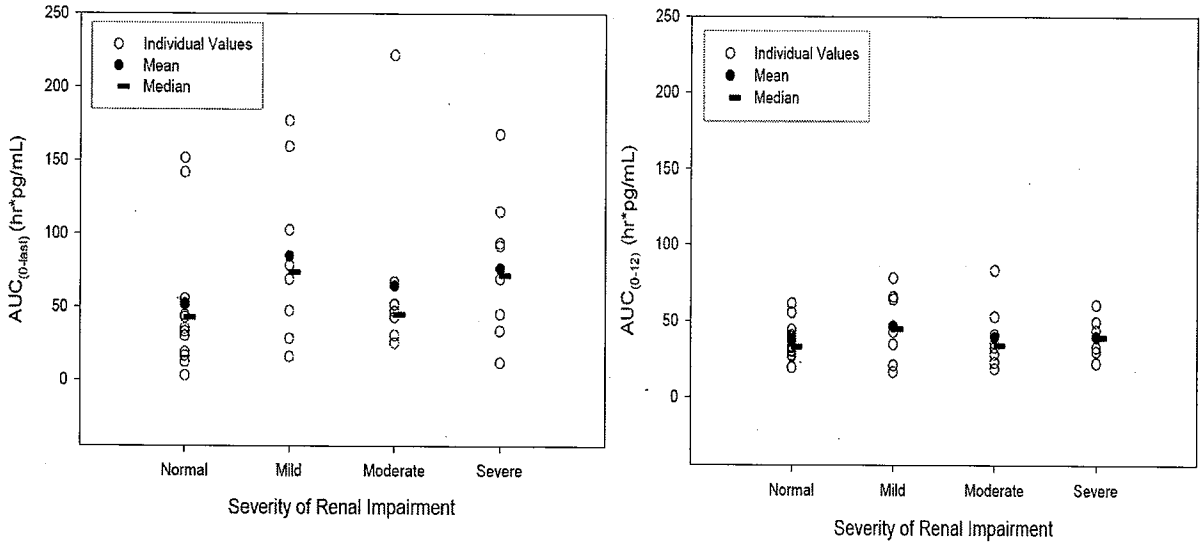


Table 2: Statistical Comparison of Arformoterol Plasma Pharmacokinetic Parameters Between Subjects with Renal Impairment and Normal Subjects Following a Single, Nebulized 50-µg Dose of Arformoterol

Parameter	Renal Function	N	Geometric LS Mean	Ratio[a]	90% CI
$AUC_{(0\text{-}12)}$ (pg*hr/mL)	Normal	13	34.97	1	--
	Mild	8	40.72	1.16	0.84 to 1.61
	Moderate	8	35.26	1.01	0.73 to 1.39
	Severe	7	37.72	1.08	0.77 to 1.51
$AUC_{(0\text{-}24)}$ (pg*hr/mL)	Normal	8	56.92	1	--
	Mild	6	63.64	1.12	0.77 to 1.63
	Moderate	6	54.59	0.96	0.66 to 1.40
	Severe	6	57.26	1.01	0.69 to 1.46
$AUC_{(0\text{-}last)}$ (pg*hr/mL)	Normal	15	37.27	1	--
	Mild	8	65.73	1.76	0.94 to 3.30
	Moderate	8	49.76	1.34	0.71 to 2.50
	Severe	8	59.84	1.61	0.86 to 3.01
C_{max} (pg/mL)	Normal	15	9.30	1	--
	Mild	8	9.98	1.07	0.67 to 1.71
	Moderate	8	7.71	0.83	0.52 to 1.32
	Severe	8	7.95	0.85	0.54 to 1.36
$t_{½}$ (hr)	Normal	15	11.55	1	--
	Mild	7	15.39	1.33	0.81 to 2.18
	Moderate	8	14.48	1.25	0.78 to 2.01
	Severe	6	14.01	1.21	0.72 to 2.04

[a] Ratios were calculated using the normal renal function group as the reference in the denominator.

Overall, the extent of exposure appears to be similar across renal function groups based on AUC(0-12), AUC(0-24), and Cmax, but was possibly higher in the renal dysfunction subjects compared to normal subjects based on AUC(0-last). There was not a clear trend toward increased exposure among the renal dysfunction groups. Although the 90% confidence intervals on the ratios for AUC(0-12), AUC(0-24), and Cmax were not within the 80% to 125% range, the ratios were close to 100%, suggesting no significant differences between groups.

Urine PK Parameters: Mean PK parameters and the correlation of Clr with renal function are presented in Table 3 and 4, respectively.

Table 3: Urine PK Parameters Following a Single, Nebulized 50-µg Arformoterol Dose in Normal Subjects and Subjects with Renal Arformoterol

	Renal Function Group			
	Normal (N=16)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
$Ae_{(0-24)}$ (ng)				
n	15	8	8	8
Mean (SD)	407.0 (224.4)	255.5 (116.6)	129.7 (54.8)	68.5 (42.1)
Median	348.3	251.4	125.2	60.7
Min, Max	43.9, 961.4	117.4, 428.2	55.7, 209.1	17.2, 141.2
CV%	55.1	45.6	42.2	61.5
Cl_r (L/hr)*				
n	14	8	8	8
Mean (SD)	9.2 (3.4)	5.3 (3.0)	2.9 (1.1)	1.4 (0.6)
Median	9.8	4.5	2.7	1.4
Min, Max	3.2, 16.5	1.6, 9.7	1.2, 4.9	0.7, 2.2
CV%	36.7	57.1	39.2	41.6
$Fe_{(0-24)}$ (%)				
n	15	8	8	8
Mean (SD)	0.8 (0.5)	0.5 (0.2)	0.3 (0.1)	0.1 (0.1)
Median	0.7	0.5	0.3	0.1
Min, Max	0.1, 1.9	0.2, 0.9	0.1, 0.4	0.0, 0.3
CV%	55.1	45.6	42.2	61.5

Cl_r was based on 6-hour outcome since most of the subject data were available for analysis at this timepoint.

Table 4: Statistical Comparison of Arformoterol Urine PK Parameters between Subjects with Renal Impairment and Normal

Parameter	Group	N	Geometric LS Mean	Comparison	Ratio*	90% CI
Cl_r (L/hr)	Mild	8	4.51	Mild/Normal	0.53	0.37, 0.76
	Moderate	8	2.70	Moderate/Normal	0.32	0.22, 0.46
	Severe	8	1.28	Severe/Normal	0.15	0.10, 0.22
	Normal	16	8.52			
fe (%)	Mild	8	0.46	Mild/Normal	0.68	0.43, 1.07
	Moderate	8	0.24	Moderate/Normal	0.35	0.22, 0.55
	Severe	8	0.11	Severe/Normal	0.17	0.11, 0.26
	Normal	15	0.68			

*Ratios were calculated using the normal renal function group as reference in denominator.

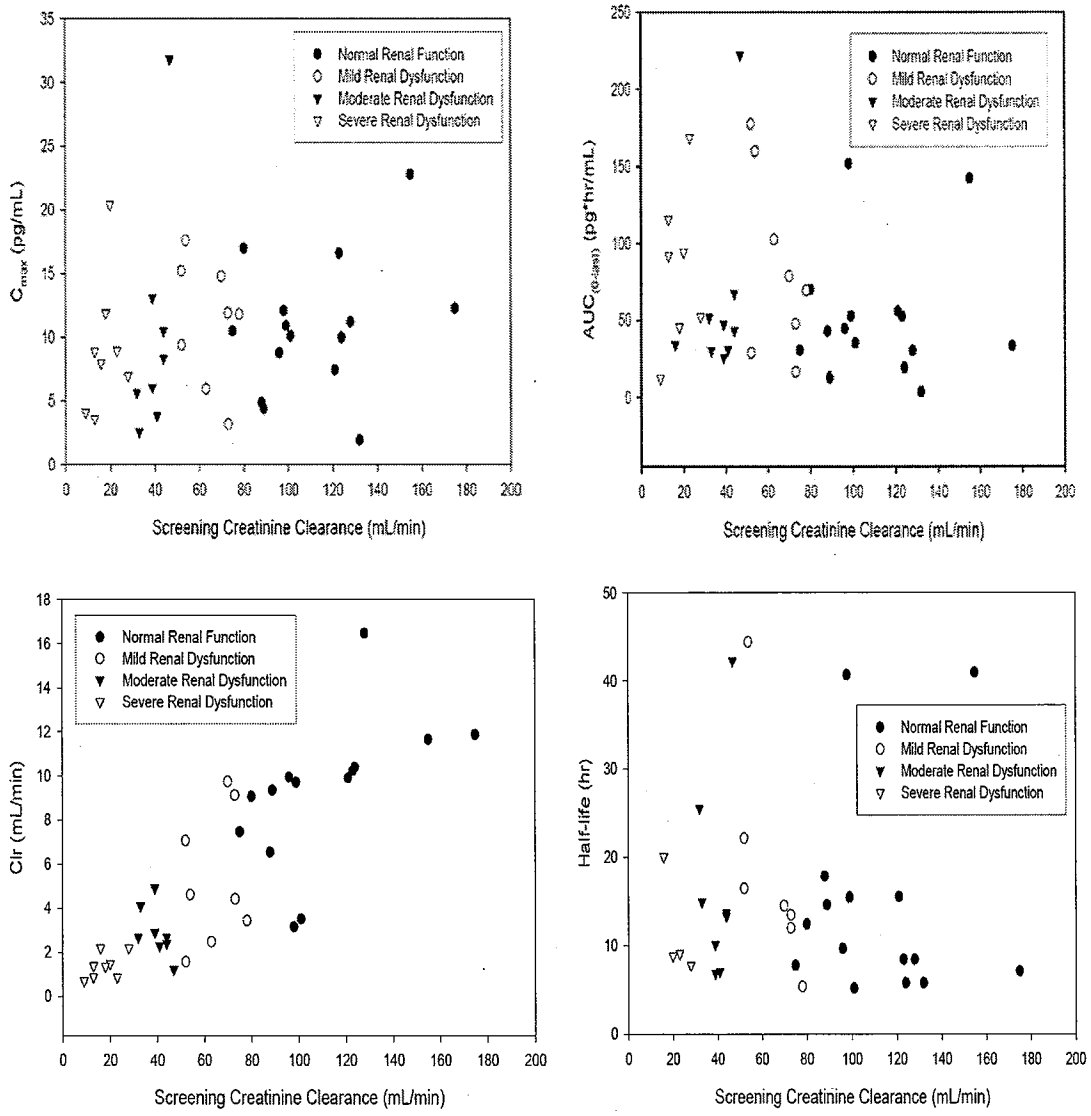
Relatively small amounts of arformoterol were recovered in the urine (less than 1% of the administered dose). There were renal function-related differences in urinary elimination of the parent compound (e.g., 407 and 68.5 ng was recovered in normal and severe renal impairment, respectively) (Table 3).

Although renal clearance decreased with an increase in renal dysfunction, it should be noted that less than 1% of the dose was eliminated unchanged in the urine in subjects with normal renal function.

3 Correlation between Primary PK Parameters and Creatinine Clearance

Plots of exposure parameters versus creatinine clearance are illustrated in Figure 4. There was no apparent relationship between creatinine clearance and exposure.

Figure 4: Individual Subject Arformoterol Cmax versus Creatinine Clearance Following Nebulization of a Single 50-µg Dose in Normal and Renal Insufficiency Subjects



There was a definitive correlation as shown by a decrease in renal clearance (CLr) of arformoterol as the severity of renal impairment increased. However, since less than 1% of the dose is eliminated unchanged in the urine, this effect may not have a major impact on exposure.

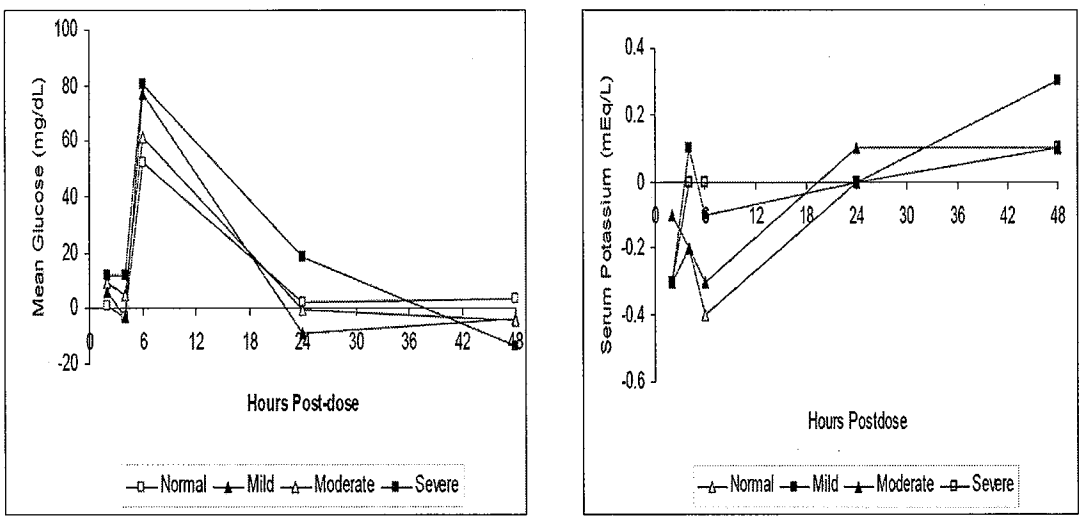
Laboratory Values Over Time: Serum potassium and glucose were collected predose and at 2, 4, and 6, 24 and 48 hrs post-dose; hypokalemia and hyperglycemia have been associated with the use of beta agonists.

Glucose.
The sponsor reported subjects with preexisting diabetes i.e., 5 (62%) with mild renal dysfunction, 4 (50%) with moderate renal dysfunction, and 1 (13%) with severe renal dysfunction, and suggested that this may have had an effect on overall serum glucose values. The mean predose serum glucose values prior to dosing on Day 1 were 93.1 mg/dL, 123.3 mg/dL, 110.4 mg/dL, and 109.8 mg/dL for subjects with normal, mild, moderate, and severe renal function, respectively. Changes in serum glucose during the first 4 hours postdose were minimal for all renal function groups. Per the sponsor, the sharp rise in serum glucose at the 6-hour postdose time point was likely a post-prandial effect, for subjects were provided with a meal after the 4-hour time point on Day 1. On Days 2 and 3 (24 and 48 hours postdose), breakfast was served after blood samples were collected. Serum glucose was slightly higher for subjects with severe renal impairment at 24 hours postdose (mean increase from baseline of 18.6 mg/dL), but dropped below predose values by the 48-hour postdose time point.

Potassium. The mean predose serum potassium value prior to dosing on Day 1 was 4.2 mEq/L for subjects with normal renal function, 4.4 mEq/L for subjects with both mild and moderate renal impairment, and 4.6 mEq/L for subjects with severe renal impairment. The mean decrease in serum potassium was minimal for all renal function groups. The largest mean decreases were observed at the 6-hour postdose time point for subjects with normal renal function (0.4 mEq/L) and moderate renal impairment (0.3 mEq/L).

The mean change in serum glucose and potassium at 2, 4, 6, 24, and 48 hours postdose for each renal function group is displayed in Figure 5.

Figure 5: Mean Change in Serum Glucose (mg/dL) (left panel) and potassium (right panel) by Renal Function Group Following a Single, Nebulized 50-µg Dose of Arformoterol



Conclusions:

The data did not demonstrate a direct relationship between the degree of renal impairment and increased exposure. The 90% CIs were not within the target range of 0.80-1.25 for the primary endpoints, Cmax and $AUC_{(0\text{-last})}$. The large variations in $AUC_{(0\text{-last})}$ were most likely due to the large variations in individual values for t_{last}. The extent of exposure appeared to be similar across renal function group based on truncated AUC values, $AUC_{(0\text{-}12)}$ and $AUC_{(0\text{-}24)}$. There was correlation in the urinary elimination of arformoterol with increasing renal impairment; however, the differences in urinary excretion and renal clearance of unchanged drug are not likely to be of clinically significance since less than 1% of the dose is eliminated in normal subjects by this minor excretion pathway.

The sponsor reported that a single 50-µg dose of arformoterol was well tolerated by subjects with renal impairment, and concluded that no dosing adjustments are necessary for patients with renal impairment based on the pharmacokinetic and safety results of this study.

Comment: Sponsor's conclusions are acceptable.

Protocol 091-015

Study Type: Single-dose, PK in subjects with hepatic impairment.

Title: Pharmacokinetics of Arformoterol Tartrate Inhalation Solution in Subjects with Hepatic Dysfunction.

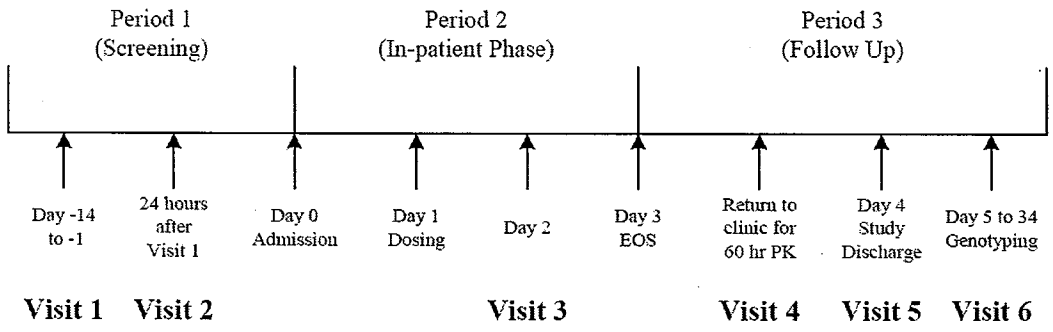
Investigators: Multi-centers

Objectives:

Primary: To describe and compare the PK of a single 50-μg dose of arformoterol in subjects with impaired hepatic function and age-, gender-, Body Mass Index (BMI)-, and weight-matched normal healthy subjects (i.e., subjects with normal hepatic function).

Secondary: To describe and compare the safety and tolerability of a single 50-μg dose of arformoterol in subjects with impaired hepatic function and age-, gender-, BMI-, and weight-matched normal healthy subjects.

Methodology: This was an open-label, single-dose study conducted enrolling three groups of hepatic-impaired subjects and one group of healthy normal subjects (18 to 75 years of age, inclusive). Arformoterol 50 μg was administered by nebulization (Lot #03501C) to 8 subjects with mild hepatic impairment (Group 1), 8 subjects with moderate-to-severe hepatic impairment (Group 2), 8 subjects with severe hepatic impairment (Group 3), and 16 subjects with normal hepatic function (Group 4). The 16 subjects with normal hepatic function were comparable to the 24 subjects with hepatic impairment in age, gender, BMI, and weight. The subject's degree of hepatic impairment was assessed based on the Child- Pugh classification system. The study schematic is shown below:



Sample collection: blood samples for PK were collected at predose, and at 5, 10, and 20 minutes, and at 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post dose. Urine was collected at pre-dose and at 0-6 hours and 6-24 hours postdose or at early termination. A blood samples for genotyping of CYP2D6 from the subjects who provided consent were collected.

Criteria for Evaluation PK: The primary PK parameters determined for arformoterol were $AUC_{(0\text{-}last)}$ and Cmax. The secondary PK parameters were tmax, $t_{1/2}$, $Ae_{(0\text{-}24)}$, fe, Clr, $AUC_{(0\text{-}12)}$, $AUC_{(0\text{-}8)}$, t_{last}, and C_{last}.

Safety: Adverse events, clinical laboratory testing, vital signs, 12-lead ECGs, 24-hour Holter monitoring, and physical examinations.

Pharmacokinetics Analysis: The PK parameters were calculated using WinNonlin 4.0 and SAS 8.2. The primary analysis was conducted using the arformoterol PK parameters $AUC_{(0\text{-last})}$ and Cmax. The effect of hepatic impairment was assessed using a linear model, via SAS. PROC MIXED, with hepatic function as the single fixed effect. The PK parameter data were natural log (ln)-transformed before analysis. The least squares means for each hepatic function group, estimated group differences, and 90% CIs for group differences were calculated. These log-transformed results were transformed back to the original scale by exponentiation to obtain adjusted means, group ratios, and 90% CIs for these ratios. Various hepatic-impaired groups were compared to the normal hepatic function group, with the normal hepatic function group as the reference. If the 90% CI for comparing the hepatic impaired groups to the normal hepatic function fell inside 80% - 125% for $AUC_{(0\text{-last})}$ and Cmax, the interpretation would be that hepatic function does not have a potential effect upon the PK of arformoterol. The same methods were used for the truncated AUCs. The secondary PK parameter of tmax was analyzed using a two-sided Wilcoxon Rank-Sum test.

3.1.1.1.1.1 RESULTS

Arformoterol PK plasma parameters: The plasma-derived PK parameters and the statistical analyses are presented for each hepatic function group in Tables 1 and 2, respectively. Mean arformoterol plasma concentration-time Profiles are shown in Figure 1. The mean, median, and distribution of Cmax, $t_{1//2}$ and AUC values across various hepatic function groups are displayed in Figure 2.

Figure 1: Mean Arformoterol Plasma Concentration-Time Profiles Following a Single 50-µg Dose in Normal Subjects and Subjects with Hepatic Impairment

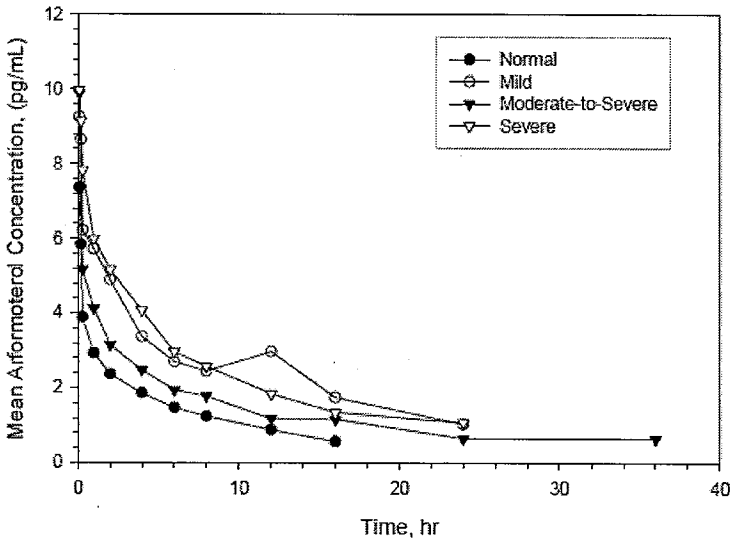


Table 1: Plasma PK Parameters Following a Single, Inhaled 50-µg Dose of Arformoterol in Normal Subjects and Subjects with Hepatic Impairment

	Hepatic Function Group			
	Normal (N=16)	**Mild (N=8)**	**Moderate-to-Severe (N=8)**	**Severe (N=8)**
		$AUC_{(0\text{-}last)}$ *(pg*hr/mL)*		
n	15	8	7	8
Mean (SD)	28.8 (14.2)	67.6 (37.4)	56.4 (36.7)	70.8 (38.1)
CV%	49.2	55.4	65.1	53.8
Median	31.1	69.2	36.9	77.7
Min, Max	7.4, 53.5	22.8, 130.2	31.3, 127.7	5.9, 111.6
		C_{max} *(pg/mL)*		
n	15	8	7	8
Mean (SD)	7.8 (4.3)	10.0 (4.8)	11.3 (7.9)	10.4 (5.6)
CV%	54.9	48.2	70.4	53.5
Median	7.6	10.8	10.1	12.8
Min, Max	0.9, 15.7	3.5, 18.9	4.5, 27.2	1.0, 16.7
		t_{max} *(hr)*		
n	15	8	7	8
Median	0.2	0.2	0.2	0.2
Min, Max	0.2, 8.1	0.2, 12.2	0.2, 0.2	0.2, 2.1
		$AUC_{(0\text{-}4)}$ *(pg*hr/mL)*		
n	15	8	7	8
Mean (SD)	15.2 (5.6)	26.8 (10.1)	22.1 (15.1)	29.6 (16.5)
CV%	36.8	37.7	68.4	55.7
Median	16.7	27.8	15.5	28.4
Min, Max	3.6, 22.7	11.0, 42.7	10.8, 54.0	4.5, 54.5
		$AUC_{(0\text{-}12)}$ *(pg*hr/mL)*		
n	13	8	6	7
Mean (SD)	24.5 (7.3)	42.8 (16.1)	35.6 (24.7)	49.2 (19.6)
CV%	29.6	37.6	69.6	39.7
Median	25.2	45.6	27.5	45.7
Min, Max	8.0, 34.6	19.0, 64.3	16.0, 82.2	23.8, 80.7
		$AUC_{(0\text{-}24)}$ *(pg*hr/mL)*		
n	6	5	6	6
Mean (SD)	38.7 (4.7)	81.8 (28.8)	48.9 (33.5)	73.9 (18.9)
CV%	12.1	35.2	68.4	25.6
Median	37.5	66.9	35.3	66.8
Min, Max	33.9, 45.2	59.4, 130.2	22.8, 111.0	52.6, 103.6
		$AUC_{(0\text{-}\infty)}$ *(pg*hr/mL)*		
n	6	6	3	6
Mean (SD)	47.1 (11.2)	77.7 (32.3)	102.1 (50.3)	97.5 (36.0)
CV%	23.8	41.6	49.2	37.0
Median	45.2	82.7	108.8	109.0
Min, Max	33.1, 64.0	36.6, 112.4	48.9, 148.8	35.5, 130.7
		C_{last} *(pg/mL)*		
n	15	8	7	8
Mean (SD)	0.8 (0.2)	1.1 (0.9)	0.9 (0.2)	0.8 (0.4)
CV%	30.0	82.2	28.3	49.4
Median	0.7	0.7	0.9	0.7
Min, Max	0.5, 1.2	0.6, 3.2	0.5, 1.2	0.5, 1.5
		t_{last} *(hr)*		
n	15	8	7	8
Mean (SD)	18.9 (9.0)	25.7 (9.3)	33.2 (10.3)	33.1 (18.0)
CV%	47.8	36.3	30.9	54.2
Median	16.2	24.2	36.1	30.2
Min, Max	6.1, 36.1	16.1, 36.2	16.1, 48.1	8.1, 60.1
		$t_{1/2}$ *(hr)*		
n	8	6	4	7
Mean (SD)	11.2 (3.8)	11.2 (4.5)	16.5 (7.7)	16.4 (6.0)
CV%	34.4	40.0	46.6	36.5
Median	10.4	10.7	16.4	16.9
Min, Max	7.7, 18.8	5.7, 18.4	8.0, 25.2	7.8, 22.9

Reference: Table 14.2.2.1.

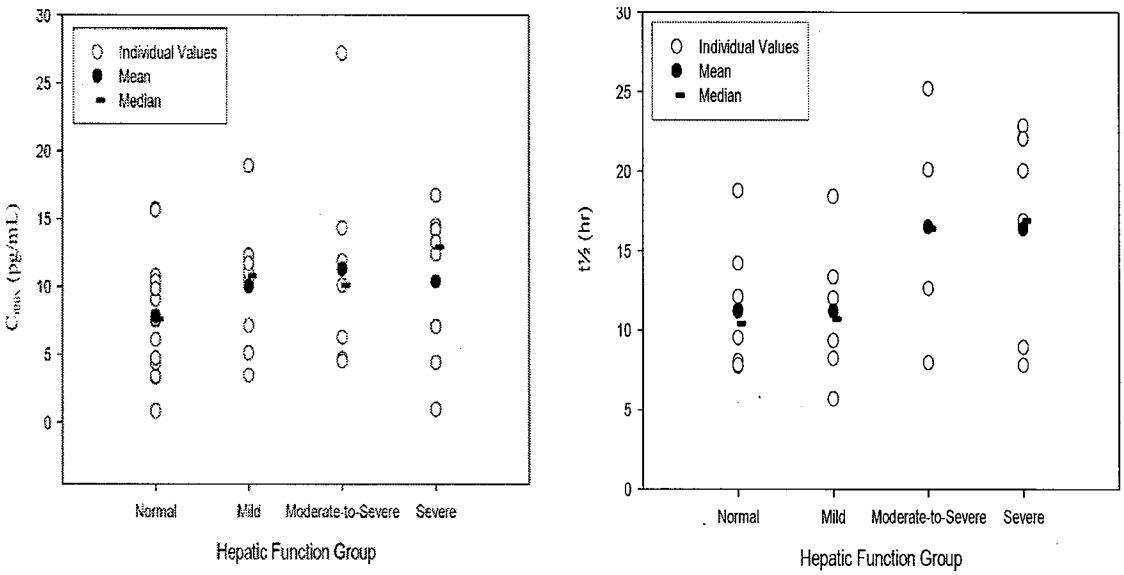
Table 2: Statistical Treatment Comparison of Plasma PK Parameters between Subjects with Normal Hepatic Function and Subjects with Hepatic Impairment after a Single Inhaled 50-μg Dose of Arformoterol

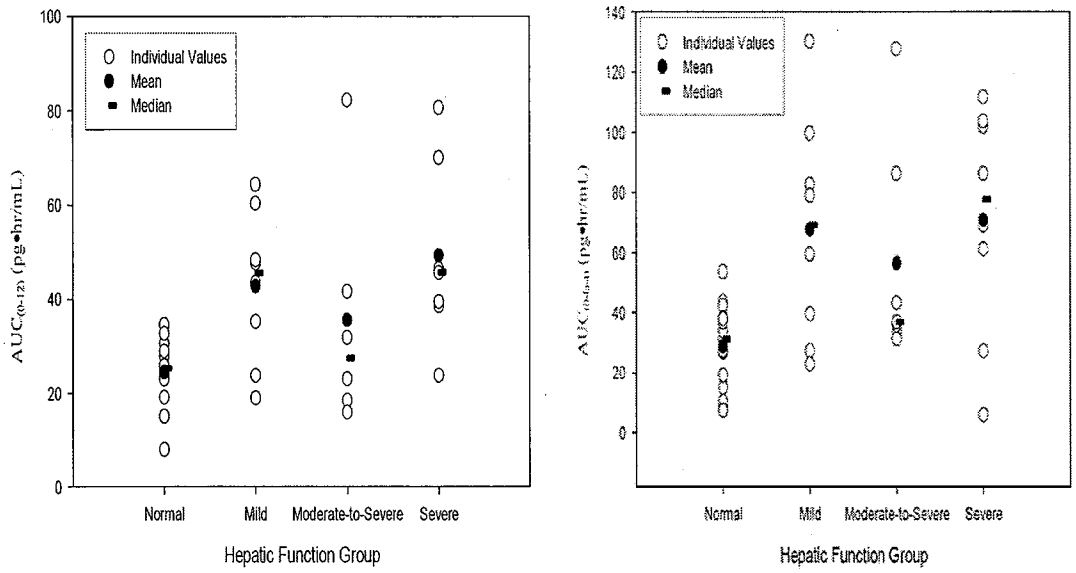
Parameter	Hepatic Impairment	N	Geometric LS Mean	Ratio[a]	90% CI
$AUC_{(0\text{-}last)}$ (pg*hr/mL)	Normal	15	24.6	1	--
	Mild	8	57.7	2.35	1.39 to 3.98
	Moderate-to-Severe	7	48.9	1.99	1.15 to 3.45
	Severe	8	53.7	2.19	1.29 to 3.70
C_{max} (pg/mL)	Normal	15	6.42	1	--
	Mild	8	8.92	1.39	0.80 to 2.41
	Moderate-to-Severe	7	9.35	1.46	0.82 to 2.59
	Severe	8	8.03	1.25	0.72 to 2.17
$t_{½}$ (hr)	Normal	8	10.7	1	--
	Mild	6	10.4	0.98	0.67 to 1.42
	Moderate-to-Severe	4	15.0	1.41	0.92 to 2.16
	Severe	7	15.3	1.43	1.00 to 2.06
t_{max}[b] (hr)	Normal	15	0.22[b]	--	--
	Mild	8	0.25[b]	--	--
	Moderate-to-Severe	7	0.17[b]	--	--
	Severe	8	0.23[b]	--	--

[a] Ratios were calculated using the normal hepatic function group as the reference in the denominator.

[b] Values for t_{max} shown are median values, p values for comparisons to normal were >0.05.

Figure 2: Individual, Mean, and Median Cmax and $t_{1/2}$ for Arformoterol Following Nebulization of a Single 50-μg Dose in Normal Subjects and Subjects with Hepatic Impairment





All hepatically impaired groups showed increased values of both AUC and Cmax, by approximately 2 times those of normal subjects. The 90% confidence intervals for these values fell outside the target range of 0.80-1.25, indicating an impact of decreased hepatic function on arformoterol pharmacokinetics. However, no clear relationship between exposure and severity of hepatic impairment was observed. The mean t½ in normal subjects and those with mild hepatic impairment was approximately 11 hours, while in subjects with moderate-to-severe and severe hepatic impairment, the t½ was slightly longer at 15 hours. Median tmax in each hepatic function group was not significantly different from normal subjects indicating hepatic dysfunction had no effect on absorption.

Arformoterol Urine Data: The urine-derived PK parameters and the Statistical analysis for the urine PK parameters are presented in Table 3 and 4, respectively.

Approximately 1% of the administered dose of arformoterol was eliminated in the urine. There were no changes in urinary elimination (as assessed by $Ae_{(0-24)}$ and $fe_{(0-24)}$) of the parent compound due to hepatic impairment. The mean CLr was 15.0 L/hr in subjects with normal hepatic function, and declined in the hepatic impairment groups.

The statistical analysis results for the urine PK parameters are shown in Table 4. Although the 90% confidence interval for CLr fell outside the 0.8 to 1.25 range, the observed differences in CLr are not clinically significant since only 1% of the dose is excreted unchanged in the urine, indicating that the urinary elimination of unchanged arformoterol is a minor excretion pathway.

Table 3: Urine PK Parameters Following a Single, Inhaled 50-µg Dose of Arformoterol in Normal Subjects and Subjects with Hepatic Impairment

	Hepatic Function Group			
	Normal (N=16)	Mild (N=8)	Moderate-to-Severe (N=8)	Severe (N=8)
		$Ae_{(0-6)}$ (ng)		
n	16	8	8	8
Mean (SD)	228.0 (123.7)	236.2 (114.6)	190.1 (123.7)	186.4 (129.9)
Median	251.3	217.4	160.3	156.9
Min, Max	7.4, 507.5	83.7, 457.2	4.3, 375.0	32.1, 414.0
		$Ae_{(0-24)}$ (ng)		
n	16	8	8	8
Mean (SD)	395.8 (200.3)	564.5 (284.9)	381.8 (119.8)	439.2 (260.5)
Median	439.5	523.5	358.5	453.9
Min, Max	16.1, 816.9	297.9, 1226.0	205.7, 632.6	67.3, 807.7
		Cl_r (L/hr)*		
n	15	8	7	8
Mean (SD)	15.0 (5.1)	10.1 (5.9)	11.0 (3.9)	6.8 (4.2)
Median	14.9	9.5	11.0	5.5
Min, Max	2.0, 24.0	3.0, 19.8	6.3, 16.5	2.2, 14.1
		$fe_{(0-6)}$(%)		
n	16	8	8	8
Mean (SD)	0.5 (0.2)	0.5 (0.2)	0.4 (0.2)	0.4 (0.3)
Median	0.5	0.4	0.3	0.3
Min, Max	0.0, 1.0	0.2, 0.9	0.0, 0.8	0.1, 0.8
		$fe_{(0-24)}$(%)		
n	16	8	8	8
Mean (SD)	0.8 (0.4)	1.1 (0.6)	0.8 (0.2)	0.9 (0.5)
Median	0.9	1.0	0.7	0.9
Min, Max	0.0, 1.6	0.6, 2.5	0.4, 1.3	0.1, 1.6

*Cl_r was based on the 0-6 hr outcome since most of the subject data were available for analysis at this time point.

Table 4: Statistical analysis for the urine PK parameters

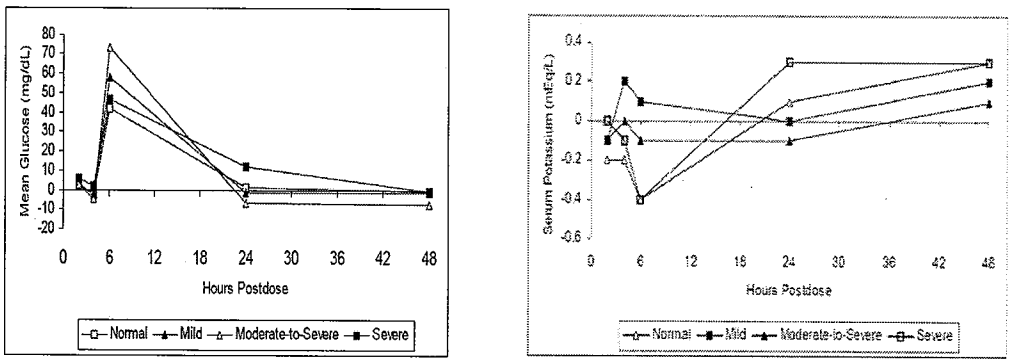
	Geometric Least Squares Means						
Order	Normal [A]	Mild [B]	Moderate-to-Severe [C]	Severe [D]	Comparison	Ratio	90% CI
AUC(0-last) (pg*hr/mL)	24.57	57.74	48.85	53.73	B/A	2.35	(1.39, 3.98)
					C/A	1.99	(1.15, 3.45)
					D/A	2.19	(1.29, 3.7)
Cmax (pg/mL)	6.42	8.92	9.35	8.03	B/A	1.39	(0.8, 2.41)
					C/A	1.46	(0.82, 2.59)
					D/A	1.25	(0.72, 2.17)
AUC(0-12) (pg*hr/mL)	23.16	39.74	30.11	46	B/A	1.72	(1.22, 2.41)
					C/A	1.30	(0.9, 1.89)
					D/A	1.99	(1.39, 2.83)
AUC(0-24) (pg*hr/mL)	38.51	78.42	41.64	71.97	B/A	2.04	(1.39, 2.98)
					C/A	1.08	(0.75, 1.56)
					D/A	1.87	(1.3, 2.69)
AUC(0-infinity) (pg*hr/mL)	46.03	71.35	92.46	89.69	B/A	1.55	(1, 2.41)
					C/A	2.01	(1.17, 3.44)
					D/A	1.95	(1.25, 3.03)
fe (%)	0.6	1.04	0.73	0.66	B/A	1.72	(0.96, 3.11)
					C/A	1.22	(0.68, 2.2)

Note: The normal Hepatic function group was used as the reference group

Glucose and Potassium levels in the Plasma:

Glucose: The mean predose serum glucose values prior to dosing on Day 1 were 92.3 mg/dL, 92.8 mg/dL, 122.4 mg/dL, and 98.8 mg/dL for subjects with normal, mild, moderate-tosevere, and severe hepatic function, respectively. The mean change in serum glucose at 2, 4, 6, 24, and 48 hours postdose for each hepatic function group is displayed in Figure 3.

Figure 3: Mean Change in Serum Glucose (mg/dL) (left panel) and potassium (right panel) by Hepatic Function Group Following a Single 50-µg Dose of Arformoterol



Changes in serum glucose during the first 4 hours postdose were minimal for all hepatic function groups. The sharp rise in serum glucose at the 6-hour postdose time point was likely a postprandial effect, for subjects were provided with a meal after the 4-hour time point on Day 1. On Days 2 and 3 (24 and 48 hours postdose), breakfast was served after blood samples were collected. Serum glucose was slightly higher for subjects with severe hepatic disease at 24 hours postdose (mean increase from baseline of 11.8 mg/dL), but had returned to near predose values by the 48-hour postdose time point.

Potassium: The mean predose serum potassium value prior to dosing on Day 1 was 4.2 mEq/L for subjects with normal hepatic function and subjects with both mild and moderate-to-severe hepatic dysfunction, and was 3.8 mEq/L for subjects with severe hepatic dysfunction. The mean change in serum potassium at 2, 4, 6, 24, and 48 hours postdose for each hepatic function group is displayed in Figure 3 (right panel). The mean decrease in serum potassium was minimal for subjects with both mild and moderate-to-severe hepatic dysfunction. Similar changes were observed in subjects with normal hepatic function and subjects with severe hepatic dysfunction, with a mean maximum decrease of 0.4 mEq/L for both groups occurring at the 6-hour postdose time point.

Genotyping of CYP2D6: Genotyping was performed for 26 of these subjects; the genotyping result could not be determined for one subject (Subject 0179-S018). Results are summarized in Table 5.

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Table 5: Genotyping of CYP2D6

		Hepatic Function			
		Normal (N=16)	Mild (N=8)	Moderate-to-Severe (N=8)	Severe (N=8)
		n (%)	n (%)	n (%)	n (%)
Genotyping of CYP2D6	Poor	1 (7.7)	1 (33.3)	0 (0.0)	0 (0.0)
	Intermediate	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
	Extensive	11 (84.6)	1 (33.3)	5 (83.3)	3 (75.0)
	Ultra-rapid	1 (7.7)	1 (33.3)	0	1 (25.0)
	Unable to obtain*	1	0	0	0
	Not done**	2	5	2	4

*The genotyping result could not be determined.

**Subject did not return for genotyping.

Conclusions

There was an increase in exposure to arformoterol observed in subjects with mild, moderate-to-severe, or severe hepatic impairment when compared with subjects with normal hepatic function, as well as a longer half-life in subjects with moderate-to-severe and severe hepatic impairment. Although exposures were higher in the hepatically impaired treatment groups, there were no significant differences in safety profiles; however, can't be concluded definitely since too few subjects participated in the study. Given the higher exposure however, arformoterol should be used cautiously in subjects with hepatic impairment and at the lowest possible dose.

Comment: Racemic formoterol (Foradil Aerolizer) have been on the market long time, and never been studied in patients with hepatic impairment. Given the higher exposure, 'arformoterol should be used cautiously in subjects with hepatic impairment' suggested by the sponsor is reasonable.

Protocol 091-016

Study Type: Single-dose, PK in mild to moderate asthmatics.

Title: An Open-Label, Single-Dose, Randomized, Five-Way Cross-Over Study of Arformoterol* Tartrate and Racemic Formoterol Fumarate in Mild to Moderate Asthmatics

Investigators: Multi-centers

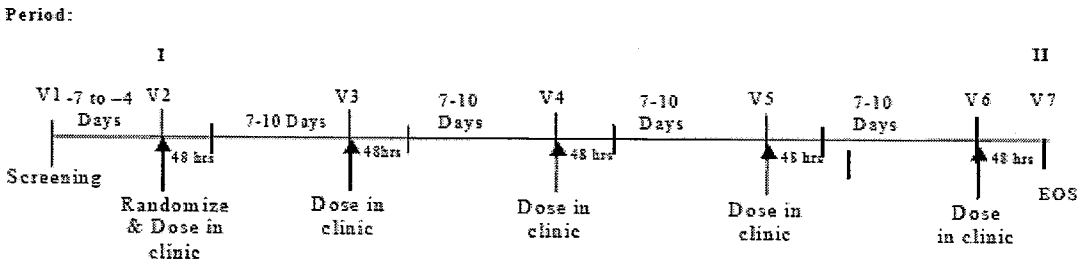
Objectives:

Primary Objective: To investigate the pharmacokinetics of (R,R)-formoterol when administered as part of a racemic mixture as compared to administration as a single isomer.

Secondary Objectives:

- To assess the potential of (R,R)-formoterol for epimerization (i.e., rearrangement of the molecule at its chiral centers).
- To determine the extent of pulmonary absorption versus gastrointestinal absorption of arformoterol administered by nebulization.
- To assess the PK/PD relationships between measures of (R,R)-formoterol systemic exposure and responses (safety, efficacy parameters).

Methodology: This was an open-label, randomized, single-dose, five-way cross-over study in mild to moderate asthmatic subjects. Twenty-three subjects were randomized, and 23 subjects completed the study. A subject's study participation involved seven clinic visits. The study schematic is shown below:



Diagnosis and Main Criteria for Inclusion: Male or female and between the ages of 18 and 60. Subjects were in general good health, with >1-year history consistent with mild to moderate asthma (baseline FEV_1 >60% and <80% of predicted volume) and demonstrated >12% reversibility after administration of two puffs of albuterol MDI.

Treatments Administered. The five treatments utilized for this study and the amounts of arformoterol free base are presented in Table 1.

Table 1. Amounts of free base (R,R)-Formoterol by Treatment

Treatment	Treatment Description	µg Free Base (R,R)-formoterol	Formulation
A	Racemic formoterol fumarate (Foradil® Aerolizer™), 12 µg	4.91	DPI
B	Arformoterol tartrate inhalation solution, 15 µg	15	Nebulization
C	Arformoterol tartrate inhalation solution, 50 µg	50	Nebulization
D	Racemic formoterol fumarate inhalation solution, 100 µg	50	Nebulization
E	Arformoterol tartrate inhalation solution, 50 µg with charcoal pre- and post-treatment	50	Nebulization

All subjects who successfully completed Visit 1 (screening) were randomized at Visit 2 to an open-label cross-over sequence. Arformoterol and racemic formoterol 100 µg were administered by nebulization with the PARI LC PLUS™ nebulizer and Dura-Neb® 3000 compressor. Racemic formoterol 12 µg was administered by Aerolizer™ Inhaler (DPI). All treatments were administered once in the morning during each treatment day according to the randomized sequence.

Sampling times: Collected for (R,R)-formoterol and (S,S)-formoterol concentrations from:
Plasma: Collected at predose, 5, 10, and 20 minutes, 1, 3, 6, 12, 24, 36, 48, and 72 hours post-dose.
Urine: at pre-dose and during the intervals 0-2, 2-4, 4-6, 6-8, 8-12, 12-16, 16-24, 24-48 and 48-72 hours post-dose.

Statistical analysis: Analysis for PK parameters used a linear model and descriptive statistics. Safety measures were summarized using descriptive statistics.

Pharmacokinetic Analysis:

- PK parameters were estimated using WinNonlin® Professional based on the individual plasma concentrations and urine excretion-time data collected after single oral dose administration.
- Statistical analysis of PK parameters used a linear model and descriptive statistics. Plasma $AUC_{(0-6)}$ and Cmax were natural-log transformed and analyzed using a linear model with sequence, treatment group, and period as fixed effects, and subject nested within sequence as a random effect. The least squares (LS) means for each treatment group, differences between the pairs listed below, and the 90% confidence intervals of the differences, were calculated. The results were transformed to the original scale by exponentiation to obtain geometric means, the ratios, and the 90% CIs of the ratios.

The pairs were: arformoterol 50 µg and racemic formoterol 100 µg, arformoterol 15 µg and racemic formoterol 12 µg, arformoterol 50 µg and racemic formoterol 12 µg, arformoterol 50 µg and arformoterol 50 µg with charcoal pre- and post-treatment.

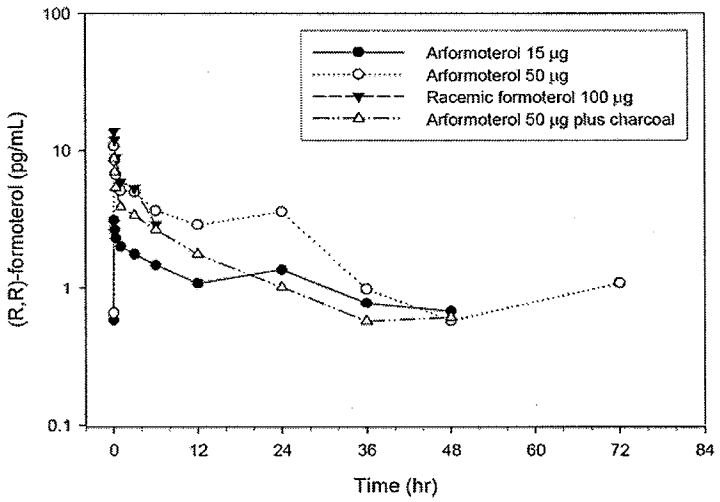
Pharmacodynamic Analysis: PD parameters were analyzed descriptively. The relationship between plasma (R,R)-formoterol concentrations and selected safety and/or efficacy parameters were provided graphically.

RESULTS

Plasma Pharmacokinetics:

(R,R)-Formoterol Plasma Concentration-Time Data: Approximately 21% of predose samples contained concentrations of (R,R)-formoterol that were greater than the LOQ. Mean plasma (R,R)-formoterol concentrations following treatment with racemic formoterol 12 µg did not exceed the limit of quantification throughout the entire sampling interval. Mean plasma concentration-time profiles are presented in Figure 1.

Figure 1: Mean (R,R)-Formoterol Plasma Concentration-Time Profiles following Arformoterol and Racemic Formoterol in Mild to Moderate Asthmatics



The mean plasma PK parameters are presented in Table 2. There were limited PK data available for the racemic formoterol 12 µg treatment (only two of 23 subjects had evaluable data). Thus, statistical analyses were not performed with this treatment group. There was also a wide variation in t_{last} (time to last observed plasma concentration) seen for all administered treatments, which resulted in large variations in $AUC_{(0\text{-}last)}$. The sponsor suspects that this may have been due to difference in the LLQ between the two assay methodologies. The chiral bioanalytical assay used for the racemic treatment samples had an LLQ (lower limit of quantification) of 2.0 pg/mL, while the achiral method for the single enantiomer had an LLQ of 0.5 pg/mL. Therefore, a truncated AUC parameter, $AUC_{(0\text{-}6)}$, was calculated in order to compare exposures across different treatments and minimize variability due to t_{last}. The results of the statistical analysis for plasma (R,R)-formoterol PK parameters are presented in Table 3.

Table 2: Mean (SD) Plasma (R,R)-Formoterol Pharmacokinetic Parameters following Arformoterol or Racemic Formoterol in Mild to Moderate Asthmatics

Treatment/ Parameter	Racemic Formoterol 12 µg N=23	Arformoterol 15 µg N=23	Arformoterol 50 µg N=23	Racemic Formoterol 100 µg N=23	Arformoterol 50 µg plus Charcoal N=23
$AUC_{(0\text{-}last)}$ (pg*hr/ml)	n=6 13.6 (17.3)	n=22 55.9 (65.4)	n=22 103.3 (64.5)	n=19 76.0 (68.4)	n=23 67.9 (57.5)
C_{max} (pg/ml)	n=6 4.9 (2.6)	n=22 3.5 (1.5)	n=22 11.8 (6.9)	n=19 17.3 (10.2)	n=23 8.7 (4.8)
$AUC_{(0\text{-}3)}$ (pg*hr /ml)	n=2 9.8, 15.5†	n=20 6.8 (3.1)	n=21 17.7 (8.5)	n=16 25.8 (12.9)	n=22 12.9 (6.7)
$AUC_{(0\text{-}6)}$ (pg*hr /ml)	n=2 16.8, 40.4†	n=19 12.6 (6.6)	n=22 30.5 (16.0)	n=16 42.4 (22.8)	n=23 21.8 (12.2)
$t_{1/2}$ (hr)	N/C	n=7 20.4 (21.0)	n=15 15.0 (7.4)	n=7 8.9 (4.2)	n=17 17.0 (13.7)
t_{last} * (hr)	n=6 1.0 (0.9 – 12.0)	n=22 24.2 (1.2 – 72.6)	n=22 42.1 (12.1 – 72.4)	n=19 12.1 (1.1 – 72.2)	n=23 24.2 (6.2 – 72.2)
t_{max} * (hr)	n=6 0.13 (0.1 – 3.0)	n=22 0.25 (0.2 – 6.1)	n=22 0.25 (0.2 – 6.1)	n=19 0.25 (0.2 – 3.1)	n=23 0.25 (0.2 – 0.5)

*t_{last} and t_{max} parameters reported as Median (Min-Max)

†Two individual subject values are presented

N/C: parameter not calculated because of limited plasma samples (n=2)

NOTE: N represents the number of subjects who completed the treatment and n represents the number of subjects with evaluable data for the indicated parameter.

Table 3: Statistical Analysis of Effect of Treatment on Primary Plasma (R,R)-Formoterol PK Parameters

Parameter	Treatment Group	n	Geometric LS Mean	Treatment Comparison	Ratio	90% CI
$AUC_{(0\text{-}6)}$ (pg*hr/ml)	Arformoterol 15 µg (B)	19	9.93			
	Arformoterol 50 µg (C)	22	25.51			
	Racemic formoterol 100 µg (D)	16	31.44	C / D	0.81	0.67 – 0.98
	Arformoterol 50 µg plus charcoal (E)	23	18.74	C / E	1.36	1.15 – 1.61
$AUC_{(0\text{-}last)}$ (pg*hr/ml)	Arformoterol 15 µg (B)	22	24.60	-	-	-
	Arformoterol 50 µg (C)	22	78.68	-	-	-
	Racemic formoterol 100 µg (D)	19	46.01	C / D	1.71	1.08 – 2.70
	Arformoterol 50 µg plus charcoal (E)	23	48.10	C / E	1.64	1.07 – 2.51
C_{max} (pg/ml)	Arformoterol 15 µg (B)	22	3.12	-	-	-
	Arformoterol 50 µg (C)	22	9.69	-	-	-
	Racemic Formoterol 100 µg (D)	19	14.10	C / D	0.69	0.57 – 0.84
	Arformoterol 50 µg plus charcoal (E)	23	7.50	C / E	1.29	1.08 – 1.55

NOTE: Treatment comparison performed on administered dose levels. Data were not dose normalized.

NOTE: For $AUC_{(0\text{-}last)}$ and C_{max}, natural log-transformed data was analyzed using a linear model containing sequence, treatment group, and period as fixed effects and subject nested within the sequence as a random effect. The results were transformed back to the original scale by exponentiation to obtain geometric LS Means, ratio, and 90% confidence interval for the ratio.

NOTE: Racemic formoterol 12 µg was not included for comparisons due to limited data.

(S,S)-Formoterol Plasma Concentrations: While statistical analysis of plasma concentrations of (R,R)-formoterol for the 12 µg dose was not performed due to limited plasma samples, plasma levels of the (S,S)-isomer were high enough (approximately 1.5 times higher than (R,R)-formoterol) to allow the analysis. Two out of 46 predose samples had measurable (S,S)-formoterol concentrations in plasma (2.5 pg/ml and 11.2 pg/ml). (S,S)-Formoterol was measurable in plasma of most subjects at the first postdose sampling time, i.e., 5 minutes after the nebulization ended. Mean PK parameters for (S,S)-formoterol are presented in Table 4.

Table 4: Mean (SD) Plasma (S,S)-Formoterol PK Parameters

Treatment/ Parameter	Racemic Formoterol 12 µg N=23	Arformoterol 15 µg N=23	Arformoterol 50 µg N=23	Racemic Formoterol 100 µg N=23	Arformoterol 50 µg plus Charcoal N=23
$AUC_{(0\text{-}last)}$ (pg*hr /ml)	n=14 19.9 (11.8)	N/D	N/D	n=21 100.4 (78.9)	N/D
C_{max} (pg/ml)	n=14 6.2 (2.9)	N/D	N/D	n=21 26.2 (15.6)	N/D
$AUC_{(0\text{-}3)}$ (pg*hr /ml)	n=13 11.7 (4.1)	N/D	N/D	n=19 38.3 (19.8)	N/D
$AUC_{(0\text{-}6)}$ (pg*hr /ml)	n=11 23.2 (11.2)	N/D	N/D	n=19 61.3 (30.5)	N/D
C_{last} (pg/ml)	n=14 2.9 (1.4)	N/D	N/D	n=21 3.3 (1.3)	N/D
$t_{1/2}$ (hr)	n=3 13.0 (8.0)	N/D	N/D	n=13 7.0 (5.1)	N/D
t_{last} * (hr)	n=14 6.0 (1.0 – 6.1)	N/D	N/D	n=21 12.2 (3.2 – 72.2)	N/D
t_{max} * (hr)	n=14 1.0 (0.1 – 3.0)	N/D	N/D	n=21 0.3 (0.2 – 0.5)	N/D

* t_{last} and t_{max} parameters reported as Median (n) / (Min-Max)

NOTE: N/D= not determined

NOTE: N represents the number of subjects who completed the treatment and n represents the number of subjects with evaluable data for the indicated parameter.

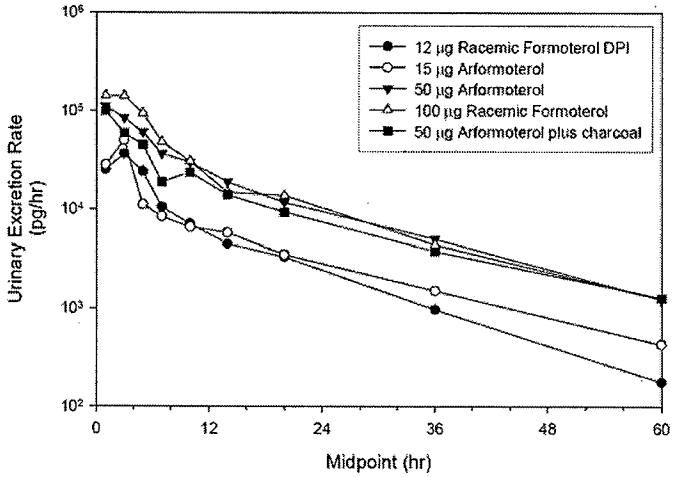
Plasma PK summary

- The rate of appearance of (R,R)-formoterol in plasma was rapid after all treatments; median tmax ranged between 0.13 and 0.25 hr.
- Large variability and substantial overlap in $t_{1/2}$ were seen across all treatments.
- Meaningful AUC plasma data were available from only two subjects after treatment with racemic formoterol 12 µg. Therefore, only limited comparisons between this treatment and the other treatments were performed.
- Comparison of Cmax and $AUC_{(0\text{-}6)}$ obtained after treatment with arformoterol 50 µg and racemic formoterol 100 µg (treatments with equal amounts of (R,R)-formoterol) indicated that racemic formoterol provided approximately 45% and 23% higher systemic exposure, (Cmax and $AUC_{(0\text{-}6)}$, respectively). However there were little or no differences in the terminal $t_{1/2}$ in plasma. Transient inhibition of first pass metabolism by (S,S)-formoterol is one hypothesis that could explain these observations (per Sponsor).
- There was approximately 30% decrease in systemic (R,R)-formoterol exposure after treatment with arformoterol 50 µg with pre-/postdose charcoal as compared to that obtained after arformoterol 50 µg alone. This suggests that a substantial portion of systemic drug exposure is due to pulmonary absorption.

Urine Pharmacokinetics:

(R,R)-Formoterol Urine Data: Sponsor indicated the use of urine PK parameters was primary method for evaluating PK results between nebulized arformoterol treatments and the racemic formoterol 12 µg treatment because only limited plasma data were greater than the assay quantitation limits for the latter treatment. A total of 12 predose urine samples (out of 115 across all treatment groups) collected from six subjects had detectable (R,R)-formoterol concentrations. Mean urinary excretion rate of (R,R)-formoterol plotted against the midpoint of the collection interval is displayed in Figure 2. Excretion rates were highest at ~2 hrs after dosing.

Figure 2: Mean Excretion Rate of (R,R)-Formoterol in Urine over Time



(R,R)-Formoterol Urine PK Parameters: The mean urine-derived PK parameters are presented in Table 5.

Table 5: Mean (SD) Urine (R,R)-Formoterol PK Parameters following Arformoterol and Racemic formoterol

Treatment/ Parameter	Racemic Formoterol 12 µg N=23	Arformoterol 15 µg N=23	Arformoterol 50 µg N=23	Racemic Formoterol 100 µg N=23	Arformoterol 50 µg plus Charcoal N=23
$A_{e(0-72)}$ (ng)	n=22 260.9 (144.5)	n=20 322.8 (328.9)	n=21 1078.0 (670.6)	n=21 1194.7 (989.6)	n=21 828.0 (518.0)
$fe_{(0-72)}$ (%)	n=22 5.3 (2.9)	n=20 2.2 (2.2)	n=21 2.2 (1.3)	n=21 2.4 (2.0)	n=21 1.7 (1.0)
Cl_r (L/hr)	N/C†	n=11 9.6 (5.4)	n=17 20.0 (9.9)	n=14 19.3 (13.0)	n=20 18.5 (7.1)
$t_{1/2ur}$ (hr)	n=22 11.7 (4.1)	n=20 13.2 (2.3)	n=22 12.5 (2.7)	n=22 13.2 (3.3)	n=23 12.6 (2.7)

† N/C = =parameter not computed due to limited data (n=2)

NOTE: N represents the number of subjects who completed the treatment and n represents the number of subjects with evaluable data for the indicated parameter.

(S,S)-Formoterol Urine PK Parameters: Urine PK parameters for (S,S)-formoterol are presented in Tables 6.

Table 6: Mean (SD) Urine PK Parameters for (S,S)-Formoterol following Arformoterol or Racemic Formoterol in Mild to Moderate Asthmatics

Treatment/ Parameter	Racemic Formoterol 12 µg N=23	Arformoterol 15 µg N=23	Arformoterol 50 µg N=23	Racemic Formoterol 100 µg N=23	Arformoterol 50 µg plus Charcoal N=23
$A_{e(0-72)}$ (ng)	n=21 367.7 (200.1)	N/D	N/D	n=21 1634.1 (1334.8)	N/D
$fe_{(0-72)}$ (%)	n=21 7.5 (4.1)	N/D	N/D	n=21 3.3 (2.7)	N/D
Cl_r (L/hr)	n=10 15.1 (13.0)	N/D	N/D	n=17 16.0 (7.1)	N/D
$t_{1/2ur}$ (hr)	n=20 7.9 (3.0)	N/D	N/D	n=22 9.6 (2.6)	N/D

N/D=not determined.

NOTE: N represents the number of subjects who completed the treatment and n represents the number of subjects with evaluable data for the indicated parameter.

Two out of 115 predose samples had detectable (S,S)-formoterol concentrations. The amount of (S,S)-formoterol recovered in urine, $Ae_{(0-72)}$, was 36-40% higher than the amount of (R,R)-formoterol recovered after administration of either dose of racemic formoterol. The mean half-life and the renal clearance of (S,S)-formoterol were similar for the two treatments, but were somewhat lower than those observed for (R,R)-formoterol.

Chiral Inversion: (S,R)-Formoterol: Trace amounts of (S,R)-formoterol were found in a few isolated (8/1000) urine samples from three (out of 23) asthmatic subjects. (S,R)-formoterol levels were observed after administration of arformoterol 50 µg or racemic formoterol 100 µg. The levels of (S,R)-formoterol were very low as compared to (R,R)-formoterol levels [(S,R)-formoterol urine levels were less than 0.2% of (R,R)-formoterol urine levels]. These data indicated that there was no systematic evidence of chiral inversion following treatment with arformoterol based on urine excretion.

Urine PK Summary

- The $t_{1/2ur}$ of (R,R)-formoterol, based upon urine excretion rates, was similar across all five treatments. The presence of (S,S)-formoterol did not impact this parameter. Further, renal clearance of (R,R)-formoterol was comparable after treatment with arformoterol 50 µg and racemic formoterol 100 µg.
- The fraction of the nominally administered dose recovered in urine (fe) was comparable after treatment with arformoterol 15 µg, arformoterol 50 µg, and racemic formoterol 100 µg, and ranged from 2.2% to 2.4%.
- The amount of (R,R)-formoterol recovered in urine ($Ae_{(0-72)}$) was similar following treatment with racemic formoterol 12 µg and arformoterol 15 µg.
- CLr was lower after arformoterol 15 µg than after arformoterol 50 µg or racemic formoterol 100 µg.

- There was approximately 30% decrease in the amount of (R,R)-formoterol recovered in urine after treatment with arformoterol 50 µg with pre-/postdose oral administration of charcoal as compared to arformoterol 50 µg given alone.
- There was no systematic evidence of chiral inversion following treatment with arformoterol. Trace amounts of (S,R)-formoterol were found in a few isolated urine samples.

Pharmacodynamic Analysis:

Correlation between PK Parameters and Efficacy Parameters:

Scatter plots for $AUC_{FEV1(0-4)}$ versus plasma $AUC_{(0-3)}$ by analyte (R,R and S,S) and treatments are displayed in Figure 3, and this plot indicated that there was no observed relationship between efficacy and systemic exposure. Sponsor stated the apparent lack of a PK/PD relationship may be attributed to substantial inter-subject variability associated with PK and PD measurements that could have masked a true PK/PD relationship.

Comment: Plot would be more meaningful if comparison was $AUC_{FEV1(0-12)}$ versus plasma $AUC_{(0-12)}$.

Correlation between Plasma Concentration and Safety Parameters:

Plots of safety parameters (changes from pre-dose in QTc-F, ventricular heart rate, potassium levels and glucose levels) versus (R,R)-formoterol plasma concentration are made. Visual inspection of these graphs suggests no apparent relationship between (R,R)-formoterol plasma concentration and QTc-F, ventricular heart rate and glucose levels (e.g., changes from pre-dose in QTc-F *vs.* (R,R)-formoterol plasma concentration is shown in Figure 4, upper panel). Serum potassium levels tended to decrease, especially at higher (R,R)- formoterol concentrations (Figure 4, lower panel).

Figure 3: Scatter Plot for $AUC_{FEV(0-4)}$ *vs.* Plasma $AUC_{(0-3)}$ by Analyte and Treatrnent Analyte=RR-formoterol, Treatment = (R,R)-formoterol 15 mcg inhalation solution

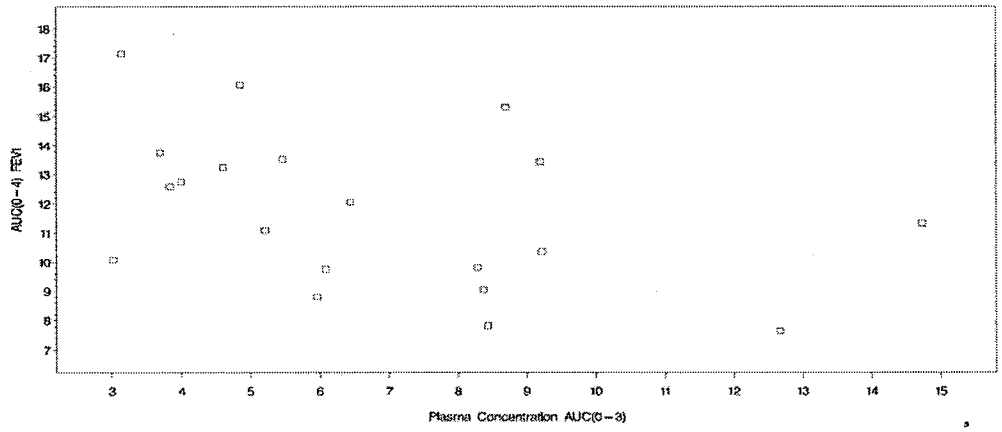
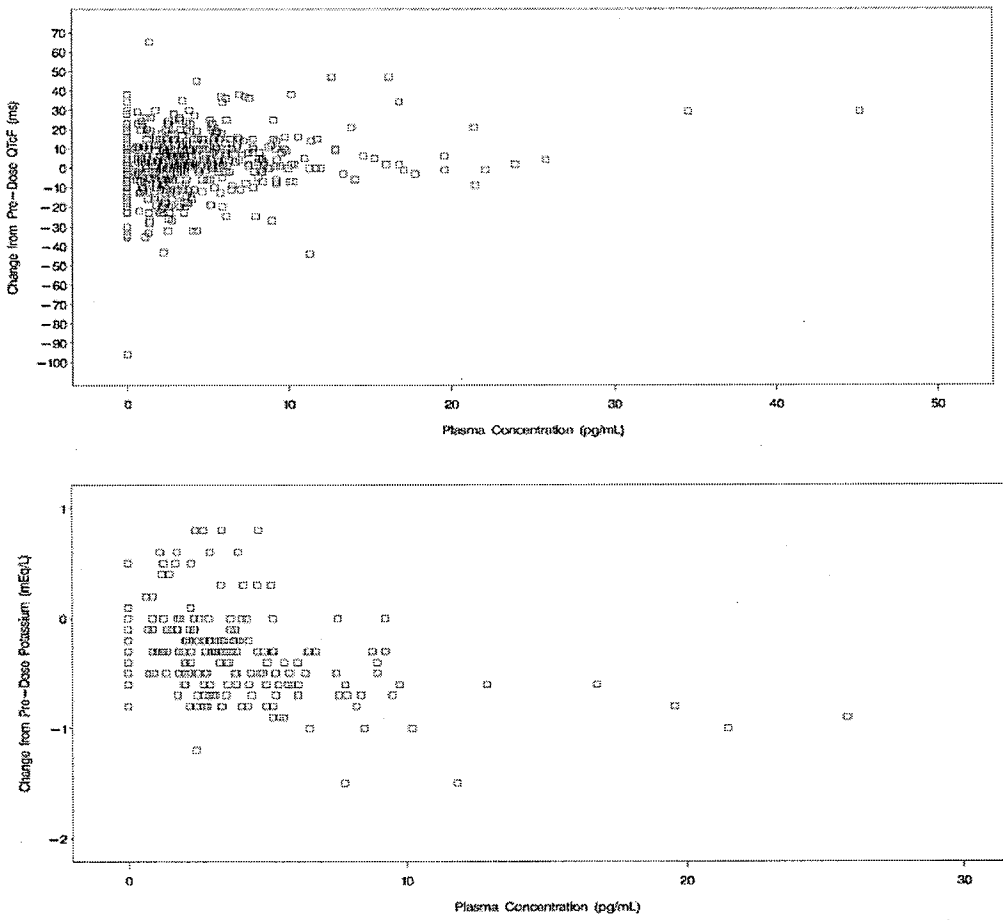


Figure 4: Scatter Plot for Changes from Pre-Dose QTc-F *vs.* (R,R)-Formoterol Plasma Concentration (upper panel) and Changes from Pre-Dose potassium level (lower panel)



PD Summary

- Inspection of the $AUC_{FEV1(0-4)}$ versus plasma $AUC_{(0-3)}$ data suggested that there was no observed relationship between efficacy and systemic exposure. The apparent lack of a PK/PD relationship may be attributed to substantial inter-subject variability associated with PK and PD measurements that could have masked a true PK/PD relationship.
- Mean changes from predose in serum potassium showed a dose-related decrease, with the highest doses resulting in a decline of approximately 0.4 mEq/L at two hours post dose. There were two subjects with serum potassium levels <3.0 mEq/L, both following treatment with arformoterol 50 μg plus charcoal, and few subjects with maximum declines >1.0 mEq/L.
- Mean changes from predose in serum glucose levels were small, and did not appear to be related to dose of arformoterol or racemic formoterol.
- Minimal mean increases in heart rate were observed in the three highest dose groups (arformoterol 50 μg, arformoterol 50 μg plus charcoal, and racemic formoterol 100 μg), with minimal mean increases in QTc across groups. There were no other clinically relevant changes in vital signs or ECG parameters following any treatment.

Overall Conclusions:

- The observed terminal half-lives estimated from urine data were similar across all five treatments (11.7 - 13.2 h) suggesting the presence of (S,S) formoterol does not impact this parameter.
- Similar amounts of unchanged (R,R)-formoterol were excreted in urine within 72 hours following inhalation of racemic formoterol 12 μg or arformoterol 15 μg nebulized dose.
- There was no systematic evidence of chiral inversion following nebulization of arformoterol in urine.
- Administration of racemic formoterol 100 μg resulted in moderately higher systemic exposure to (R,R)-formoterol as compared to treatment with arformoterol 50 μg (both treatments contain equivalent amounts of (R,R)-formoterol). Transient inhibition of first pass metabolism by (S,S)-formoterol is one hypothesis that could explain these observations.
- There was a 26% decrease in systemic (R,R)-formoterol exposure after treatment with arformoterol 50 μg with pre-/postdose charcoal as compared to that obtained after arformoterol 50 μg alone. This suggests that a substantial portion of systemic drug exposure is due to pulmonary absorption.

Comment: Study conclusions are acceptable.

Protocol 091-018

Study Type: DDI, multiple-dose, in healthy subjects.

Title: A Drug-Drug Interaction Study of Multiple-Dose Arformoterol Inhalation Solution Administered Concomitantly with Multiple-Dose Paroxetine to Normal Healthy Volunteers.

Investigators: Multi-center

Objectives:

- To evaluate the effects of paroxetine, a potent inhibitor of cytochrome P450 2D6 (CYP2D6), on the PK profile of arformoterol at steady state in healthy volunteers (Primary).
- To evaluate the effects of arformoterol on the PK profile of paroxetine at steady state in healthy volunteers and evaluate the safety and tolerability of arformoterol administered concomitantly with paroxetine (Secondary Objectives).

Methodology: This was an open-label, nonrandomized, multicenter, in- and out-patient, multiple-dose study of healthy adult subjects classified as extensive CYP2D6 and normal UGT1A1 metabolizers.

No. of Subjects: Planned: 30 enrolled subjects, with a minimum of 24 subjects completing the study. Analyzed: 34 (ITT population) and 31 (PK population).

Diagnosis and Main Criteria for Inclusion: Healthy, nonsmoking male or female subjects, between 18 and 55 years, inclusive, who were classified as extensive CYP2D6 and normal UGT1A1 metabolizers with a body mass index of less than 30 kg/m2. Subjects identified as poor, intermediate, or ultra-rapid CYP2D6 metabolizers or reduced UGT1A1 metabolizers were excluded from the study.

Products used: 50 µg (2 mL) QD Arformoterol tartrate inhalation solution (lot 02403C) and 20 mg QD paroxetine (lot 3533B11).

Duration of Treatment: 7 consecutive days of arformoterol alone followed by a 7-day wash-out period, 10 consecutive days of paroxetine alone, and 7 consecutive days of arformoterol administered concomitantly with paroxetine followed by a 7-day wash-out period.

Blood PK sampling times were as follows:

- arformoterol dosing period and subsequent wash out period: Predose on Days 1, 5, 6, and 7 and at 5, 15, 30 minutes and 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hrs after last arformoterol dose on Day 7.
- paroxetine dosing period: predose on Days 14 (168 hrs after last arformoterol dose on Day 7), 21, 22, and 23 and at 30 minutes and 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours after last paroxetine dose on Day 23;
- paroxetine + arformoterol dosing period and subsequent wash out period: predose on Days 24 (24 hours after last paroxetine dose on Day 23), 28, 29, and 30 and 5, 15, 30 minutes and 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after last combination dose on Day 30.

Criteria for Evaluation:

PK: Arformoterol and paroxetine plasma PK parameters; $AUC_{(0-\tau)}$, $AUC_{(0-t)}$, Cmax tmax, $t_{1/2}$.

Note: $AUC_{(0-\tau)}$, area under the plasma concentration-time curve over the dosing interval (τ), i.e., 0-24 hrs, was calculated using the linear trapezoidal rule, based on actual sample times.

Safety: adverse events, laboratory parameters, vital signs, 12-lead ECG, 24-hour Holter monitoring, and physical examination findings.

Statistical Methods: The ITT population was defined as all subjects who received at least one dose of study drug. The ITT population was used for the safety and plasma concentration analyses. The PK population was defined as all ITT subjects who had any PK parameter data available. The PK population was used for the analysis of PK parameters.

PK: The primary statistical analysis was a comparison of $AUC_{(0-\tau)}$, and Cmax for arformoterol when administered alone and coadministered with paroxetine. The $AUC_{(0-\tau)}$ and Cmax data were each natural (ln) log-transformed, paired by subject, and the difference between arformoterol in the presence of paroxetine and the absence of paroxetine (the reference) was calculated. The mean difference was estimated, and the 90% CI was derived based on a t-distribution. The ln-transformed results were transformed back to the original scale by exponentiation to obtain ratios and 90% CIs for these ratios. If the 90% CI for the treatment ratio fell within 80% to 125% for both $AUC_{(0-\tau)}$ and Cmax, then it would be concluded that the PK of arformoterol are not affected by concomitant administration of paroxetine.

Secondary analyses included the $AUC_{(0-\tau)}$ and Cmax of paroxetine alone, and were analyzed in the same manner as described for the primary analysis. The $AUC_{(0-\infty)}$ of arformoterol was also analyzed as a secondary endpoint using the same approach as described for the primary analysis.

The achievement of steady state was assessed by visual examination of the graphical displays of mean trough plasma concentrations.

Plasma concentrations at each blood sample collection time, as well as the derived PK parameters $AUC_{(0-\tau)}$, $AUC_{(0-\infty)}$, Cmax, tmax, C_{last}, t_{last}, $t_{1/2}$, and λz were summarized by treatment period using descriptive statistics.

Safety: Descriptive statistics.

RESULTS

Arformoterol Data

Mean arformoterol plasma concentrations over time following multiple-dose administration of arformoterol alone and multiple-dose coadministration with 20 mg paroxetine are summarized in Table 1 and Figure 1. Arformoterol PK parameters and the result of statistical analysis are presented in Table 2 and 3, respectively. Visual inspection of mean trough arformoterol concentrations and individual plasma concentration-time plots indicated that steady state was achieved by the 5th day of arformoterol alone dosing and by the 5th day of combination dosing (Figure 3).

Table 1: Mean (SD) Arformoterol Plasma Concentrations after 7 Daily Doses of 50 µg Inhaled Arformoterol Alone and after Coadministration with 20 mg Paroxetine (ITT Population)

Arformoterol Alone (N=34)				Arformoterol with Paroxetine (N=31)			
Day	Time (hour)	n	Concentration (pg/mL)	Day	Time (hour)	n	Concentration (pg/mL)
1	0*	31	BLQ	24	0*	31	BLQ
5	0*	33	1.19 (0.98)	28	0*	29	1.16 (1.22)
6	0*	32	1.19 (0.79)	29	0*	30	1.20 (1.07)
7	0*	31	1.05 (0.74)	30	0*	30	1.39 (1.11)
7	0.083	31	11.08 (7.16)	30	0.083	30	12.64 (10.71)
7	0.25	31	7.77 (4.53)	30	0.25	30	8.75 (6.20)
7	0.5	31	6.52 (3.55)	30	0.5	30	7.30 (4.66)
7	1	31	5.19 (2.66)	30	1	30	6.10 (4.09)
7	2	31	4.33 (2.38)	30	2	30	4.99 (3.27)
7	4	31	3.99 (3.01)	30	4	30	3.72 (2.39)
7	6	31	3.09 (1.72)	30	6	30	3.43 (2.58)
7	8	31	2.94 (1.54)	30	8	30	3.24 (2.25)
7	10	31	3.12 (2.00)	30	10	30	2.64 (1.68)
7	12	31	2.89 (2.00)	30	12	30	2.36 (1.19)
7	16	31	2.32 (1.93)	30	16	30	1.98 (1.13)
8	24	31	1.59 (1.46)	31	24	30	1.70 (0.91)
8	36	31	1.33 (1.96)	31	36	28	1.41 (1.27)
9	48	31	0.70 (0.94)	32	48	29	1.69 (4.07)
10	72	31	BLQ	33	72	29	0.79 (1.06)
11	96	27	BLQ	34	96	29	BLQ
12	120	31	BLQ	35	120	30	BLQ
13	144	31	0.67 (2.16)	36	144	30	BLQ
14	168	31	BLQ	37	168	30	BLQ

*predose
Note: BLQ = Below the lower limit of quantitation (0.5 pg/mL)
Cross Reference: Tables 14.1.1 and 14.2.1.1

Figure 1: Mean Arformoterol Plasma Concentration-Time Profiles Following Daily Inhaled Doses of 50 µg Arformoterol Alone and after Coadministration with 20 mg Paroxetine for 7 Days (steady state)

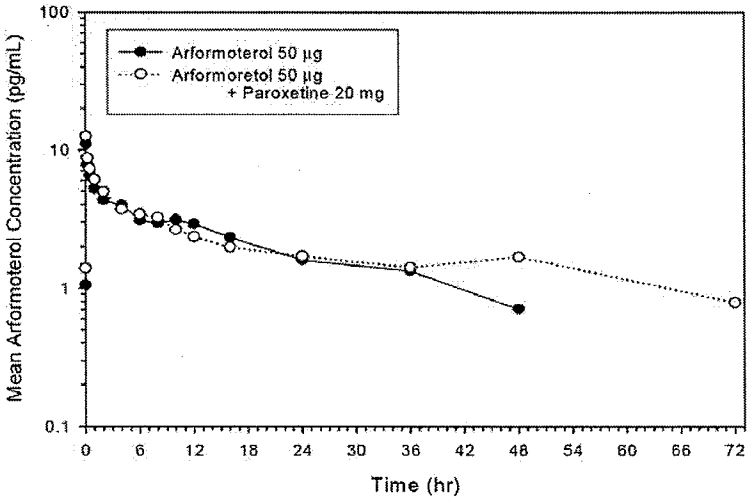


Table 2: Plasma Arformoterol PK Parameters after Daily Inhaled Doses of 50 µg Arformoterol Alone and after Coadministration with 20 mg Paroxetine for 7 Days (PK Population)

Parameter	Arformoterol 50 µg QD (N=31)	Arformoterol 50 µg + Paroxetine 20 mg QD (N=31)
C_{max} (pg/mL)	n=29 12.3 (6.6)	n=30 12.7 (10.7)
$AUC_{(0-\tau)}$ (hour*pg/mL)	n=28 74.3 (37.9)	n=30 70.5 (41.4)
$AUC_{(0-\infty)}$ (hour*pg/mL)	n=14 111 (90.0)	n=14 158 (93.9)
t_{max} (hour)	n=29 0.25 (0.1, 10.2)	n=30 0.25 (0.2, 12.2)
$t_{1/2}$ (hour)	n=17 18.9 (7.59)	n=20 25.4 (12.82)

[a] t_{max} is reported as median (minimum, maximum).

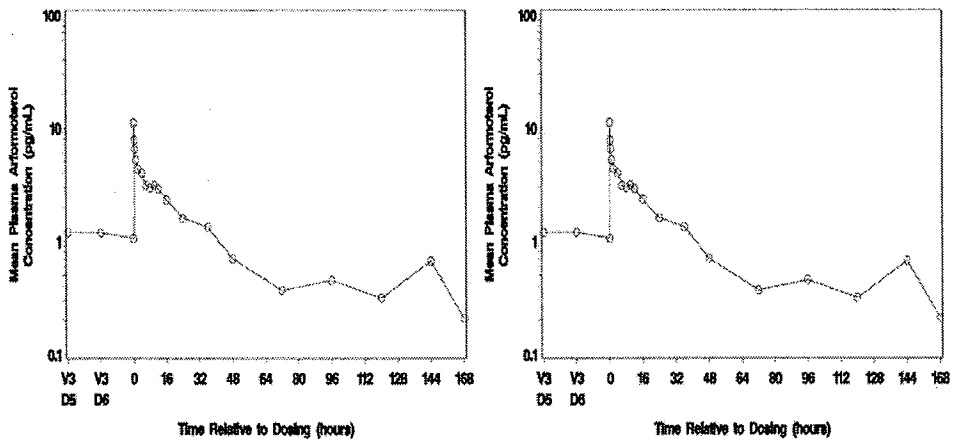
Mean $AUC_{0-\infty}$ was 31% higher (90% CI on the ratio: 116 to 149) during concomitant therapy with arformoterol and paroxetine. This difference was mostly due to LLQ concentrations (less than 50% of subjects had estimable $AUC_{0-\infty}$ values), thus, limiting the ability to draw definitive conclusions.

Table 3: Statistical Analysis of Drug Interaction Effect on Plasma PK Parameters of Arformoterol

Parameter	Treatment Group	n	Mean	With Paroxetine versus Arformoterol Alone	
				Ratio (%)	90% CI
$AUC_{(0-\tau)}$ (hour*pg/mL)	ARF 50 µg	28	74.3	100.7	86.6 – 117.1
	ARF 50 µg + PAR 20 mg	30	70.5		
C_{max} (pg/mL)	ARF 50 µg	29	12.3	100.8	84.5 – 120.4
	ARF 50 µg + PAR 20 mg	30	12.7		

ARF=arformoterol; PAR=paroxetine.

Figure 2: Mean (Steady state) Arformoterol plasma concentration-time profiles following QD doses of 50 µg arformoterol alone (left panel) and after coadministration with 20 mg Paroxetine for 7 Days (right panel)



Paroxetine Data: Results are presented in Figure 4 and Tables 4-5.

Figure 4: Mean Paroxetine Plasma Concentration-Time Profiles Following 10 Daily Oral Doses of 20 mg Paroxetine Alone and Following 7 Days of Coadministration with 50 µg Inhaled Arformoterol

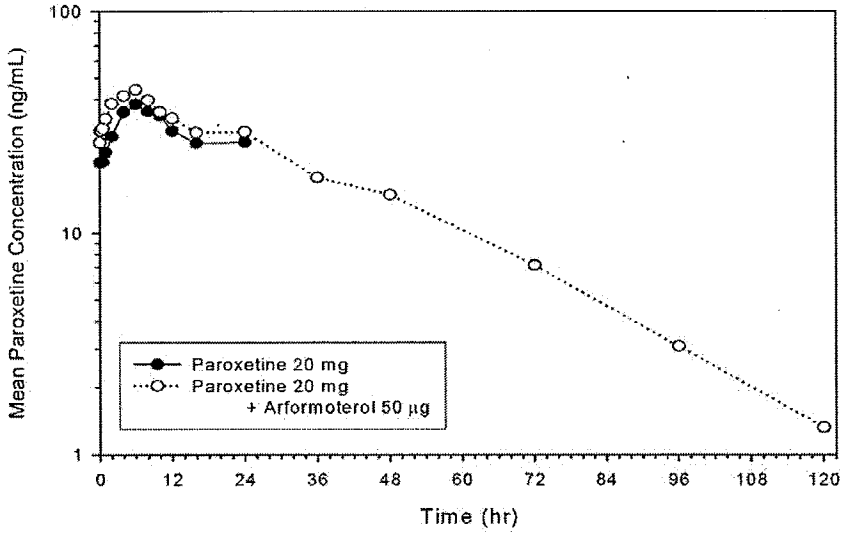


Table 4: Plasma Paroxetine PK Parameters after 10 Daily Doses of 20 mg Paroxetine Alone and after Coadministration for 7 days

Parameter	Paroxetine 20 mg QD (N=31)	Paroxetine 20 mg + Arformoterol 50 µg QD (N=31)
C_{max} (ng/mL)	n=31 42.2 (22.5)	n=30 46.6 (24.9)
$AUC_{(0-\tau)}$ (hour*ng/mL)	n=30 718 (418)	n=30 812 (464)
$t_{max}^{\#}$ (hour)	n=31 6.00 (4.0, 12.0)	n=30 6.18 (1.2, 10.1)
$t_{1/2}$ (hour)	--	n=30 19.7 (9.68)

-- indicates value was not calculated. $t_{1/2}$ was not determined for paroxetine alone, because the sampling period (24 hours) was too short and did not cover the terminal phase.
$^{\#}t_{max}$ is reported as median (minimum, maximum).

Table 5: Statistical Analysis of Drug Interaction Effect on Plasma PK Parameters of Paroxetine

Parameter	Treatment Group	n	Mean	With Arformoterol versus Paroxetine Alone	
				Ratio (%)	90% CI
$AUC_{(0-\tau)}$ (hour*ng/mL)	PAR 20 mg	30	718	115.7	103.2 – 129.8
	ARF 50 µg + PAR 20 mg	30	812		
C_{max} (ng/mL)	PAR 20 mg	31	42.2	110.3	99.9 – 121.7
	ARF 50 µg + PAR 20 mg	30	46.6		

ARF=arformoterol; PAR=paroxetine.

Pharmacokinetic Conclusions:

- Arformoterol $AUC_{(0-\tau)}$ and Cmax were similar when arformoterol was administered in combination with paroxetine, compared to arformoterol given alone. The exposure parameter ratios were near 100% and the 90% CIs on the ratios fell within the 80 to 125% equivalence limits. The median tmax was 0.25 hours following treatment with arformoterol alone and when given with paroxetine. The mean $t_{1/2}$, however, was somewhat longer in the presence of paroxetine. These data suggest that CYP2D6 does not play an important role in the metabolism of arformoterol.
- Paroxetine $AUC_{(0-\tau)}$ and Cmax values were increased slightly (15.7% and 10.3% higher, respectively) when paroxetine was administered in combination with arformoterol, compared with paroxetine given alone. The 90% CI for Cmax was within the 80 to 125% equivalence limits, but the upper limit of the 90% CI for $AUC(0-_{\tau})$ fell marginally above the 125% upper equivalence limit. The slight increase in exposure parameters was not considered clinically meaningful.

Comment: $AUC_{(0-\tau)}$ (instead of $AUC_{0-\infty}$) and Cmax as indicator of drug interaction is acceptable because these represents values at steady state, therefore, the sponsor's conclusion is considered adequate.

Protocol 091-026

Study Type: Phase 2, Dose-finding study.

Title: 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)

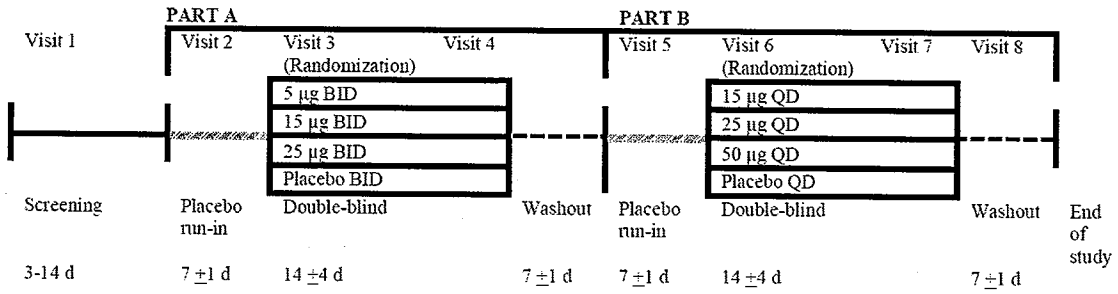
Investigators: Multicenter study

Objectives:

Primary Objective: Part A: To evaluate the relevant airway function endpoints for arformoterol over a 14-day treatment period when administered at doses of 5, 15, and 25 µg twice daily (BID) for 14 days and to compare these with those of placebo. Part B: To evaluate the relevant airway function endpoints for arformoterol over a 14-day treatment period when administered at doses of 15, 25, and 50 µg once daily (QD) for 14 days and to compare these with those of placebo.

Secondary Objectives: For Parts A and B, 1) to compare the safety and tolerability of arformoterol with those of placebo in subjects with chronic obstructive pulmonary disease (COPD), 2) to thoroughly characterize the effect of inhaled arformoterol on cardiovascular safety outcomes in subjects with COPD (especially its effects on electrocardiographic (ECG) parameters, including QTc interval), 3) to evaluate any dose-response trend among the doses of arformoterol, 4) to evaluate clinical effects of withdrawal from therapy, and 5) to explore the relationship between plasma concentrations of arformoterol and selected pharmacodynamic endpoints.

Methodology: This was a placebo-controlled, double-blind, randomized, multicenter, 2-part, parallel-group, dose-ranging study of the efficacy, safety, 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. Study Schematic is shown below:



The same subjects participated in both parts of the study; randomization in Parts A and B was done independently.

No. of Subjects: Planned: 215. Analyzed: Part A, 215 subjects (54, 54, 54, and 53 subjects in the placebo and arformoterol 5, 15, and 25 µg BID groups, respectively); Part B, 191 subjects (49, 48, 47, and 47 subjects in the placebo and arformoterol 15, 25, and 50 µg QD groups, respectively).

Diagnosis and Main Criteria for Inclusion: Males or females aged ≥35 years who had a primary diagnosis of COPD, a minimum smoking history of 15 pack-years, a score of ≥2 on the Medical Research Council (MRC) Dyspnea Scale, a baseline value for forced expiratory volume in 1 second (FEV_1) that was ≥65% of the predicted normal value and >0.70 L before randomization (at Visit 1 or 2), and a FEV1/forced vital capacity (FVC) ratio (calculated as the highest FEV1 obtained divided by the highest FVC obtained of 2 efforts conducted) of ≥70% before randomization were eligible for the study. Subjects were also required to demonstrate a ≥10% improvement in FEV1 within 15 to 30 minutes after inhalation of 2 puffs (180 µg) of racemic albuterol MDI before randomization (at Visit 1 or 2). Subjects who 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), a known history of a-1 antitrypsin deficiency-related emphysema, a blood eosinophil count of >5% of total white blood cell count, clinically significant cardiac, hepatic, renal, gastrointestinal, endocrine, metabolic, neurologic, or psychiatric disorder that may have interfered with the successful completion of the study, or a history of cancer other than non-melanoma skin cancer were excluded from the study.

Meal Relationship: Subjects were not required to fast before taking the study medication.

Lot Numbers: Arformoterol 5 µg/2 mL (00803B), 15 µg/2 mL (00902B), 25 µg/2 mL (00902C), 50 µg/2 mL (00902D), and Placebo (00803A and 00902A)

Duration of Treatment: Subjects were to participate in the study for 8 weeks, including the 1-week, single-blind, placebo run-in period before randomization into Part A; the 2-week placebo or arformoterol treatment period for Part A; the 1-week washout period following Part A; the 1-week, single-blind, placebo run-in period before randomization into Part B; the 2-week placebo or arformoterol treatment period for Part B; and the 1-week washout period following completion of the Part B treatment period.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoints were as follows:

- Part A: The time-normalized area under the curve for FEV1 percent change from predose over 12 hours ($_nAUC_{0\text{-}12\text{-}P}$) 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 ($nAUC_{0\text{-}24\text{-}P}$) at Visit 7 (after 14 days of double-blind treatment).

The 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 included: 1) the 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; 2) the 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); 3) the percent change in FEV1 from predose to each time point after dosing; 4) the peak percent change in FEV1; 5) peak percent of predicted FEV1 after dosing; 6) ipratropium bromide and racemic albuterol use; 7) morning and evening peak expiratory flow rate (PEFR); 8) exacerbations of COPD; 9) COPD symptom ratings; 10) the effects of withdrawal of therapy; and 11) the relationship between plasma concentrations of arformoterol and selected pharmacodynamic parameters.

The additional endpoints 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 derived post hoc to maintain consistency in efficacy parameters across the arformoterol development program.
Pharmacokinetics: The steady-state PK parameters estimated on Visit 4 (Part A) and Visit 7 (Part B) were area under the concentration-time curve from time 0 to last quantifiable plasma concentration (AUC(0-last)), time 0 to end of the dosing interval (AUC(0-t)), time 0 to 24 hour (AUC(0-24)), maximum plasma concentration (Cmax), time to maximum plasma concentration (tmax), elimination rate constant (.z), and half-life (t½).

Blood samples were collected at predose and postdose at 15, 45 min, and at 2 and 6 hrs at Visit 3 and 6. At Visit 4, pre-1st dose, at 15 and 45 min and 2 and 6 hrs post-1st dose (pre-2nd dose), and at 15, 30, and 45 min and at 1, 2, 6, 8 and 12 hrs post-2nd dose with additional at 36 and 60 hrs post-second dose. At Visit 7, pre-dose and post-dose at 15, 30, and 45 min and at 1, 2, 6, 8, 12, 24, 48 and 72 hr.

Safety: Adverse events; ECG findings, clinical laboratory parameters, and physical examination findings.

Statistical Methods:

Efficacy: The efficacy analysis was based on the intent-to-treat (ITT) population, which included all subjects who received at least 1 dose of double-blind study medication. The primary efficacy endpoint ($_{n}AUC_{0\text{-}12\text{-}P}$ for Part A and $_{n}AUC_{0\text{-}24\text{-}P}$ for Part B) was analyzed using 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 (predose at Visit 4 for Part A or Visit 7 for Part B) as a covariate and treatment group as a fixed effect. Comparisons of each arformoterol dose with placebo and between the 3 arformoterol BID (Part A) or QD (Part B) doses were made. The percent change in FEV_1 from baseline to 24 hours post-first dose (trough) value for Parts A and B were analyzed using the same model as defined for the primary efficacy endpoint with the exception that the covariate was the last FEV_1 measurement that was collected before the first dose of double-blind medication was administered at the 6-hour in-clinic visit (Visit 3 predose for Part A or Visit 6 predose for Part B).

Pharmacokinetics: PK parameters, estimated using WinNonlin® Professional, were based on the individual plasma concentrations. The PK parameters were summarized descriptively and graphically.

Pharmacodynamics: Plasma concentration 15 minutes postdose was paired with immediately postdose FEV1 percent change, and plasma concentration at 45 minutes postdose was paired with 30 minutes postdose FEV1 percent change because the time to peak systemic concentrations (tmax) appeared earlier than the time of peak percent change in FEV1. A Pearson linear correlation analysis between plasma concentration of arformoterol and corresponding FEV1 percent changes was performed by time, visit, and treatment group. Scatter plots of serum potassium level versus plasma concentration of arformoterol were produced by visit. Similar scatter plots were produced for serum glucose level and heart rate.

Safety: Safety parameters were summarized. The ECG parameters were summarized, and obtained QTc intervals (QTc-F and QTc-B).

RESULTS

Efficacy: The primary efficacy endpoint was the time-normalized area under the FEV1 percent change from predose curve over 12 hours (nAUC0-12-P) at the 24-hour visit (Visit 4) in Part A, and from predose curve over 24 hours (nAUC0-24-P) at the 24-hour visit (Visit 7) in Part B. In addition, Dose-Response relationship among the arformoterol doses when examined for clinically meaningful responder rates. Responders were defined as those who achieved a trough change from study baseline of ≥10% or ≥15% after 14 days of double-blind treatment. The results are shown below.

The results showed that there was Dose-Response relationship.

Part A

Figure 1: Mean Percent Change in FEV1 From Baseline Over 24 Hours After 14 Days of Dosing (Visit 4)

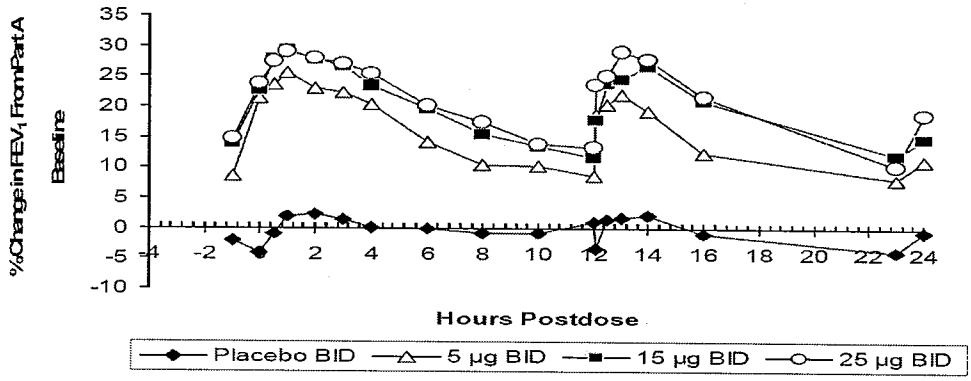


Table 1: Proportion of Subjects With ≥10% and ≥15% Improvement in FEV1 at Trough (24 Hours) After 14 Days of Double-blind Treatment

% Improvement	Placebo BID N=54	ARF 5 µg BID N=54	ARF 15 µg BID N=54	ARF 25 µg BID N=53
≥10%	26.7% (8/30)	56.4% (22/39)	52.2% (21/40)	56.8% (21/37)
≥15%	16.7% (5/30)	35.9% (14/39)	45.0% (18/40)	54.1% (20/37)

Note: The 24-hour in FEV_1 values within 6 hours of prior supplemental/rescue medication use were excluded.

Part B

Figure 2: Mean Percent Change in FEV1 from Baseline over 24 Hours after 14 days of dosing (Visit 7)

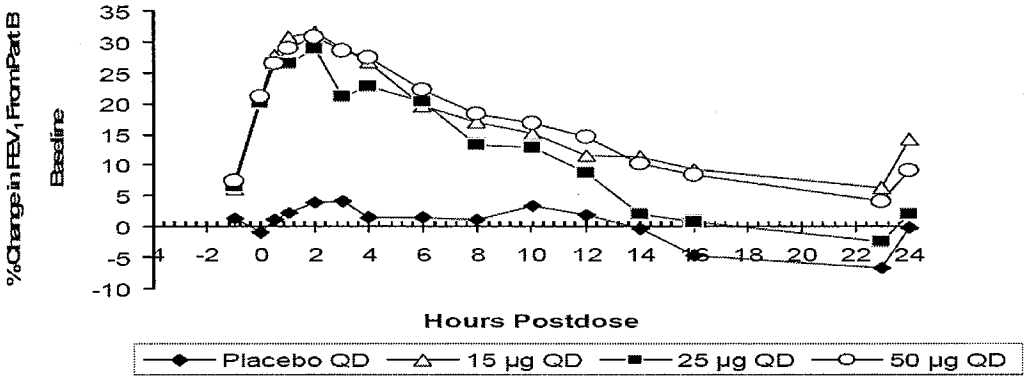


Table 2: Proportion of Subjects With ≥10% and ≥15% Improvement in FEV1 at Trough (24 Hours) After 14 Days of Double-blind Treatment

% Improvement	Placebo QD N=49	ARF 15 µg QD N=48	ARF 25 µg QD N=47	ARF 50 µg QD N-47
≥10%	23.5% (8/34)	52.8% (19/36)	41.2% (14/34)	27.6% (8/29)
≥15%	14.7% (5/34)	41.7% (15/36)	20.6% (7/34)	27.6% (8/29)

Note: The 24-hour in FEV_1 values within 6 hours of prior supplemental/rescue medication use were excluded.

Pharmacokinetics:

Mean steady-state Arformoterol Plasma Concentration-Time Profiles are shown in Figure 3, and PK parameters values are shown in Tables 3-4.

Figure 3: Mean Steady-State Arformoterol Plasma Concentration-Time Profiles Following Multiple Inhaled Doses; Part A (left) and Part B (right)

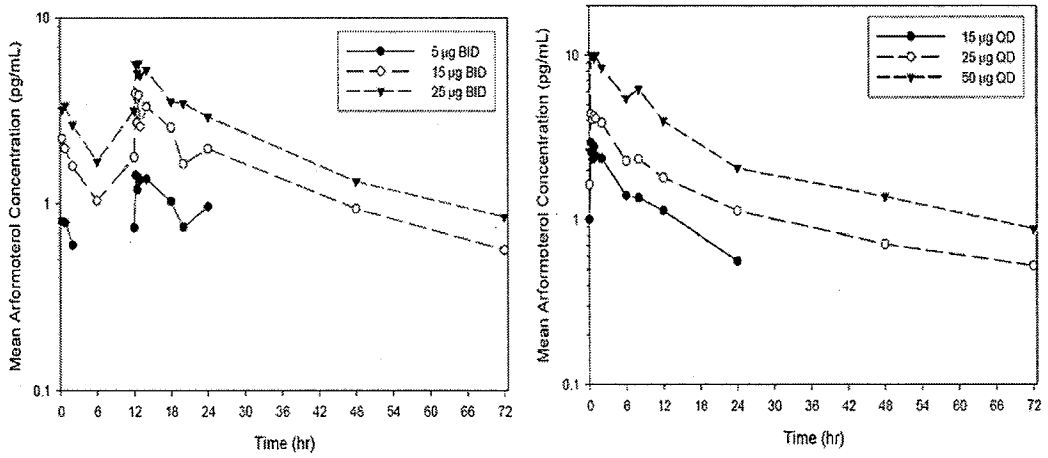


Table 3: Mean (SD) Steady-State Plasma Arformoterol PK Parameters After Multiple BID Doses of Arformoterol for 14 Days in Subjects with COPD in Part A of the Study

Parameter	ARF 5 µg BID N=54	ARF 15 µg BID N=54	ARF 25 µg BID N=53
C_{max} (pg/mL)	n=44 1.9 (1.0)	n=49 4.3 (2.7)	n=48 7.0 (4.2)
$AUC_{(0-t)}$[1] (hr*pg/mL)	n=36 16.6 (8.1)	n=44 34.5 (18.5)	n=45 50.5 (26.5)
$AUC_{(0-24)}$ (hr*pg/mL)	n=36 32.9 (18.1)	n=44 69.0 (37.0)	n=45 102 (49.4)
t_{max}[2] (hr)	n=44 0.71 (0 - 2.25)	n=49 0.57 (0.32 - 8.23)	n=48 0.86 (0 - 8.20)
$t_{1/2}$ (hr)	n=15 18.3 (9.4)	n=35 25.6 (11.1)	n=34 25.2 (8.6)

[1] $AUC_{(0-t)} = AUC_{(0-12)}$

[2] t_{max} reported as median (min-max).

Note: Tabulated values have been rounded to 3 significant figures for presentation.

Cross-reference: Part A, Table 14.2.58 and Ad Hoc Listing 16.2.6.7.1.

Table 4: Mean (SD) Steady-State Plasma Arformoterol PK Parameters After Multiple QD Doses of Arformoterol for 14 Days in Subjects with COPD in Part B of the Study

Treatment/ Parameter	ARF 15 µg QD N=48	ARF 25 µg QD N=47	ARF 50 µg QD N=47
C_{max} (pg/mL)	n=44 3.5 (2.0)	n=44 5.2 (3.4)	n=43 11.7 (6.6)
$AUC_{(0-t)}$[1] (hr*pg/mL)	n=26 40.7 (13.3)	n=35 59.5 (33.0)	n=41 110 (52.5)
t_{max}[2] (hr)	n=44 0.90 (0 - 12.2)	n=44 0.92 (0 - 12.3)	n=43 0.92 (0.33 - 8.30)
$t_{1/2}$ (hr)	n=23 22.7 (17.3)	n=21 17.9 (7.3)	n=28 28.5 (12.7)

[1] $AUC_{(0-t)} = AUC_{(0-24)}$

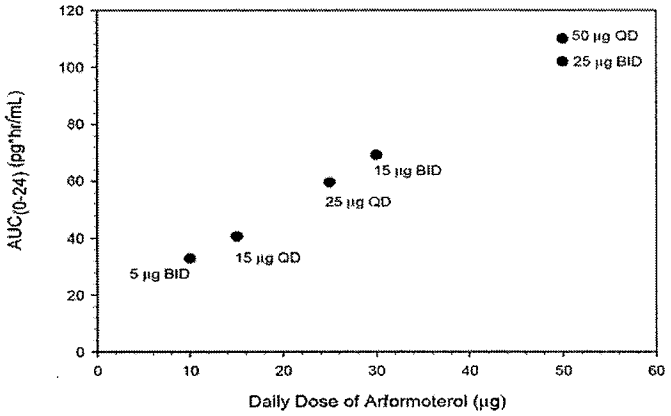
[2] t_{max} reported as median (min-max)

Note: Tabulated values have been rounded to 3 significant figures for presentation.

Reference: Part B, Table 14.2.58 and Ad Hoc Listing 16.2.6.7.1.

Figure 4 presents the relationship between AUC_{0-24h} and total daily dose and it suggested that the exposure with dose was nearly dose proportional.

Figure 4: Daily Exposure (AUC_{0-24}) Versus Daily Arformoterol Dose in Subjects with COPD Receiving Multiple Inhaled BID Doses of 5, 15, or 25 µg Arformoterol or Multiple Inhaled Doses of 15, 25, or 50 µg for 14 Days in Parts A and B of the Study



PK Conclusion:

- Median tmax values ranged from 0.6 to 0.9 hours across all 3 dose levels after BID or QD dosing.
- A mean $t_{1/2}$ of 17.9 to 28.5 hours for arformoterol was observed across all treatments.
- The change in systemic exposure to arformoterol with the daily dose was nearly dose proportional.
- Based upon mean concentrations at 0.75 hours postdose (approximate tmax), the steady-state accumulation index was 1.71 to 1.84 with BID doses and 1.07 to 1.34 with QD doses.

Note: PK/PD (efficacy and safety) relationship was evaluated by the phamacometric reviewer.