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Exposure-Response Relationship for Nebulized Arformoterol in Subjects with COPD

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Abstract

Aim: Arformoterol (ARF) is a highly selective, potent, long-acting β_2-adrenoceptor agonist under development in the US for the maintenance treatment of bronchoconstriction associated with COPD. An initial population pharmacokinetic/pharmacodynamic (PK/PD) model described the relationship between the % change in FEV_1 (%ΔFEV_1) and (R,R)-formoterol plasma concentrations (Cp), and the variability in key PD parameters.

Methods: Data were obtained from one Phase 2 and two Phase 3 studies of nebulized ARF tartrate inhalation solution in COPD subjects, with doses ranging from 5µg BID to 50µg QD. Individual predicted ARF Cp were obtained from Bayesian parameter estimates derived from a previous population PK model. Biophase distribution PK/PD link models were evaluated, as the hysteresis in the plot of %ΔFEV_1 vs. ARF Cp suggested a time delay.

Results: A total of 13,294 FEV_1 observations obtained after single-dose (SD) and steady-state (SS) dosing of ARF in 501 subjects were evaluated. An E_{max} (maximum drug response) link model best described the relationship between ARF Cp and %ΔFEV_1, with separate residual variability (RV) for Phase 2 and 3 data. Following SD ARF, the E_{max} was 38 %ΔFEV_1 from study baseline, with a relatively small EC_{50} (concentration at 50% of E_{max}) of 5.1 pg/mL. The E_{max} at SS was 55 %ΔFEV_1, with an EC_{50} of 5.23 pg/mL. The estimated first-order distribution rate constant (k_{e0}) was 1.49 hr^{-1} [0.47 hr half-life ($t_{1/2}$)] for SD and 3.78 hr^{-1} (0.18 hr $t_{1/2}$) for SS, which was consistent with the hysteresis plots. Model parameters were well estimated (%SEM ≤ 21%).

Conclusions: The developed PK/PD model demonstrated that a clear exposure-response relationship exists between Cp and FEV_1 response after nebulized ARF, and accounts for the small lag time between the time course of drug exposure and drug response observed in the studies.

Background

- Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema
- COPD affects nearly 14 million individuals in the US, with a current prevalence of ~11% (representing an increase of 41.5% since 1982). Worldwide, COPD is the 5th leading cause of death.
- Bronchodilator therapies approved for COPD include short- and long-acting inhaled β_2-adrenergic agonists, the majority of which are racemic mixtures of (R)- and (S)-enantiomers.
- Arformoterol is the (R,R)-isomer of formoterol, which possesses long-acting β-agonist activity and therapeutic bronchodilation characteristics.
- Arformoterol is being developed as an inhalation solution for nebulization, as there are currently no nebulized long-acting β_2-adrenergic receptor agonists available for the treatment of COPD.

Objective

To develop a population PK/PD model which describes an exposure-response relationship between arformoterol Cp and percent change in FEV_1 from study baseline (%ΔFEV_1) following nebulized dosing in subjects with COPD.

Methods

- All data preparation and presentation were performed using SAS® software.
- PD analyses were performed using the computer program NONMEM®, Version 5, Level 1.1 (FOCE method with interaction).

Study Design/Data

- Data were pooled from COPD patients enrolled in one Phase 2 and two Phase 3 studies (parallel design)
- Dosing regimens (2 to 12 weeks of chronic dosing):
  BID: 5 µg, 15 µg, and 25 µg, QD: 15 µg, 25 µg, and 50 µg
- Sampling
  - Following single-dose: PK (n=3~4) and PD (n=7~9) samples collected up to 6 hr post-dose
  - At SS: PK (n=6~12 for Phase 2; n=3~4 for Phase 3) and PD (n~15 for Phase 2; n~10 for Phase 3) samples collected up to 24 hr post-last dose

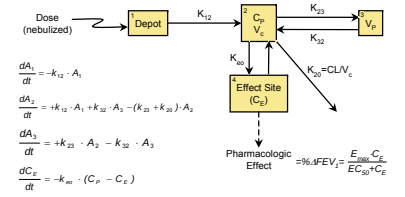
Biophase Distribution PK/PD 'Link' Model

- A hypothetical effect site compartment was used to link the drug concentration-time profile with a delayed pharmacologic effect.
- PD Endpoint: Percent change from study baseline in forced expiratory volume in 1 second (%ΔFEV_1)
- PK Model: 2-CMT with 1st-order input and elimination
- PD Model: stimulatory E_{max} function describing %ΔFEV_1 vs. effect site ARF concentration, where:

  E_{max} = the estimated maximum %ΔFEV_1;
  EC_{50} = the estimated effective arformoterol effect site concentration required to produce 50% of the maximum %ΔFEV_1; and
  C_E = predicted arformoterol effect site concentration.

- Sequential PK/PD modeling was employed: the PK model was established *a priori*, and the E_{max} model was fit to the PD data conditioned upon the Bayesian PK parameter estimates.
- K_{e0}: first-order distribution rate constant describing the transfer of drug between the central plasma compartment and the hypothetical effect site compartment
- Interindividual variability (IIV) models: exponential error for k_{e0} and EC_{50}; constant coefficient of variation error for E_{max}
- Residual variability (RV) model: additive error (separate model for Phase 2 vs. Phase 3 data)

Figure 1: Biophase Distribution PK/PD Model



Results

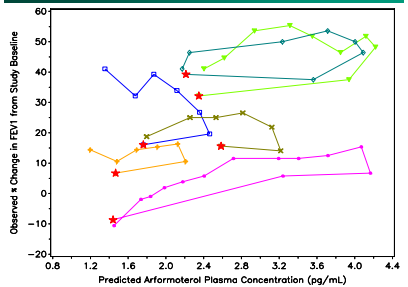
- A total of 13,294 FEV_1 measurements from 501 subjects (191 from Phase 2 and 310 from Phase 3) were available for analysis.
- Summary statistics of demographic characteristics for subjects with SD and SS data are summarized in Table 1.

Table 1: Summary Statistics for Demographic Characteristics of Subjects Included in the PK/PD Analysis of Arformoterol

	SD (n=479)	SS (n=452)
Age (years) [mean ± SD (range)]	62.5 ± 9.0 (40-87)	62.7 ± 8.9 (41-87)
Weight (kg) [mean ± SD (range)]	81.5 ± 20.4 (39.5-194)	81.5 ± 20.6 (39.5-194)
Gender, N (%)		
Males	280 (58.5)	259 (57.3)
Females	199 (41.5)	193 (42.7)
Ethnicity, N (%)		
Caucasian	449 (93.7)	428 (94.7)
Black	23 (4.8)	18 (4.0)
Asian	3 (0.6)	3 (0.6)
Hispanic	3 (0.6)	2 (0.4)
Other	1 (0.2)	1 (0.2)

- A small, but persistent time lag (a.k.a. hysteresis) between the time course of arformoterol concentrations in the plasma and drug response (%ΔFEV_1) is demonstrated in Figure 2.

Figure 2: Observed Individual %ΔFEV_1 vs. Predicted Arformoterol Cp



- Biophase distribution PK/PD link models were constructed to address the hysteresis.
- Separate, models were developed for SD and SS data to better characterize underlying differences in the PD behavior between SD and multiple dosing.
- The final PD parameter estimates, including measures of precision (%SEM), from the SD and SS population PK/PD models are summarized in Table 2 and Table 3, respectively. Model diagnostic plots are shown in Figure 3.

Table 2: Parameter Estimates and Standard Errors for the PK/PD Link Model Applied to SD Arformoterol Data

Parameter	Final Parameter Estimate		Magnitude of IIV	
	Population Mean	%SEM	%CV	%SEM
K_{e0} (1/hr)	1.49	12.8	125.70	12.5
E_{max} (%ΔFEV_1)	37.9	5.1	68.70	9.1
EC_{50} (pg/mL)	0.609	20.1	122.88	14.8
Gamma	1.00	Fixed	—	—
RV				
PK Proportional (%CV)	8.65	13.6	—	—
PK Additive (SD)	0.50	Fixed	—	—
PD Additive (SD) for Phase 2 Data	10.10	13.0	—	—
PD Additive (SD) for Phase 3 Data	6.63	6.2	—	—

Figure 3: Goodness-of-Fit Plots for the Population PK/PD Link Model Fit to the SD and SS %ΔFEV_1-Arformoterol Concentration Data

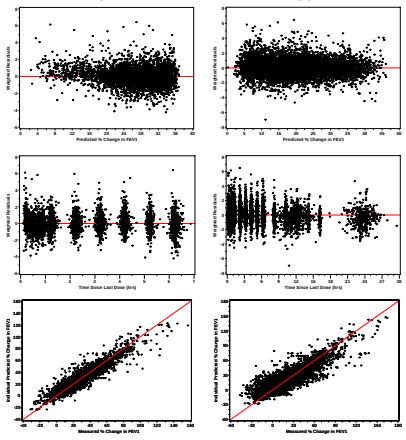


Table 3: Parameter Estimates and Standard Errors for the PK/PD Link Model Applied to SS Arformoterol Data

Parameter	Final Parameter Estimate		Magnitude of IIV	
	Population Mean	%SEM	%CV	%SEM
K_{e0} (1/hr)	3.78	10.8	94.97	21.6
E_{max} (%ΔFEV_1)	54.9	8.5	82.10	11.0
EC_{50} (pg/mL)	5.23	14.3	120.83	17.5
Gamma	1.00	Fixed	—	—
RV				
PK Proportional (%CV)	14.42	10.8	—	—
PK Additive (SD)	0.50	Fixed	—	—
PD Additive (SD) for Phase 2 Data	13.78	11.5	—	—
PD Additive (SD) for Phase 3 Data	10.10	8.3	—	—

- k_{e0} was estimated to be 1.49 hr^{-1} for SD data and 3.78 hr^{-1} for SS data.
- The associated $t_{1/2}$ delays in effect following ARF exposure were ~28 and ~11 minutes, respectively.
- The estimated maximum improvement in lung function (E_{max}) was slightly higher for SS data (54.9 %ΔFEV_1) vs. SD data (37.9 %ΔFEV_1).
- The estimated EC_{50} was considerably lower for SD (0.609 pg/mL) vs. SS data (5.23 pg/mL).
- Predicted %ΔFEV_1 values following SD nebulization exhibit an asymptotic E_{max} shape in the range of predicted C_E < 6 pg/mL; predicted FEV_1 values at SS are more linear within the range of predicted C_E.
- SS EC_{50} values were not influenced by race, gender, or corticosteroid use.

Conclusions

- A clear exposure-response relationship between arformoterol Cp and %ΔFEV_1 was best described by a biophase distribution PK/PD link model.
- Considerable inter-individual variability existed in both the SD and SS PD of arformoterol.
- Although a marked increase in EC_{50} between first dose and SS was observed, 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.
- The estimate of k_{e0} was larger (3.78 hr^{-1}) during SS compared to SD (1.49 hr^{-1}), suggesting a diminution in the $t_{1/2}$ delay for the onset of observed pharmacologic effect.
- E_{max} at SS was more difficult to model due to the lack of ample informative data at sufficiently high concentrations (> EC_{50}) and a high degree of correlation with the EC_{50} parameter. Additional analyses and modeling efforts are in progress to address this concern.
- There was no apparent impact of race, gender, or corticosteroid use upon model estimates of EC_{50} at SS.

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