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Population Pharmacokinetics of Nebulized Arformoterol in Subjects with COPD

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Abstract

Aim: (R,R)-Formoterol (ARF) is a highly selective, potent and long-acting β_2-adrenoceptor agonist currently under development in the US for the long-term maintenance treatment of bronchoconstriction associated with COPD. The objectives of this analysis were to develop a population pharmacokinetic (PPK) model for nebulized ARF, and define the magnitude and variability of systemic exposure in subjects with COPD.

Methods: Data were pooled from one Phase 2 and two Phase 3 studies evaluating nebulized ARF tartrate inhalation solution administered at doses ranging from 5 µg BID to 50 µg QD. Both 1- and 2-compartment (CMT) models were evaluated using NONMEM®. Subject covariates were evaluated using stepwise forward (α = 0.05) and backward (α = 0.001) selection.

Results: A total of 6,401 ARF plasma concentrations were available from 503 subjects. A 2-CMT model with first-order absorption and elimination best described the data. Weight was a significant predictor of central volume of distribution (Vc/F), total body clearance (CL/F), and intercompartmental clearance (Q), where body weight was positively associated with increases in these parameter values. Mean (SD) Bayesian estimates of the area under the concentration-time curve (AUC) suggested dose-proportionality over this range. Measures of the precision and accuracy were unbiased, with a mean individual prediction error of 1.9%.

Conclusions: A PPK model was developed for nebulized ARF, and thus provides a valid and unbiased tool for estimating AUC in support of future exposure-response analyses.

Methods

- PPK analyses were performed using NONMEM®, Version 5, Level 1.1, using the first-order conditional estimation (FOCE) method, with interaction.
- Both 1- and 2-CMT models were evaluated, and various combinations of interindividual (IIV), interoccasion (IOV), and residual variability (RV) models were evaluated.
- Covariates evaluated: age, body weight, race (Caucasian, Black, or other), gender, creatinine clearance (CrCL) (estimated by the Cockcroft and Gault method), and alanine aminotransferase.
- Statistical significance was assessed by the change in log likelihood obtained from the NONMEM® objective function
  - For univariate forward selection analyses, covariates contributing at least a 3.84 decrease in the minimum value of the objective function (α = 0.05, one degree of freedom) were considered significant.
  - For univariate backward elimination, a covariate was considered significant if it contributed to at least a 10.83 increase in the objective function value (α = 0.001, one degree of freedom) when removed from the model.
- The general procedure followed for the development of the PPK model is outlined below:
  1. Base structural model development
  2. Subject covariate analyses (forward selection)
  3. Evaluation of the full multivariable model and statistical error model
  4. Backward elimination analysis of covariates
  5. Model refinement and establishment of the final PPK model
  6. Model verification

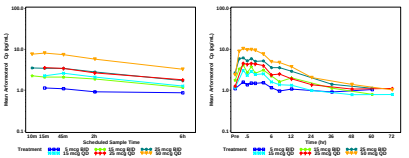
Results

- A total of 6401 drug concentrations from 503 subjects (191 from Phase 2 and 312 from Phase 3) were available for analysis.
- Summary statistics and concentration-time profiles for this population are shown in Table 1 and Figure 1, respectively.

Table 1: Summary Statistics of the Subjects Included in the PPK Analysis of Arformoterol, Total Population (n = 503)

Age (years) [mean ± SD (range)]	[62.5 ± 9.0 (40.0–87.0)]
Weight (kg) [mean ± SD (range)]	[81.5 ± 20.4 (39.5–194.0)]
Gender, N (%)	
Males	295 (58.7)
Females	208 (41.3)
Ethnicity, N (%)	
Caucasian	473 (94.0)
Black	23 (4.6)
Asian	3 (0.6)
Hispanic	3 (0.6)
Other	1 (0.2)

Figure 1: Semi-Logarithmic Plots of Single-Dose and Steady-State Arformoterol Cp vs. TSLD, Stratified by Treatment



- The PPK model for arformoterol was a linear, 2-CMT model with first-order absorption and elimination.
  - Relative bioavailability (F_1) was parameterized using the data from the 5 µg twice-daily dosing regimen as a reference (F_1=1).
    - IIV and IOV were utilized to characterize the between-subject random variability in F_1 and the random variability in F_1 between evaluation visits within each subject, respectively.
  - Significant relationships were identified between body weight (kg) and apparent Vc/F, as well as between CrCL and both the apparent CL/F and Q.
  - The significance of CrCL as a predictive covariate was an unexpected finding because only ~1% of arformoterol is excreted unchanged in the urine.
    - Because CrCL, a surrogate index for renal function, is calculated based upon other important covariates (such as age, body weight, and gender), it may serve as an indirect marker of these variables.
    - Additional analyses revealed that the impact of body weight upon arformoterol clearance was mainly responsible for the artifactual finding of CrCL significance.

Final Model

- In the final population model, body weight replaced CrCL as the important predictor of CL/F and Q.
- Final PPK model parameter estimates, summary statistics, and diagnostic plots are provided in Table 2, Table 3, and Figure 2.

Table 2: Final Parameter Estimates and Standard Errors for the Final PK Model

	Final Parameter Estimate		Magnitude of IIV	
Parameter	**Population Mean**	**%SEM**	**%CV**	**%SEM**
K_a (1/hr)*	6.90	7.6	71.34, 83.31	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
Vc/F (L)	5510	5.3	40.25	17.2
Q (L/hr)	404	8.3	39.62	46.4
Vp/F (L)	6980	10.9	34.93	63.3
IOV 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	—	—
RV, proportional component (%CV)	14.97	8.9	—	—
RV, additive component (SD)	0.50	FIXED	—	—

* IIV in K_a corresponding to the population of subjects enrolled in Phase 2 and Phase 3, respectively

- Equations describing the influence of body weight on respective parameters:

$$TVCL_i \text{ (L/hr)} = 427 \cdot (WTKG_i/81.5)^{0.388}$$

$$TVVc_i \text{ (L)} = 5510 \cdot (WTKG_i/81.5)^{0.532}$$

$$TVQ_i \text{ (L/hr)} = 404 + 4.58 \cdot (WTKG_i - 81.5)$$

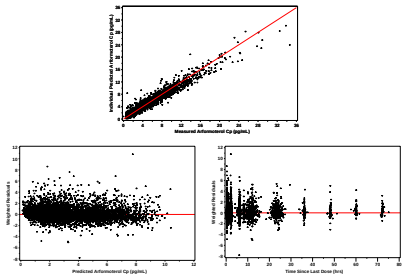
Table 3: Summary Statistics of the Individual Bayesian Predicted PK Parameter Estimates from the Final PPK Model

	Total Population				
Parameter	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
K_a (1/hr)	6.51	2.52	0.75	6.62	15.09
F_1*	0.79	0.24	0.33	0.75	2.18
CL/F (L/hr)	429.9	103.9	184.5	424.4	768.4
Vc/F (L)	5528	1829.4	2313	5324	12750
Q (L/hr)	412.5	115.1	164.5	396.0	1025.4
Vp/F (L)	7036	551.5	3996	6982	12422

*5 µg BID dose used as reference point, where the F_1 parameter is set to unity.

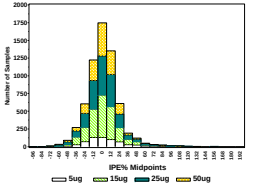
- Race was not identified as a statistically significant covariate, suggesting that exposure to arformoterol is not significantly different between Caucasians, Blacks, and other races/ethnicities.
- Use of corticosteroids (29.6% patients on a stable regimen 14 days prior to and during study) did not alter arformoterol PK.
  - The mean (SD) apparent Bayesian clearance for individuals taking corticosteroids was 418.2 (105.4) L/hr compared to 435.8 (99.8) L/hr for subjects not taking corticosteroids.

Figure 2: Goodness-of-Fit Plots for the Final PPK Model Incorporating Body Weight as a Predictor of Vc/F, CL/F, and Q



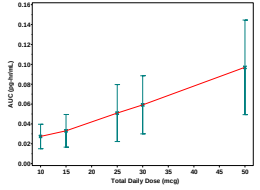
- Model verification, based on measures of precision and accuracy for the model predictions at the individual level (i.e., by accounting for IIV and IOV) were unbiased with a mean individual prediction error percent (IPE%) of 1.9% (Figure 3).

Figure 3: Plots of the Distributions of the IPE% for the Final PPK Model



- Examination of Bayesian estimates of the AUC (Figure 4) suggested that the PK were essentially dose-proportional over the range of dosing regimens evaluated.

Figure 4: Plot of AUC vs. Total Daily Dose After Including Relative Bioavailability in the PK Model



Conclusions

- The population pharmacokinetics of nebulized arformoterol in subjects with COPD were linear, dose proportional for the range of doses evaluated, and best described using a 2-CMT model with a first-order absorption process.
- Body weight (kg) was found to be a significant positive predictor of both the apparent clearance and central volume of distribution. The change in CL/F with body weight was not considered of clinical significance.
  - Other subject covariates (including age, gender, renal clearance, and race) had no additional predictive value once body weight was incorporated into the PK model for CL/F and Vc/F.
  - Exposure to arformoterol was not significantly different based upon race, gender, or corticosteroid use.
- These results support the utility of the model as a valid and unbiased instrument for estimating individual specific exposure for subsequent PK/PD analyses.

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