4.3. Pharmacometric Review

Office of Clinical Pharmacology
Pharmacometrics

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Summary

Chronic obstructive pulmonary disease (COPD) is a widespread health problem in the United States, affecting nearly 14 million individuals. Arformoterol is a highly selective, potent and long-acting beta2-adrenoceptor agonist. Sponsor evaluated the effects 5, 15 and 25 µg BID in Phase 2 studies along with 15µg BID, 25 µg BID and 50 µg QD in pivotal trials on FEV_1. Sponsor conducted exposure-response analysis using population PK-PD approach. Effects of various covariates were tested for their clinical significance. There was no covariate identified that would result in dose adjustment. Based on overall safety and effectiveness, sponsor proposed 15 µg BID dose as the effective dose for registration purposes.

Comments to be conveyed to sponsor

None

Introduction

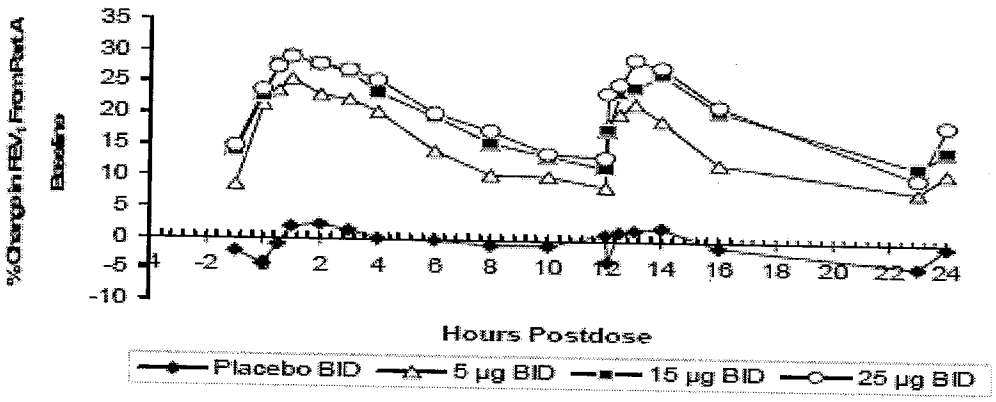
Chronic obstructive pulmonary disease (COPD) is a widespread health problem in the United States, affecting nearly 14 million individuals. Data has shown that the prevalence of this disease has increased dramatically since the early 1980s, with approximately 11% of the US population currently impacted by this disease. COPD is generally a progressive disease that is characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema. Several inhaled medications are currently approved for COPD indications in the US. These include both short- and long-acting inhaled beta-adrenergic agonists, which have all shown, to some degree, an improvement in lung function and reduction in the severity of breathlessness in COPD subjects.
Arformoterol is a selective long-acting beta2-adrenergic receptor agonist (beta2-agonist). Compared to racemic formoterol, arformoterol showed greater affinity for both beta adrenergic receptor subtypes and also greater selectivity for the beta2 receptor. Arformoterol has been extensively characterized in standard *in vivo* and *in vitro* models and has been shown to preferentially bind to beta2-adrenergic receptors.

Sponsor conducted exposure-response analysis for the data collected in Phase 2 and pivotal studies. The aim of this review is to comment on the sponsor's analysis and any labeling statements based on exposure-response analysis.

Question Based Review

1. Is there an evidence of dose/concentration-response supporting the sponsor requested approval of 15 mg BID dosing regimen?

There is evidence of dose/concentration-response relationship. Sponsor explored the effects of various dose levels and dosing regimens (BID vs QD) on FEV_1. Figure below shows the relationship between concentration and changes in FEV_1 in early dose finding (Phase 2) studies.



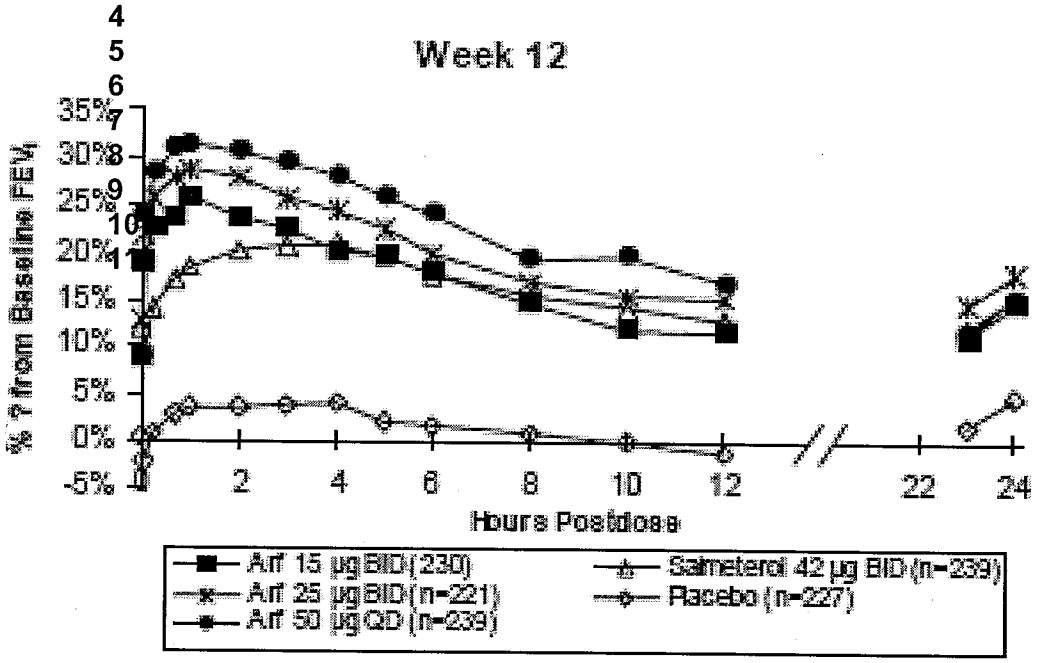
Proportion of Subjects With ≥10% and ≥15% Improvement in FEV_1 at Trough (24 Hours) After 14 Days of Double-blind Treatment in Part A of the Study

% 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.

Evaluation of the FEV1 at trough for the responders who achieved ≥10% improvement demonstrated greater efficacy for all 3 arformoterol BID doses than for placebo but showed no dose-response relationship among the 3 arformoterol BID doses. Evaluation of the FEV1 at trough for the responders who achieved ≥15% improvement corroborated the dose-response relationship among the 5, 15, and 25 µg BID doses in 24-hour postdose trough, with the percentage of responders increasing by approximately 9 percentage points with increasing arformoterol dose.

Based on the findings from Phase 2 studies, sponsor explored doses of 15, 25 ug BID and 50 ug QD in pivotal trials. Figure below shows the time course of FEV1 after 15, 25 and 50 ug BID dosing regimens in pivotal trials.



2. Are there any effects of arformoterol on QT prolongation that would be a safety risk?

No. The table below shows the effects of arformoterol on QTc prolongation by max-mean approach and concentration-QTc analysis. It can be concluded that the degree of QTc prolongation observed does not constitute a safety risk.

Dose (ug BID)	Mean (90% CI)		QTc Effect
	Concentration-QT	Max-Mean	
15	0.7 (0.5-0.9)	3.2 (0.9-5.5)	No/No
25	1.2 (0.9-1.3)	3.7 (1.5-5.9)	No/No

Sponsor's Analysis

Methods

Clinical Studies (Effectiveness)

Sponsor conducted two Phase 2, two pivotal and one long term clinical trial(s) to evaluate the potential benefit and risk in patients with COPD. The brief summary of the studies is mentioned here:

Study 091-021 (Phase 2)

- 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 (Phase 2)

- 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. There were separate randomization procedures for parts A and B with a 2-week washout period between segments. 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 $nQUC_{0\text{-}24\text{-}P}$)

Study 091-050, 091-051 (Phase 3)

- 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 with 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.

Clinical Studies (Effects on QT prolongation)

The cardiovascular safety of arformoterol was characterized using data collected from study 091-026 (Phase 2 study). Effects on cardiac repolarization, ECG abnormalities, Holter Monitor abnormalities, and cardiovascular adverse events overall. Sponsor states that they incorporated many design components of 'thorough QT study' as mentioned in Draft ICH E-14 guidance. The following is the summary of the data collected by the sponsor for characterizing the effects on QT prolongation.

Electrocardiograms were extracted at various time points throughout the dosing interval from 12-lead Holter Monitors during the baseline, post-first dose, and steady-state (after 14 days of dosing) periods for both parts of the study. Part A assessments included triplicate ECGs at 17 time points (predose and at 15 and 45 minutes and at 1, 2, 4, 6, 8, 12 hours post-first dose of study medication (pre-second dose); at 15, 30, and 45 minutes and at 1, 2, 6, 8, and 12 hours post-second dose of study medication at Visit 2 (baseline for Part A) and Visit 4 (steady-state for Part A), and Part B assessments included triplicate ECGs at 13 time points (predose and at 15, 30, and 45 minutes and at 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours postdose at Visit 5 (baseline for Part B) and Visit 7 (steady-state for Part B). Additional ECGs were obtained from the Holter Monitors at Visits 3 and 6 following the first dose of study medication for each part of the study for additional safety monitoring. A central ECG laboratory, eRT, processed and interpreted each ECG using standardized procedures. Ventricular heart rate, QT interval, P-R interval, QRS durations, R-R interval, and the QTc intervals from the central ECG over-read were analyzed.

Data Analysis

Effectiveness

Exposure-response analysis was performed using nonlinear mixed effects modeling approach. For population PK analysis a total of 6807 plasma drug concentrations from 513 subjects (Phase II + Phase III) were included.

A total of 13,316 (94.1%) FEV1 measurements from 501 subjects were included in population PK/PD analysis.

Model building (basic structural and covariate models) were built using standard approaches i.e., log-likelihood ratio, observed vs predicted plots, residual plots. For greater details please refer to the sponsor's population PK and PK/PD analysis report.

Safety

Effects on QT interval

An individual subject-specific QT interval corrected for heart rate, QTc-M, was derived from the subject baseline period interval data (QT and R-R, Parts A and B baseline periods combined) by using random coefficient linear regression methods, where QT was the dependent variable and R-R was the independent variable. The QT and R-R measurements were recorded in milliseconds. A random subject effect was included in the model in order to estimate subject-specific deviations from the population mean intercept and slope. This model generates the following QT correction formula:

$$QTc\text{-}Mij = QTij + (ß + \delta j)(1000\text{-}RRij)$$

Where ß was the estimated population mean slope (fixed effect), δj was the estimated deviation (random effect) from the population mean slope for the jth subject, and i was the ith assessment time point.
To validate the assumption of no time effect on the relationship between QT and R-R between the Part A placebo run-in period and the Part B placebo run-in period, the fixed effect of the random coefficient model, fitted separately for Part A and Part B was examined.
If a statistically significant difference was observed, QTc-M was derived separately using the Part A single-blind, placebo run-in period for Part A and the Part B single-blind, placebo run in period for Part B, and the analyses specified above were repeated.

The QTc-M (QTc corrected by individual specific baseline linear regression model) was used as the primary measure for the analysis of QT interval throughout the dosing interval. The QTc interval derived according to the Fridericia's formula (QTc-F=QT/(R-R/1000 ms)1/3) and the QTc interval derived according to the Bazett's formula (QTc-B=QT/(R-R/1000 ms)1/2) were analyzed as secondary measures.

For all ECG parameters (including QTc-M interval), the baseline for Part A was defined as the average of all 24 hours of assessments that were collected during the single-blind, placebo run-in period (Visit 2). If a subject re-took the reversibility test at Visit 2 (i.e., received a short-acting beta-agonist), the assessments that were collected within the first 12 hours were excluded from the Part A baseline calculation. The baseline for Part B was the average of all 24 hours of assessments that were collected during the Part B single-blind, placebo run-in period (Visit 5).

The mean change from baseline in the QTc intervals (QTc-M, QTc-F, and QTc-B) at steadystate was defined as the mean of changes from baseline to 12 hours post-first dose at Visit 4 for Part A and the mean change from baseline to 24 hours postdose at Visit 7 for Part B. Placebo-controlled changes were also calculated.

The maximum QTc interval change from baseline was defined as the maximum change from baseline of all assessments that were obtained after dosing. For Part A, it was the maximum change within the first 12 hours after the first dose of study medication at Visit 4. For Part B, it was the maximum change within the 24 hours after dosing at Visit 7. The QTc interval change from baseline at maximum plasma concentration was the corresponding QTc interval change at tmax.

Time-normalized area under the QTc changes from baseline curve at 24 hours (AUC0-24) were calculated for Parts A and B, using the trapezoidal rule,

The above analyses were also performed excluding the subjects who had used rescue medication during the assessment period.

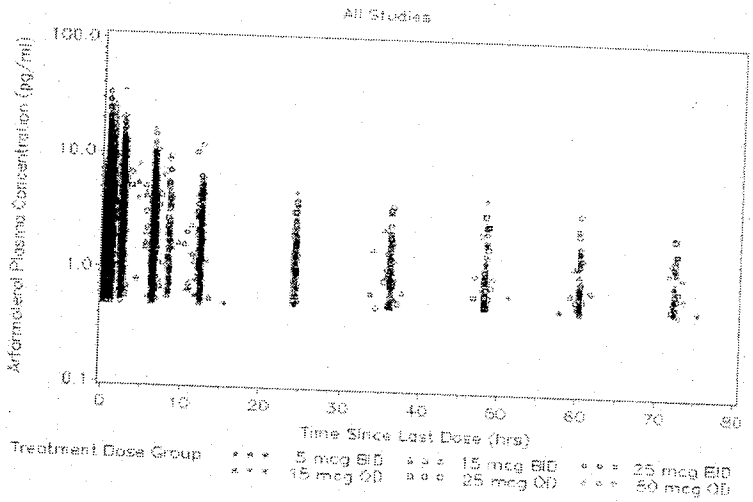
Effects on serum biomarkers

Graphical displays were generated to understand the relationship between plasma drug concentrations and changes in serum glucose, potassium levels.

Sponsor's Conclusions

Population PK model

The following figure shows the semi-logarithmic scatterplot of arformoterol concentration vs time since last dose across studies.



The table below shows the summary statistics of the subjects included in the population pharmacokinetic analysis of arformoterol.

Total Population								
Variable	N (%)	Mean	SD	Min	25th %	Median	75th %	Max
Age (years)	503	62.5	9.0	40.0	57.0	62.0	69.0	87.0
Weight (kg)	503	81.5	20.4	39.5	68.0	79.0	92.0	194.0
Height (cm)	503	170.8	10.0	142.0	163.0	171.0	178.0	194.0
Body Surface Area (m^2)	503	2.0	0.3	1.3	1.8	1.9	2.1	3.1
Creatinine Clearance (mL/min)	503	96.8	36.5	20.80	73.1	89.7	112.4	301.0
Alanine Aminotransferase (U/L)	503	22.6	9.9	6.0	16.0	21.0	26.0	72.0
Gender								
Males	295 (58.7)							
Females	208 (41.3)							
Total	503 (100.0)							
Ethnicity								
Caucasian	473 (94.0)							
Black	23 (4.6)							
Asian	3 (0.6)							
Hispanic	3 (0.6)							
Other	1 (0.2)							
Total	503 (100.0)							

The summary of the pharmacokinetic parameters is shown below:

Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
K_a (1/hr)	6.90	7.6	71.34[b] 83.31[c]	22.4 18.6
F_1	0.736	5.1	26.17	29.5
CL/F (L/hr)	427	5.1	32.40	17.2
V_c/F (L)	5510	5.3	40.25	17.2
Q (L/hr)	404	8.3	39.62	46.4
V_p/F (L)	6980	10.9	34.93	63.3
Interoccasion Variability in F_1 (%CV)			28.76	9.0
Power for body weight on V_c/F	0.532	18.2		
Power for body weight on CL/F	0.388	23.2		
Slope for body weight on Q	4.58	27.9		
Residual Variability, proportional component (%CV)	14.97	8.9		
Residual Variability, additive component (SD)	0.50	FIXED		

[a] MVOF: 5202.958

[b] Interindividual variability in K_a corresponding to the population of subjects enrolled in Study 091-026

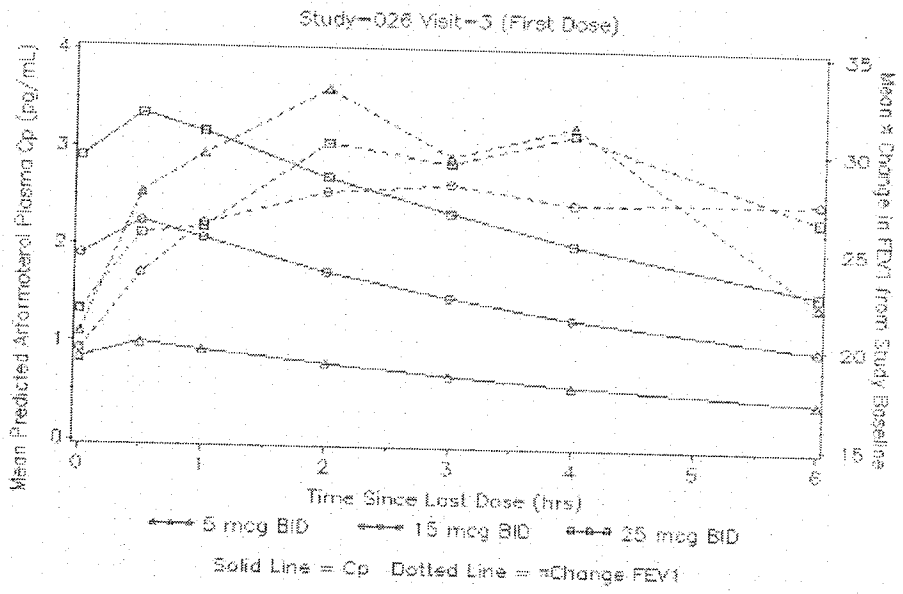
[c] Interindividual variability in K_a corresponding to the population of subjects enrolled in Studies 091-050 and 091-051

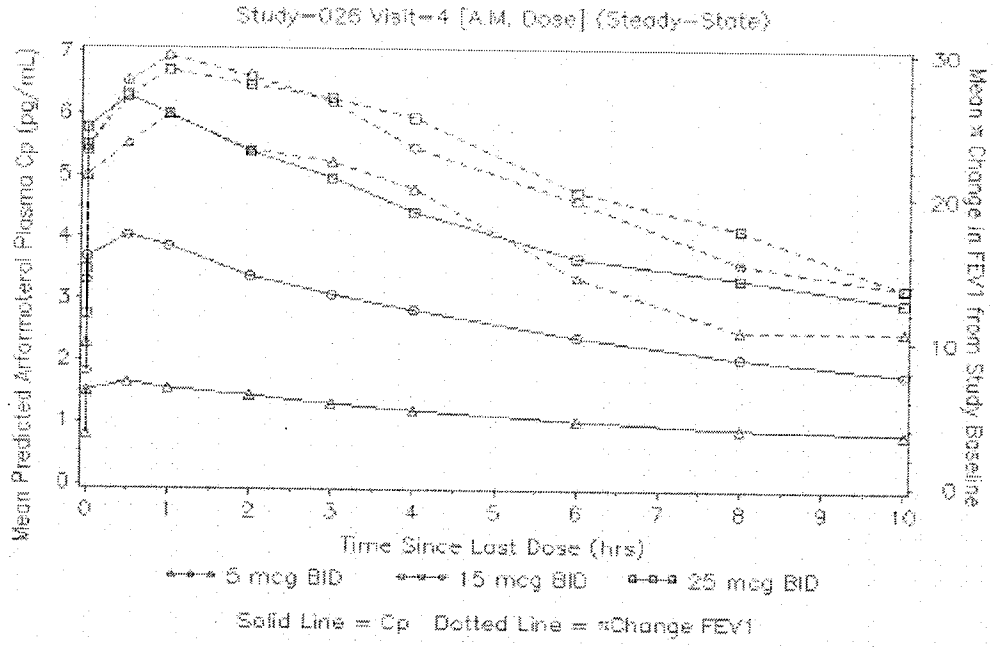
The summary of the population pharmacokinetic analysis is as follows:

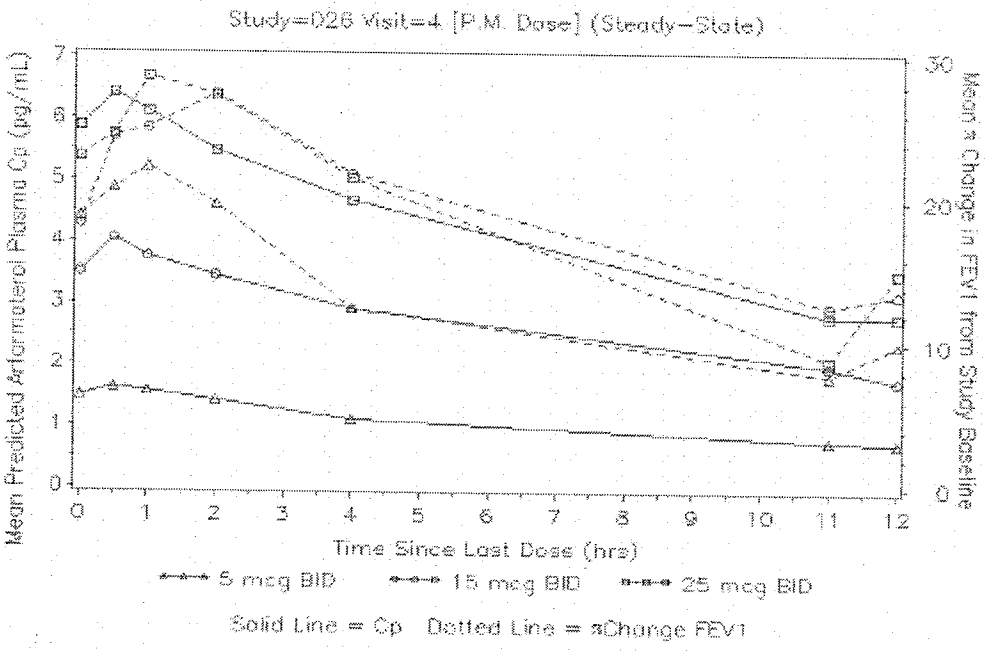
- The population pharmacokinetics of arformoterol in subjects with COPD (after nebulized administration) were linear and best described using a two compartment model with a first-order absorption process.
- Body weight (kg) was found to be a significant positive predictor of both the apparent clearance and apparent central volume of distribution. The change in CL/F with body weight was not considered 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.
- The magnitude of interindividual variability in clearance, central volume of distribution, intercompartmental clearance, and absorption rate constant was 32%, 40%, 40%, and ~77%, respectively.
- The interindividual and interoccasion (between-visit) variability in relative bioavailability for the 15 µg through 50 µg doses was 26% and 29%, respectively.
- Residual variability was notably small at ~15%.
- Examination of Bayesian estimates of AUC suggested that the pharmacokinetics were essentially dose-proportional for the range of dosing regimens evaluated.
- Model verification, based on measures of precision, suggested that the model was unbiased with a mean individual prediction error of 1.9%.

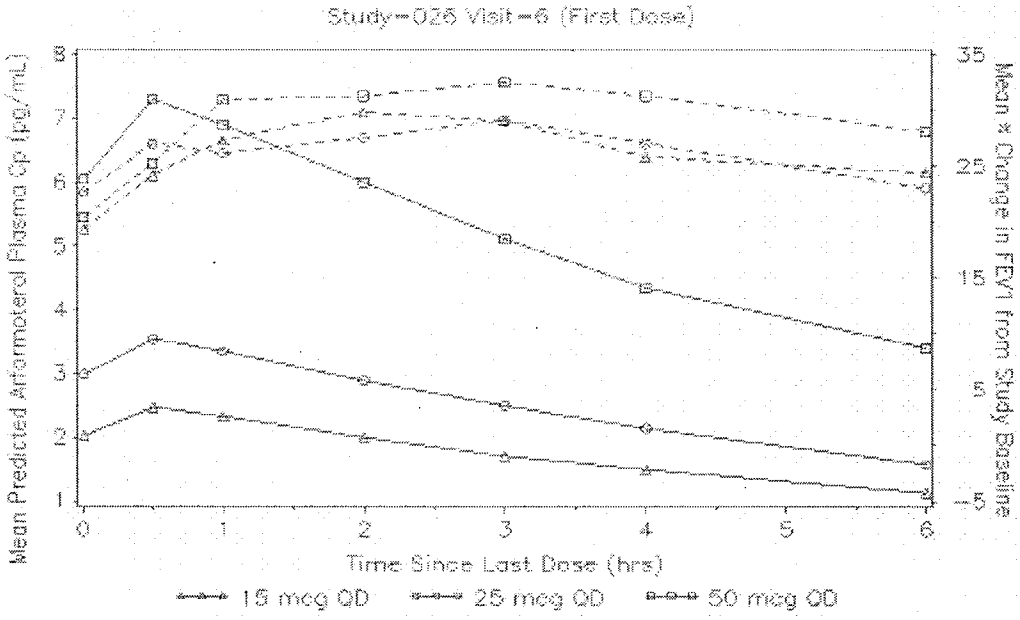
Population PK/PD model

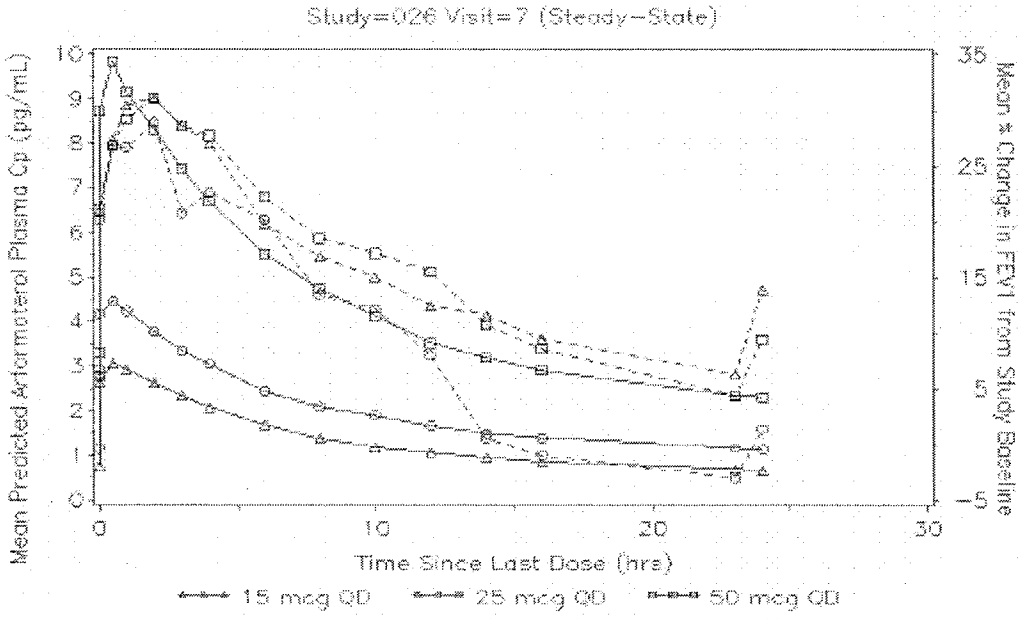
A sequential modeling process was employed for the population PK/PD analysis; the pharmacokinetics of arformoterol were established *a priori*, and then a model was fit to the pharmacodynamic data while being conditioned on PK parameter estimates derived from the population PK model. Various adaptations of pharmacodynamic Emax models were evaluated to describe the relationship between %ΔFEV1 response and arformoterol concentrations. Direct effect PK/PD models were initially constructed to characterize the exposure-response relationship. Due to some degree of model misspecification, several types of biophase distribution PK/PD link models were also assessed. The figures below show the overlay plots of mean observed %ΔFEV1 and mean predicted arformoterol plasma concentrations versus time Since last dose, stratified by study, visit, and dose. As can be seen from figures below for various visits (Study 026, 050, 051) there is a delay between drug concentrations and response after single dose, but the delay is not clearly seen at steady state due to the presence of residual drug concentrations.



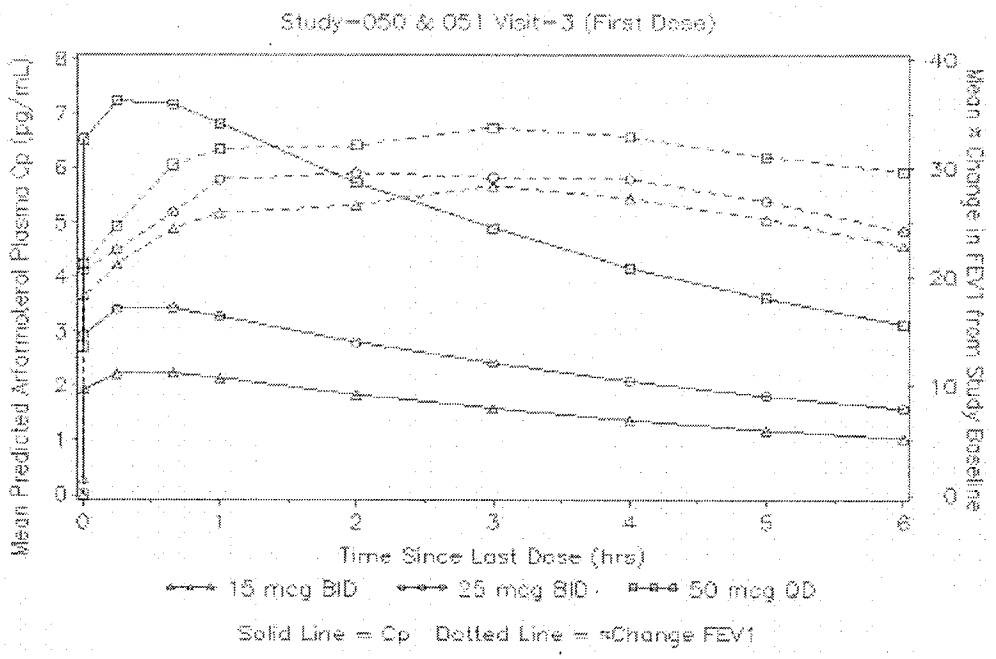


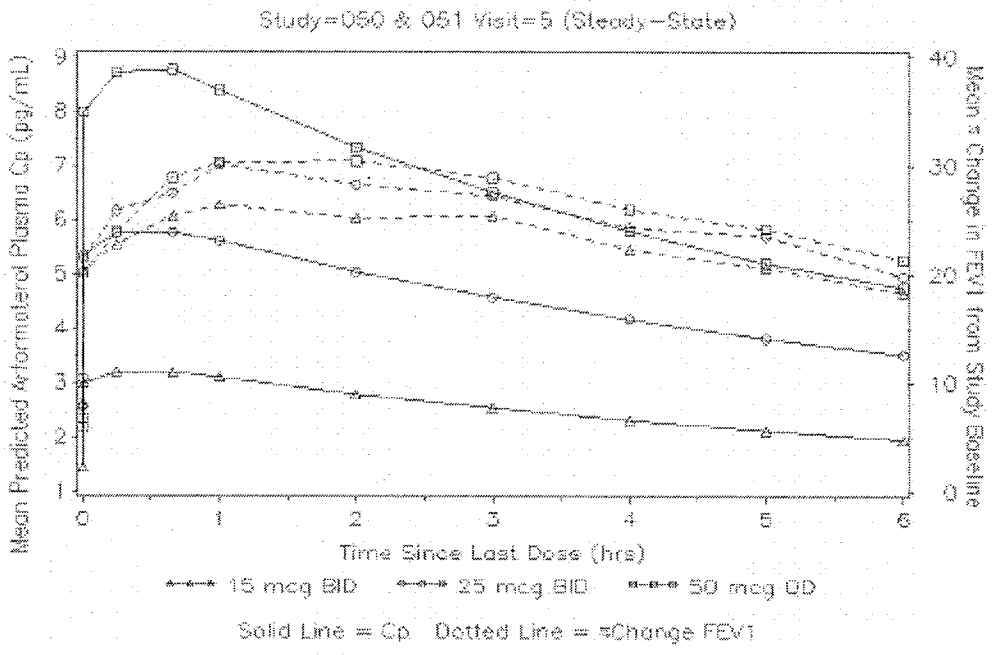


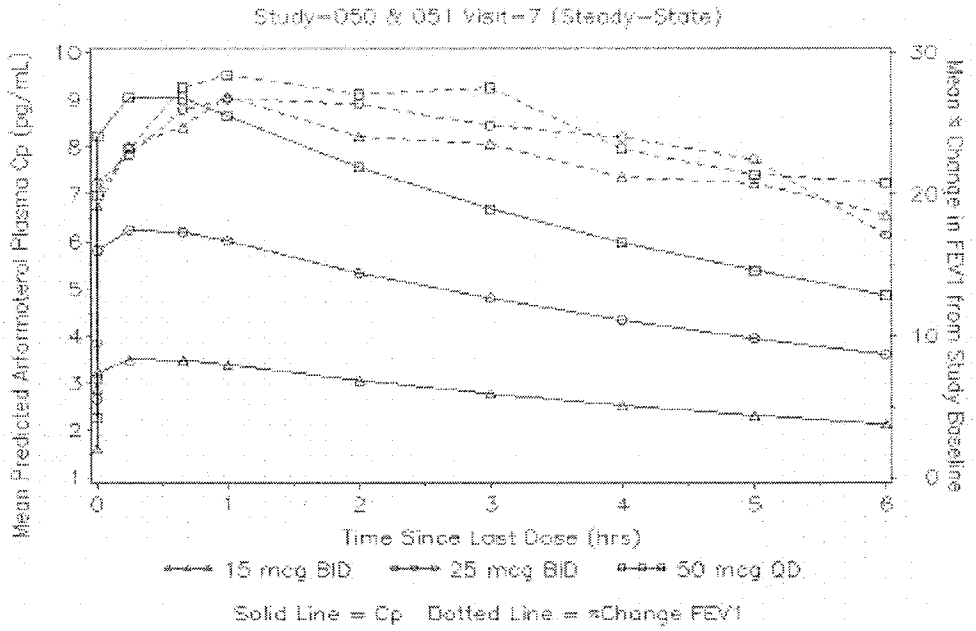




Solid Line = Cp Dotted Line = %Change FEV1







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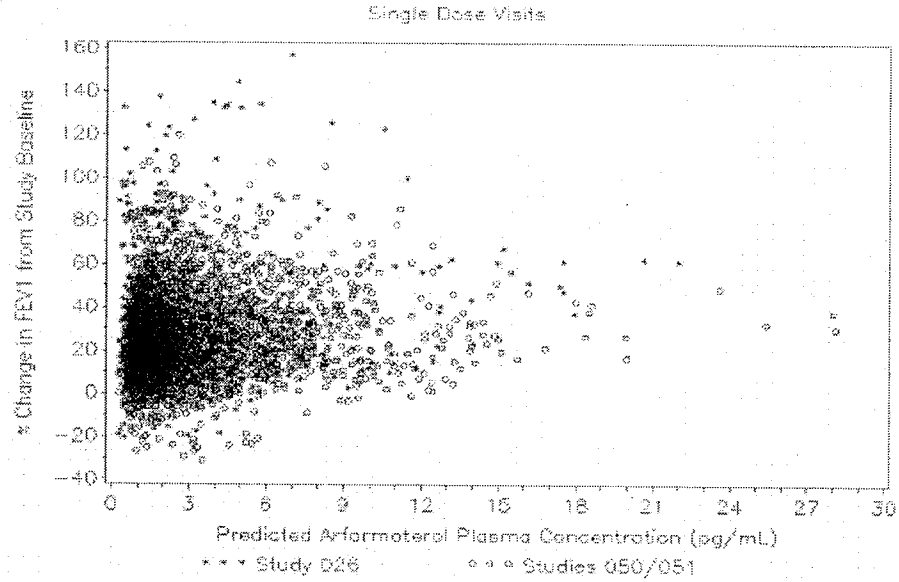
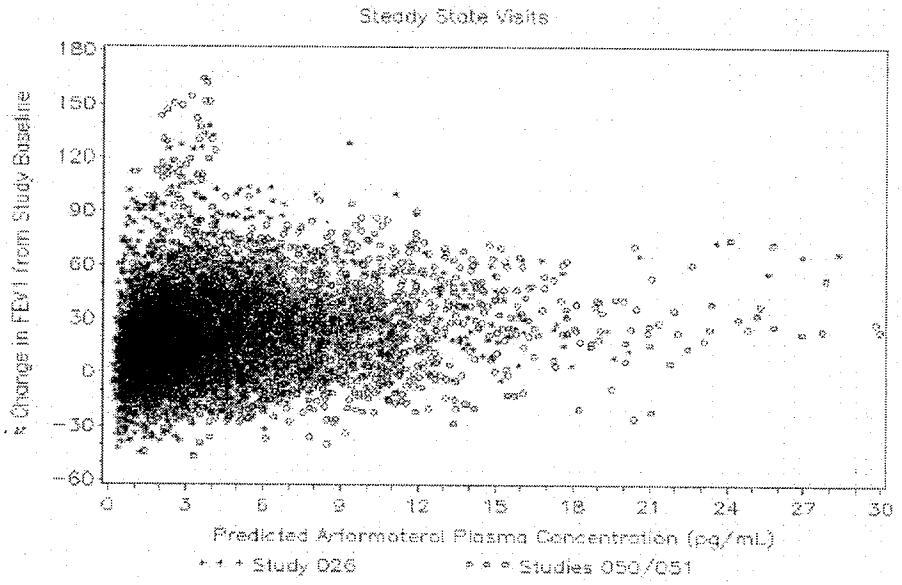
The relationship between %ΔFEV1 and predicted arformoterol plasma concentrations is shown in figure below.





The parameter estimates and standard errors for the PK/PD link model applied to single-dose are shown below.

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability	
	Population Mean	%SEM	%CV	%SEM
K_{eo} (1/hr)	1.49	12.8	125.70	12.5
E_{max}*	37.9	5.1	68.70	9.1
EC_{50} (pg/mL)	0.609	20.1	122.88	14.8
Gamma	1.00	Fixed		
Proportional RV for PK (%CV)	8.65	13.6		
Additive RV for PK	0.50	Fixed		
Additive RV for PD; Phase 2 Study 091-026 (SD)	10.10	13.0		
Additive RV for PD; Phase 3 Studies 091-050 and 091-051 (SD)	6.63	6.2		

*E_{max} is expressed in % change in FEV_1 score from study baseline.

The parameter estimates and standard errors for the PK/PD link model applied to steady state data are shown below.

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability	
	Population Mean	%SEM	%CV	%SEM
K_{eo} (1/hr)	3.78	10.8	94.97	21.6
E_{max}*	54.9	8.5	82.10	11.0
EC_{50} (pg/mL)	5.23	14.3	120.83	17.5
Gamma	1.0	Fixed		
Proportional RV for PK (%CV)	14.42	10.8		
Additive RV for PK	0.50	Fixed		
Additive RV for PD: Phase 2 Study 091-026 (SD)	13.78	11.5		
Additive RV for PD; Phase 3 Studies 091-050 and 091-051 (SD)	10.10	8.3		

*E_{max} is expressed in % change in FEV_1 score from study baseline.

The following are the conclusions derived by the sponsor:

- A population PK/PD model was developed that adequately described a clear exposure - response relationship between predicted arformoterol plasma concentration and %ΔFEV1 from study baseline.
- A biophase distribution PK/PD link model was necessary to account for the hysteresis between the time course of arformoterol plasma concentration and %ΔFEV1 through the estimation of a keo.
- Considerable interindividual 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 estimate of keo was larger (3.78 hr^{-1}) during steady-state compared to single-dose (1.49 hr^{-1}), suggesting a diminution in the half-life delay for the onset of observed pharmacologic effect. This is indicative of a fairly 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 at baseline upon model estimates of EC50 at steady-state.

Reviewer Comments

No comments. There are no major issues with the analysis.

Effects on QT prolongation

Several metrics were evaluated by the sponsor to show that arfomorterol does not prolong QT in comparison to placebo which are discussed below:

Average QTc interval changes

Table below summarizes the steady-state (following 14 days of treatment) change in QTc-M averaged over the first 12 hours in Part A (Visit 4) and averaged over 24 hours in Part B (Visit 7) of the study.

PART A				
Change From Baseline (ms)[1,2]	Placebo BID N=54	ARF 5 µg BID N=54	ARF 15 µg BID N=54	ARF 25 µg BID N=53
ALL SUBJECTS				
n	47	48	51	47
Mean (SD)	-2.9 (8.2)	-3.3 (11.0)	-0.2 (8.9)	-2.2 (10.5)
Placebo-corrected Change (95% CI)[3]		-0.4 (-4.4, 3.5)	2.7 (-1.2, 6.6)	0.7 (-3.3, 4.6)
EXCLUDING SUBJECTS WHO RECEIVED IN-CLINIC RESCUE MEDICATION				
n	27	38	43	38
Mean (SD)	-1.0 (8.5)	-3.1 (11.1)	-0.3 (9.1)	-1.6 (11.0)
Placebo-corrected Change (95% CI)[3]		-2.1 (-7.1, 2.9)	0.8 (-4.1, 5.6)	-0.6 (-5.6, 4.4)
PART B				
Change From Baseline (ms)[1,2]	Placebo QD N=49	ARF 15 µg QD N=48	ARF 25 µg QD N=47	ARF 50 µg QD N=47
ALL SUBJECTS				
n	46	46	44	43
Mean (SD)	1.4 (7.5)	-0.4 (6.3)	0.6 (8.0)	0.9 (7.7)
Placebo-corrected Change (95% CI)[3]		-1.8 (-4.8, 1.3)	-0.8 (-3.9, 2.3)	-0.5 (-3.6, 2.6)
EXCLUDING SUBJECTS WHO RECEIVED IN-CLINIC RESCUE MEDICATION				
n	28	36	26	31
Mean (SD)	2.5 (8.0)	0.4 (6.5)	2.0 (9.7)	0.4 (8.7)
Placebo-corrected Change (95% CI)[3]		-2.1 (-6.2, 2.0)	-0.6 (-5.0, 3.9)	-2.1 (-6.3, 2.1)

1 Electrocardiograms were centrally over-read by a licensed cardiologist.

2 Baseline was calculated as the average of values collected during the single-blind period for each subject (Visit 2 for Part A and Visit 5 for Part B). The mean change from baseline was calculated by averaging each subject's changes from baseline at each time point during the first 12 hours postdose in Part A and 24 hours postdose in Part B.

3 A placebo-corrected change is defined as the difference between the arformoterol and placebo doses.

The mean change in QTc-M averaged over the 12-hour dosing interval (BID dosing) or 24-hour dosing interval (QD dosing) indicates no effect of arformoterol on cardiac repolarization either when all subjects are included in the analysis or when subjects who used in-clinic rescue medication are excluded from the analysis. When the data are corrected for placebo response, the conclusion is the same, with all mean placebo-corrected changes ≤2.7 msec and the upper limit of the 95% CIs all <7 msec.

Maximum Change in QTc

Table below summarizes the maximum change from baseline (after 14 days of doubleblind treatment) in QTc-M over 12 hours in Part A (Visit 4) and over 24 hours in Part B (Visit 7) of the study.

PART A				
Maximum Change From Baseline (ms)[1,2]	**Placebo BID N=54**	**ARF 5 µg BID N=54**	**ARF 15 µg BID N=54**	**ARF 25 µg BID N=53**
ALL SUBJECTS				
n	47	48	51	48
Mean (SD)	15.4 (10.5)	16.5 (13.0)	17.3 (9.6)	15.7 (13.2)
Median	13.1	14.4	17.9	15.0
25th, 75th Percentiles	8.2, 19.5	7.0, 26.4	10.1, 23.8	9.5, 24.1
10th, 90th Percentiles	4.4, 27.3	1.8, 35.4	4.9, 28.1	4.0, 30.0
95% CI[3]	12.3, 18.5	12.7, 20.3	14.6, 20.0	11.9, 19.5
EXCLUDING SUBJECTS WHO RECEIVED IN-CLINIC RESCUE MEDICATION				
n	20	32	39	34
Mean (SD)	14.7 (9.6)	17.7 (13.8)	16.6 (10.1)	16.1 (13.2)
Median	13.0	17.4	17.9	15.1
25th, 75th Percentiles	7.1, 20.1	6.4, 29.0	8.6, 25.7	11.0, 26.8
10th, 90th Percentiles	4.1, 29.1	1.8, 35.4	2.4, 28.1	4.0, 30.0
95% CI[3]	10.2, 19.2	12.7, 22.7	13.3, 19.8	11.5, 20.7
PART B				
Maximum Change From Baseline (ms)[1,2]	**Placebo QD N=49**	**ARF 15 µg QD N=48**	**ARF 25 µg QD N=47**	**ARF 50 µg QD N=47**
ALL SUBJECTS				
n	46	46	44	43
Mean (SD)	16.9 (12.3)	15.1 (8.2)	15.7 (9.8)	16.2 (9.1)
Median	15.5	13.5	15.5	14.0
25th, 75th Percentiles	9.3, 22.8	8.7, 21.6	9.8, 21.2	10.4, 20.9
10th, 90th Percentiles	4.5, 27.2	6.0, 27.0	5.1, 25.7	6.9, 26.9
95% CI[3]	13.2, 20.6	12.6, 17.5	12.8, 18.7	13.3, 19.0
EXCLUDING SUBJECTS WHO RECEIVED IN-CLINIC RESCUE MEDICATION				
n	28	36	26	31
Mean (SD)	18.8 (14.0)	15.6 (8.3)	16.6 (10.7)	16.4 (10.1)
Median	16.3	14.0	16.6	14.2
25th, 75th Percentiles	12.0, 23.1	8.8, 22.1	10.8, 20.9	9.0, 21.5
10th, 90th Percentiles	4.5, 38.6	6.0, 27.0	2.4, 27.3	4.5, 26.9
95% CI[3]	13.3, 24.2	12.8, 18.4	12.3, 20.9	12.7, 20.1

1 Electrocardiograms were centrally over-read by a licensed cardiologist.

2 Baseline was calculated as the average of values collected during the single-blind period for each subject (Visit 2 for Part A and Visit 5 for Part B).

3 95% confidence interval of the mean change.

The maximum change in QTc-M was comparable between the placebo and arformoterol BID and QD groups, with no consistent dose-response relationship observed across the 3 arformoterol BID or 3 arformoterol QD doses either when all subjects were included in the analysis or when subjects who received in-clinic rescue medication were excluded from the analysis.

QTc at tmax

Table below summarizes the change from baseline in QTc-M at tmax for Parts A and B of the study.

PART A				
Change From Baseline in QT_{c-M} at t_{max} (ms)[1,2]	Placebo BID N=54	ARF 5 µg BID N=54	ARF 15 µg BID N=54	ARF 25 µg BID N=53
ALL SUBJECTS				
n	45	29	42	40
Mean (SD)	-0.4 (12.1)	-8.0 (14.6)	0.7 (11.4)	-2.8 (12.8)
Median	-1.3	-6.1	0.0	-2.2
25th, 75th Percentiles	-5.8, 5.6	-13.4, 2.0	-4.4, 7.0	-9.3, 5.8
10th, 90th Percentiles	-10.7, 17.1	-27.2, 9.1	-13.5, 16.4	-16.0, 12.6
95% CI[3]	-4.1, 3.2	-13.5, -2.4	-2.9, 4.2	-6.9, 1.3
EXCLUDING SUBJECTS WHO RECEIVED IN-CLINIC RESCUE MEDICATION				
n	19	22	34	29
Mean (SD)	-1.8 (10.8)	-7.6 (16.0)	0.5 (11.7)	-2.5 (14.0)
Median	-2.1	-5.5	0.1	-1.3
25th, 75th Percentiles	-6.0, 5.6	-14.0, 3.1	-7.6, 7.1	-9.2, 6.1
10th, 90th Percentiles	-15.6, 10.8	-21.9, 9.1	-14.9, 16.4	-17.6, 14.9
95% CI[3]	-7.0, 3.4	-14.6, -0.5	-3.6, 4.6	-7.9, 2.8
PART B				
Change From Baseline in QT_{c-M} at t_{max} (ms)[1,2]	Placebo QD N=49	ARF 15 µg QD N=48	ARF 25 µg QD N=47	ARF 50 µg QD N=47
ALL SUBJECTS				
n	44	39	34	31
Mean (SD)	-1.7 (10.7)	-4.3 (11.2)	-1.1 (12.5)	-2.7 (12.0)
Median	-1.9	-5.7	0.1	-2.0
25th, 75th Percentiles	-6.4, 4.9	-11.3, 3.1	-8.0, 5.5	-10.7, 5.7
10th, 90th Percentiles	-14.9, 9.6	-20.0, 10.7	-18.6, 11.0	-18.5, 10.2
95% CI[3]	-4.9, 1.5	-7.9, -0.7	-5.4, 3.3	-7.1, 1.7
EXCLUDING SUBJECTS WHO RECEIVED IN-CLINIC RESCUE MEDICATION				
n	28	29	22	21
Mean (SD)	-2.1 (10.1)	-3.3 (11.5)	1.1 (13.7)	-4.3 (13.3)
Median	-1.9	-3.4	2.6	-5.2
25th, 75th Percentiles	-6.1, 4.4	-9.6, 3.3	-8.0, 7.5	-13.0, 5.5
10th, 90th Percentiles	-14.9, 9.4	-20.0, 10.7	-18.6, 17.9	-21.2, 10.2
95% CI[3]	-6.0, 1.9	-7.7, 1.1	-5.0, 7.2	-10.4, 1.7

1 For each subject, the time-matched QTc change from baseline at tmax was computed. Because the QTc change from baseline at tmax is not available for placebo, the mode of the tmax for the 3 arformoterol dose groups was used (e.g., 15 minutes postdose)

2 Baseline was calculated as the average of values collected during the single-blind period for each subject (Visit 2 for Part A and Visit 5 for Part B).

3 95% confidence interval of the mean change from baseline at tmax.

There was no increase in QTc-M at tmax across the 3 arformoterol BID or 3 arformoterol QD doses tested when all subjects were included in the analysis or when subjects who received in-clinic rescue medication were excluded from the analysis.

Categorical Analyses

Table below summarizes the percentage of subjects with categorical QTc-M changes from baseline after 14 days of double-blind treatment in Part A (Visit 4) and Part B (Visit 7) of the study.

PART A				
	Placebo BID N=54 n (%)	ARF 5 µg BID N=54 n (%)	ARF 15 µg BID N=54 n (%)	ARF 25 µg BID N=53 n (%)
ALL SUBJECTS				
QT_{c-M} >450 ms at any postdose time point[1]	1 (1.9)	5 (9.3)	4 (7.4)	4 (7.4)
QT_{c-M} >500 ms at any postdose time point[2]	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)
Change in QT_{c-M} ≥60 ms at any postdose time point	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Change in QT_{c-M} ≥30 ms at any postdose time point but <60 ms at all time points	4 (7.4)	9 (16.7)	4 (7.4)	5 (9.4)
EXCLUDING SUBJECTS WHO RECEIVED IN-CLINIC RESCUE MEDICATION				
QT_{c-M} >450 ms at any postdose time point[1]	1 (1.9)	3 (5.6)	3 (5.6)	5 (7.5)
QT_{c-M} >500 ms at any postdose time point[2]	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)
Change in QT_{c-M} ≥60 ms at any postdose time point	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Change in QT_{c-M} ≥30 ms at any postdose time point but <60 ms at all time points	2 (3.7)	7 (13.0)	2 (3.7)	4 (7.5)
PART B				
	Placebo QD N=49 n (%)	ARF 15 µg QD N=48 n (%)	ARF 25 µg QD N=47 n (%)	ARF 50 µg QD N=47 n (%)
ALL SUBJECTS				
QT_{c-M} >450 ms at any postdose time point[1]	5 (10.2)	2 (4.2)	3 (6.4)	4 (8.5)
QT_{c-M} >500 ms at any postdose time point[2]	0 (0.0)	1 (2.1)	0 (0.0)	1 (2.1)
Change in QT_{c-M} ≥60 ms at any postdose time point	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Change in QT_{c-M} ≥30 ms at any postdose time point but <60 ms at all time points	2 (4.1)	5 (10.4)	4 (8.5)	2 (4.3)
EXCLUDING SUBJECTS WHO RECEIVED IN-CLINIC RESCUE MEDICATION				
QT_{c-M} >450 ms at any postdose time point[1]	3 (6.1)	1 (2.1)	3 (6.4)	4 (8.5)
QT_{c-M} >500 ms at any postdose time point[2]	0 (0.0)	1 (2.1)	0 (0.0)	1 (2.1)
Change in QT_{c-M} ≥60 ms at any postdose time point	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Change in QT_{c-M} ≥30 ms at any postdose time point but <60 ms at all time points	2 (4.1)	5 (10.4)	3 (6.4)	2 (4.3)

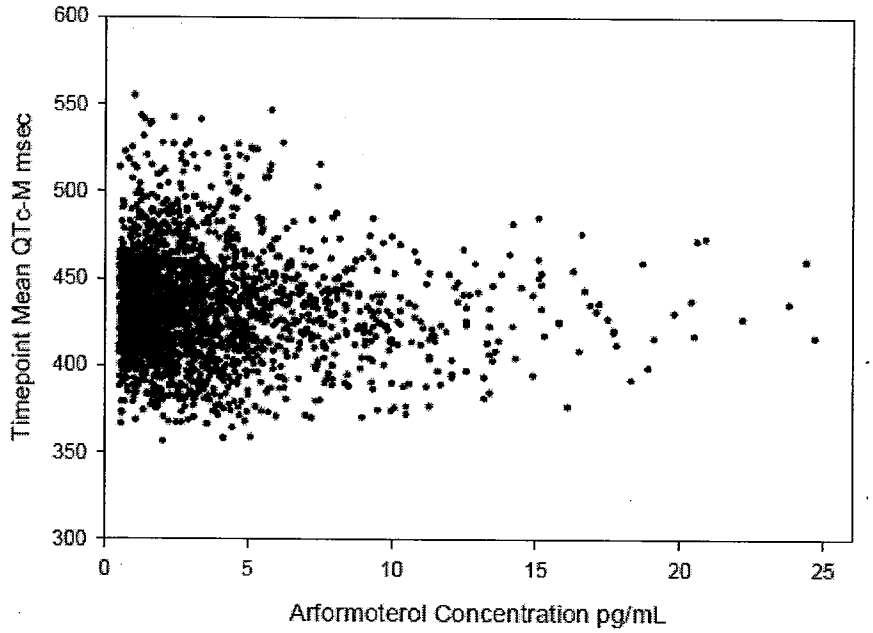
[1] Subjects who had QT_{c-M} values of >450 ms at baseline were excluded; subjects who had more than one postdose QT_{c-M} value of >450 ms were counted once.

[2] Subjects who had QT_{c-M} values of >500 ms at baseline were excluded; subjects who had more than one postdose QT_{c-M} value of >500 ms were counted once.

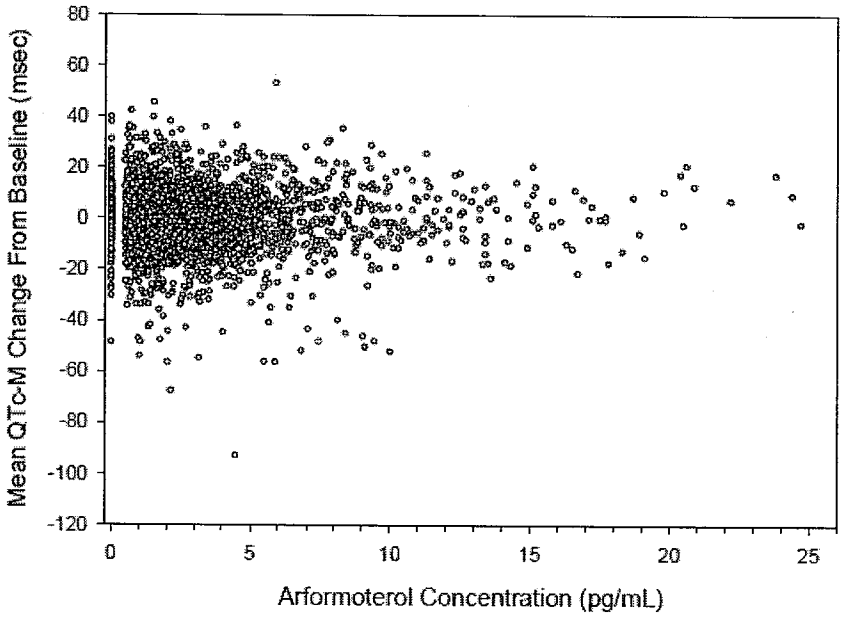
Although the rates of subjects with a QTc-M >450 ms postdose were higher in all of the arformoterol BID dose groups than in the placebo BID dose group, this trend was not observed in Part B of the study in which the rates in all of the arformoterol QD dose groups were lower than in the placebo QD group. Therefore, no consistent dose-related increase was observed across the arformoterol BID or QD doses in the proportion of outliers based on QTc-M.

Scatterplot of Time-matched Individual Mean QTc-M With Plasma Concentration

Figure below displays time-matched individual mean QTc-M intervals by plasma concentration (excluding placebo and pretreatment values).



Note: All mean QT_{cM} values at Visit 4 (after 14 days of double-blind treatment in Part A) and at Visit 7 (after 14 days of double-blind treatment in Part B) were displayed for subjects who received arformoterol 5, 15, or 25 µg BID in Part A of the study and for subjects who received arformoterol 15, 25, or 50 µg in Part B of the study; data were not displayed for subjects who received placebo in either Part A or B of the study.



The sponsor concluded that visual inspection of the above plot suggested no association of prolonged QTc with plasma concentration.

Effects on serum biomarkers

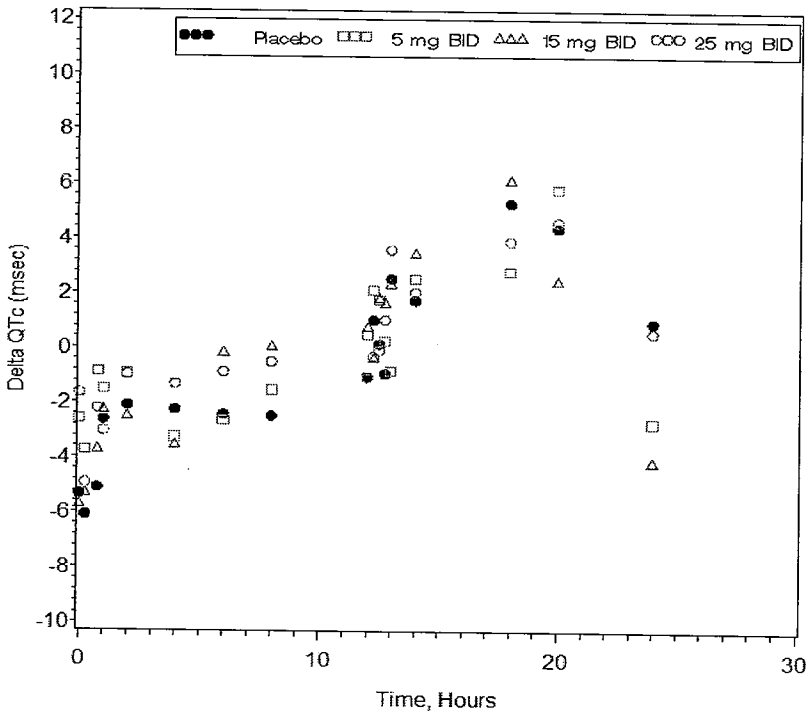
The sponsor states that dose-related decreases in serum potassium and increases in serum glucose were observed at higher doses (50 µg QD), but there was no clear visual trend with plasma arformoterol concentrations. The lack of a relationship between concentration and these effects may be attributed,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

Reviewer Comments

The analysis performed by the sponsor is not same as that proposed in E14 guidance. The sponsor reported results which reflect "Mean of the Maximum QTc prolongation" instead of "Maximum of Mean QTc prolongation". Since the current application is for an enantiomer of a racemic mixture which is already in market, it was decided to infer any effects on QTc prolongation using concentration-QTc relationship. The sponsor "visually" concluded that there are no effects on QTc prolongation. The reviewer however, performed mixed-effects analysis of the QTc (Individual corrected) data submitted by the sponsor (also referred as QTcM by sponsor).

Reviewer's Analysis

Figure below shows the mean QTc effects (change from baseline) in placebo, 5 mg BID, 15 mg BID and 25 mg BID dose groups. There are no differences in effects between the three dose groups.

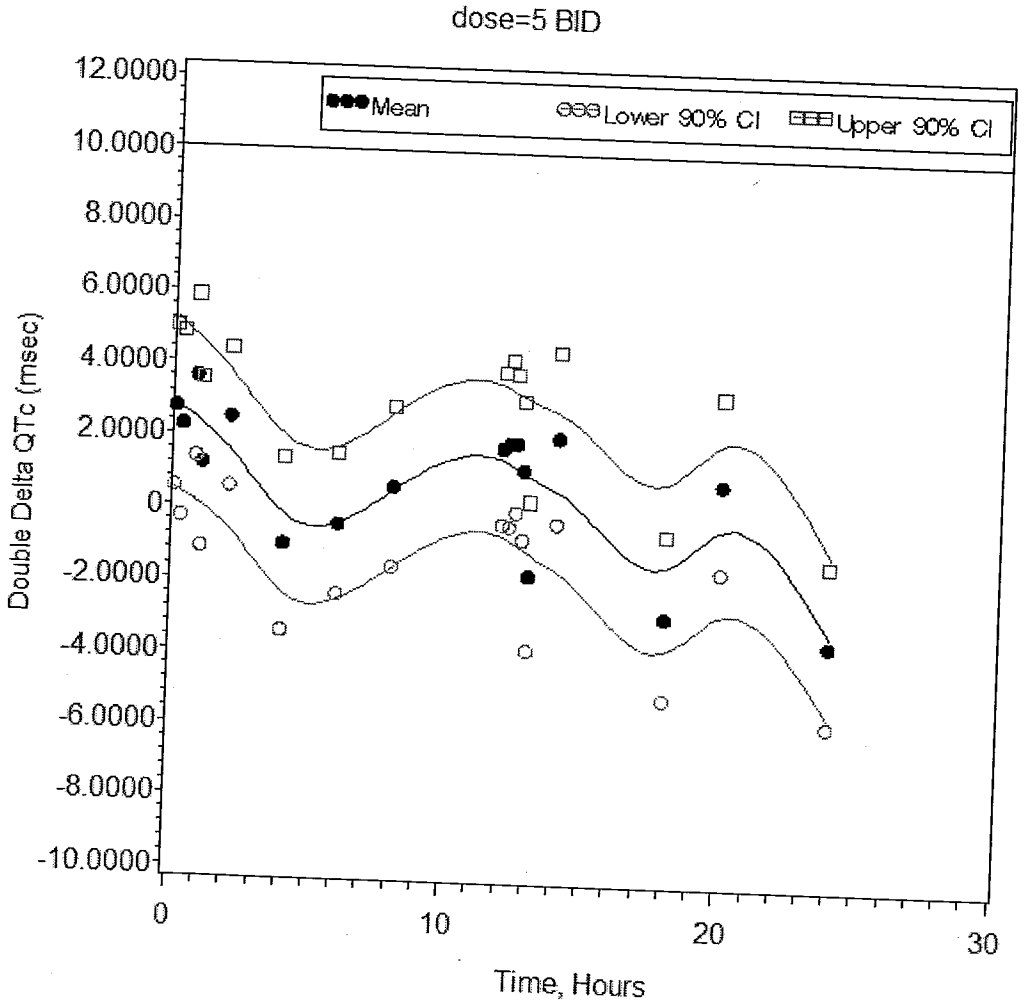


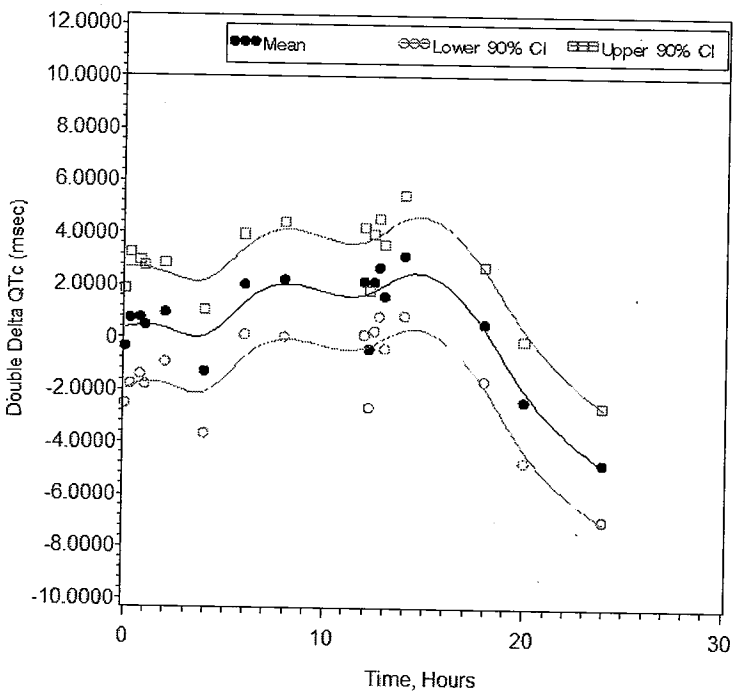
Two types of analysis were conducted:

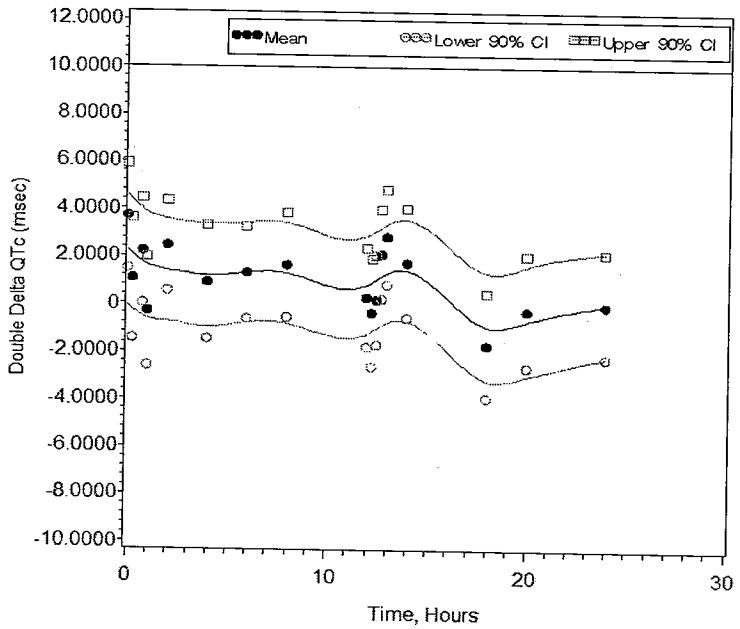
1. Analysis as mentioned in E14 guidance using SAS (Ver 8.02)
2. Concentration effect analysis using NONMEM (Ver V).

1. Analysis as mentioned in E14 guidance

Based on the data submitted by the sponsor, mean QTc prolongation in placebo group were calculated. The placebo effects were subtracted from baseline corrected QTc values and the data was analyzed using PROC MIXED in SAS. LSMEANS were computed at each time using time*treatment interaction. 90% CI were computed and the results are shown in Figure below. As can be seen in figures below the upper 90% CI does not include 10 msec indicating that the arformoterol does not prolong QT after 5 mg BID, 15 mg BID or 25 mg BID.





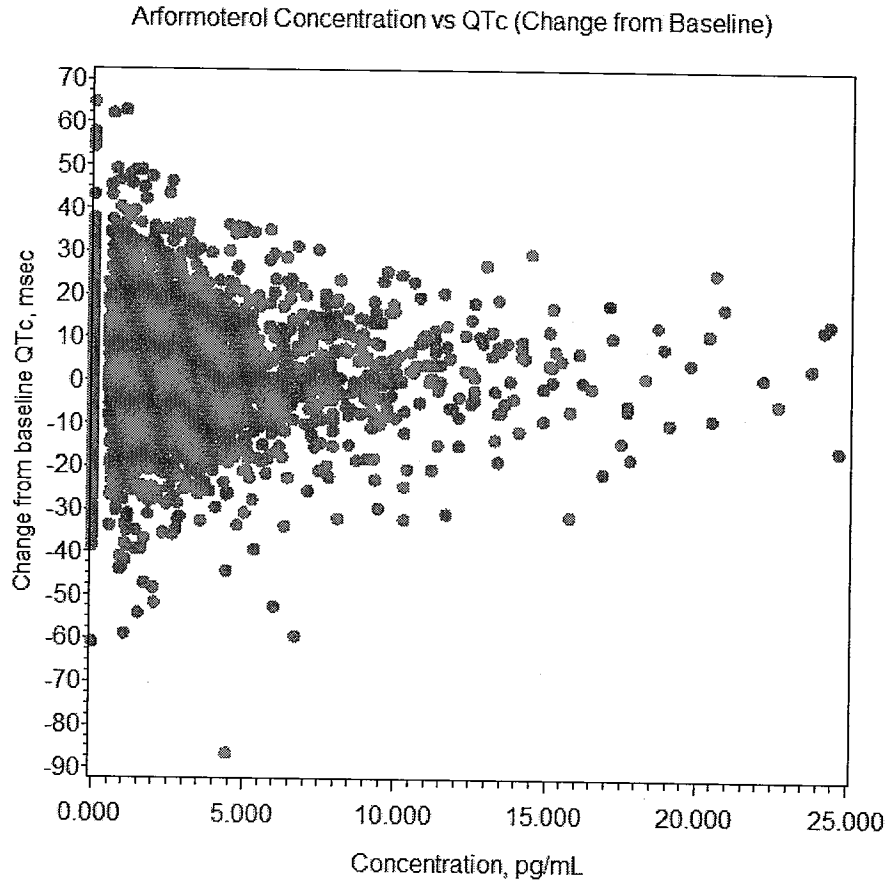


The SAS code used for data analysis is shown below:

```
proc mixed data=trt_placebo1;
   class dose time usubjid;
   model ddelta=dose time dose*time /ddfm=SATTERTH;;
   repeated time/sub=usubjid(dose) type=un;;
   lsmeans dose*time/ alpha=0.10;
   make 'LSMEANS' out=lsmeans; /*Saves the lsmeans in a data set
*/
   title1 "LSmean for QT data";
run;
```

2. Concentration-QT analysis

Figure below shows the relationship between arformoterol concentrations and QTc data (Individual corrected Change from baseline).



Time matched concentration-QT analysis was performed using NONMEM®. A linear model was used to describe the relationship between individual corrected QTc and concentrations. Although the model converged, it was not possible to estimate the standard errors of slope and intercept. However, upon fixing the estimate of interindividual variability of intercept, it was possible to estimate the standard errors. It is not clear what impact fixing the variability of intercept would have on other parameters. The reviewer also attempted to determine the confidence intervals using log-likelihood profiling, but the profiling was also unsuccessful. Attempts were made at estimating standard errors by varying the significant digits, estimation methods, but none of them were successful. However, the variance-covariance matrix was obtainable using linear mixed effects in SPLUS. The estimates of the parameters and their standard errors (SE) are shown in table below:

Parameter	Estimate (SE)	Interindividual Variability (SE)
Intercept (msec)	-2.24 (0.61)	7.27
Slope (msec/pg/mL)	0.16 (0.12)	0.91
Residual Variability (msec)	10.70	

Based on the estimated slope, the mean and 90% QTc prolongation at steady state Cmax at 15 (Cmax: 4.25 pg/mL), 25 ug (Cmax: 6.98 pg/mL) BID doses were calculated.

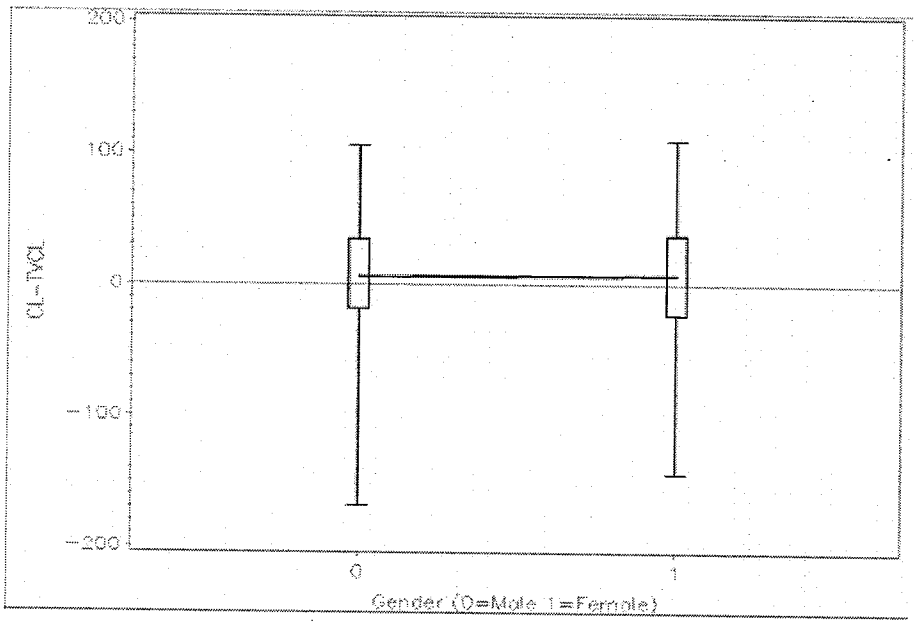
To summarize, the table below shows the effects of arformoterol on QTc prolongation by max-mean approach and concentration-QTc analysis. It can be concluded that the observed degree of QTc prolongation does not constitute a safety risk.

Dose (ug BID)	Mean (90% CI)		QTc Effect
	Conc-QT	Max-Mean	
15	0.7 (0.5-0.9)	3.2 (0.9-5.5)	No/No
25	1.2 (0.9-1.3)	3.7 (1.5-5.9)	No/No

Sponsor Proposed Labeling Statements
The following are the statements proposed by the sponsor in the label which are based on population pharmacokinetic analysis.

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

Reviewer's Comments: This statement is based on the eta plots (CL-TVCL) vs gender as shown below. The reviewer finds it a reasonable statement.



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.

Reviewer's Comments: This statement is based on the table (from sponsor's report; 091-000-CP01.pdf) as shown below. The reviewer finds it a reasonable statement.

Table 4.2.8-1: Summary Statistics of Bayesian Apparent Clearance (CL/F) from the Final Population PK Model, Stratified by Race

	Bayesian CL/F (L/hr)				
Race/Ethnicity	Mean	SD	Minimum	Median	Maximum
Caucasians (n=473)	431.7	102.9	184.5	424.4	768.3
Blacks (n=23)	405.5	72.6	246.1	413.5	525.2
Other* (n=7)	443.4	100.9	318.3	452.1	558.4

* 'Other' category includes Asian, Hispanic, and Other Races/ethnicities

OCP (Pharmacometrics) Proposed Labeling Statements

No comments

4.4. OCP Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-912**	**Brand Name**	**None**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Arformoterol tartrate**
Medical Division	**DPADP**	**Drug Class**	Selective β2 agonist
OCPB Reviewer	Shinja Kim	**Indication(s)**	Treatment of COPD
OCPB Team Leader	Emmanuel Fadiran	**Dosage Form**	**Nebulized inhalation**
PM Reviewer		**Dosing Regimen**	15 mcg Bid long term maintenance treatment of broncho-constriction in patients with COPD, including chronic bronchitis and emphysema
Date of Submission	**December 8, 2005**	**Route of Administration**	**Oral inhalation**
Estimated Due Date of OCPB Review	August 8, 2006	**Sponsor**	**Sepracor**
PDUFA Due Date	**October 8, 2006**	**Priority Classification**	Standard
Division Due Date	August 8, 2006		

Clin. Pharm. and Biopharm. Information

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

multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:	X			
In-vitro:				
Subpopulation studies -				
ethnicity:	X			
gender:	X			
pediatrics:				
geriatrics:	X			
renal impairment:	X			
hepatic impairment:	X			
PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		24		16 Clinical studies, Pop PK. PK-PD analyses and 6 *in-vitro* studies

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	**Since this is a NME, QBR questions will follow strictly as CPB review template suggested.**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Shinja Kim, Ph. D**	
Secondary reviewer Signature and Date	**Emmanuel Fadiran, Ph. D**	

Overview of Clinical Pharmacokinetics and Pharmacodynamics

Arformoterol (R,R-formoterol) is a selective, long acting β_2-adrenoceptor agonist for the long-term maintenance treatment of bronchoconstriction associated with COPD, including chronic bronchitis and emphysema. Foradil® Aerolizer™ (formoterol fumarate inhalation powder; racemic mixture of formoterol) is approved in the U.S.

The arformoterol clinical development program is comprised of 16 clinical studies. Of these, 14 studies (091-003, 091-004, 091-007, 091-012, 091-013, 091-014, 091-015, 091-016, 091-018, 091-021, 091-026, 091-050, 091-051, and 091-060) involved pharmacokinetic and/or pharmacodynamic assessments. Studies 091-003, 091-004 and 091-021 were initiated early in the development program with a less sensitive bioanalytical method.

Studies 091-007, 091-012, 091-013, 091-014, 091-015, and 091-018 were Phase I studies performed in healthy subjects and/or in special populations free of respiratory disease. Study 091-016 included subjects with mild to moderate asthma and was designed, in part, to characterize the absorption of arformoterol from the lung and GI tract. Studies 091-026, 091-050, 091-051, and 091-060 included patients with a diagnosis of COPD. Data collected for the population pharmacokinetic and pharmacodynamic analyses were obtained from three clinical trials: one Phase 2 trial (Study 091-026) and two Phase 3 trials (Studies 091-050 and 091-051). In addition six in vitro studies were conducted.

The sponsor summarized results from these studies as follows:

- Arformoterol appears rapidly in the systemic circulation following nebulization in both healthy and COPD subjects.

- After administration of a single oral 35 μg dose of ^{3}H-arformoterol (2 mCi), ~90% of the administered radio active dose was recovered in urine (67%) and feces (22%). Approximately 1 to 3.5% of the dose was recovered in urine as unchanged arformoterol.

- Most systemic exposure and excretion of radioactivity was due to arformoterol sulphate and glucuronide conjugates. O-Demethylation of arformoterol and conjugation of the O-desmethyl metabolite were relatively minor pathways in man accounting for less than 17% of the dose recovered in urine and feces.

- Phase II metabolism is the predominant route of clearance, and several UGT isoforms are likely to be involved in the clearance of arformoterol. Phase I metabolism is considered a secondary clearance pathway.

- Arformoterol does not inhibit common cytochrome P450 enzymes.

- Arformoterol is not highly bound to plasma proteins.

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- There was no impact of renal impairment upon exposure to arformoterol. No dose adjustment is necessary for patients with renal impairment.

- A preliminary population PK/PD model was developed. A good fit between predicted and observed % ΔFEV was observed. A responder analysis using this model support the conclusion that 15 μg BID should be considered the recommended starting/core dose for COPD subjects.

Recommendation: The Office of Clinical Pharmacology and Biopharmaceuticals/Division of Clinical Pharmacology-II has reviewed NDA 21-912 submitted on December 8, 2005 and finds the submission is fileable.

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

/s/

Shinja Kim
8/4/2006 02:49:00 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
8/4/2006 02:55:27 PM
BIOPHARMACEUTICS
I concur

Atul Bhattaram
8/4/2006 03:13:20 PM
BIOPHARMACEUTICS
Doses mentioned as mg should read as mcg.

Jogarao Gobburu
8/4/2006 03:20:09 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-912**	**Brand Name**	**None**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Arformoterol tartrate**
Medical Division	**DPADP**	**Drug Class**	**Selective β2 agonist**
OCPB Reviewer	**Shinja Kim**	**Indication(s)**	**Treatment of COPD**
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	**Nebulized inhalation**
PM Reviewer		**Dosing Regimen**	15 mcg Bid long term maintenance treatment of broncho-constriction in patients with COPD, including chronic bronchitis and emphysema
Date of Submission	**December 8, 2005**	**Route of Administration**	**Oral inhalation**
Estimated Due Date of OCPB Review	**August 8, 2006**	**Sponsor**	**Sepracor**
PDUFA Due Date	**October 8, 2006**	**Priority Classification**	**Standard**
Division Due Date	**August 8, 2006**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X			
Isozyme characterization:	X			
Blood/plasma ratio:	X			
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:	X			
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:	X			
In-vitro:				
Subpopulation studies -				
ethnicity:	X			
gender:	X			
pediatrics:				

geriatrics:	X			
renal impairment:	X			
hepatic impairment:	X			
PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**24**		16 Clinical studies, Pop PK. PK-PD analyses and 6 *in-vitro* studies

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	**X**	
Comments sent to firm ?		
QBR questions (key issues to be considered)	**Since this is a NME, QBR questions will follow strictly as CPB review template suggested.**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Shinja Kim, Ph. D**	
Secondary reviewer Signature and Date	**Emmanuel Fadiran, Ph. D**	

Overview of Clinical Pharmacokinetics and Pharmacodynamics

Arformoterol (R,R-formoterol) is a selective, long acting β_2-adrenoceptor agonist for the long-term maintenance treatment of bronchoconstriction associated with COPD, including chronic bronchitis and emphysema. Foradil® Aerolizer™ (formoterol fumarate inhalation powder; racemic mixture of formoterol) is approved in the U.S.

The arformoterol clinical development program is comprised of 16 clinical studies. Of these, 14 studies (091-003, 091-004, 091-007, 091-012, 091-013, 091-014, 091-015, 091-016, 091-018, 091-021, 091-026, 091-050, 091-051, and 091-060) involved pharmacokinetic and/or pharmacodynamic assessments. Studies 091-003, 091-004 and 091-021 were initiated early in the development program with a less sensitive bioanalytical method.

Studies 091-007, 091-012, 091-013, 091-014, 091-015, and 091-018 were Phase I studies performed in healthy subjects and/or in special populations free of respiratory disease. Study 091-016 included subjects with mild to moderate asthma and was designed, in part, to characterize the absorption of arformoterol from the lung and GI tract. Studies 091-026, 091-050, 091-051, and 091-060 included patients with a diagnosis of COPD. Data collected for the population pharmacokinetic and pharmacodynamic analyses were obtained from three clinical trials: one Phase 2 trial (Study 091-026) and two Phase 3 trials (Studies 091-050 and 091-051). In addition six in vitro studies were conducted.

The sponsor summarized results from these studies as follows:

- Arformoterol appears rapidly in the systemic circulation following nebulization in both healthy and COPD subjects.
- After administration of a single oral 35 μg dose of ^{3}H-arformoterol (2 mCi), ~90% of the administered radio active dose was recovered in urine (67%) and feces (22%). Approximately 1 to 3.5% of the dose was recovered in urine as unchanged arformoterol.
- Most systemic exposure and excretion of radioactivity was due to arformoterol sulphate and glucuronide conjugates. O-Demethylation of arformoterol and conjugation of the O-desmethyl metabolite were relatively minor pathways in man accounting for less than 17% of the dose recovered in urine and feces.
- Phase II metabolism is the predominant route of clearance, and several UGT isoforms are likely to be involved in the clearance of arformoterol. Phase I metabolism is considered a secondary clearance pathway.
- Arformoterol does not inhibit common cytochrome P450 enzymes.
- Arformoterol is not highly bound to plasma proteins.
- The sponsor claims that there is no chiral inversion of (R,R)-formoterol to (S,S)-formoterol, (R,S)-formoterol and (S,R)-formoterol was observed in human plasma after a single- and multiple-dose administration of arfonnoterol. Only a trace amount of (S,R)-formoterol was found in a few isolated human urine samples.

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

/s/

Shinja Kim
2/10/2006 02:12:42 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
2/10/2006 02:29:36 PM
BIOPHARMACEUTICS
I concur.