

Population Pharmacokinetic Analyses for BC-3781 Using Phase 2 Data

C. M. Rubino¹, B. Xue¹, S. M. Bhavnani¹, W. T. Prince², Z. Ivezic-Schoenfeld², W. W. Wicha², P. G. Ambrose¹
¹Institute for Clinical Pharmacodynamics, Latham, NY, US; ²Nabriva Therapeutics AG, Vienna, Austria

BC-3781

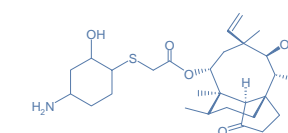


Figure 3. Precision of the individual clearance estimates from the final population PK model

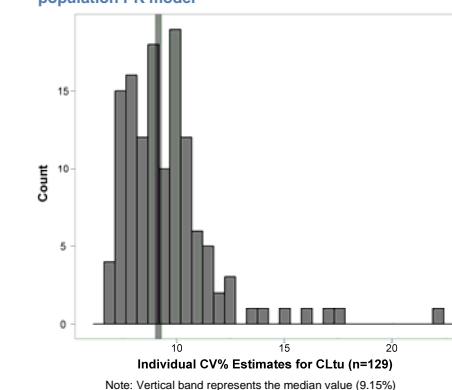


Table 1. Summary statistics for BC-3781 PK exposure estimates and half-life

Parameter	Dose (mg)	Mean (SD)	Median (Min. – Max.)
C_{max} (Day 1) ($\mu\text{g/mL}$)	100	1.57 (0.974)	1.46 (0.515 - 8.11)
	150	1.90 (0.705)	1.88 (0.633 - 4.38)
AUC_{0-24} (Day 1) ($\mu\text{g}\cdot\text{hr/mL}$)	100	10.9 (5.97)	9.87 (3.86 - 48.3)
	150	14.1 (5.76)	12.8 (4.29 - 35.1)
Half-life (hr)	100	11.0 (5.18)	9.74 (0.838 - 23.5)
	150	13.2 (5.79)	12.4 (3.38 - 23.5)

CONCLUSIONS

- A simple three-compartment population PK model incorporating saturable protein binding provided a robust fit to the plasma data from the Phase 2 study.
- Significant covariate relationships were not evident.
- Given the precision of the clearance estimates, the population PK model and the sparse PK sampling scheme have allowed for the estimation of PK exposure in each patient, thus enabling the conduct of PK-PD analyses for efficacy and simulations to support Phase 3 dose selection [2].

REFERENCES

- Rubino CM et al. 50th ICAAC. Abstract A1-018. Boston, MA. Sept. 12-15, 2010.
- Bhavnani SM et al. 51st ICAAC. Abstract A2-042. Chicago, IL. Sept. 17-20, 2011.
- Bauer RJ. S-ADAPT/MCPEM User's Guide: Software for Pharmacokinetic, Pharmacodynamic and Population Data Analysis. Berkeley, CA: 2006.

ABSTRACT

Background: BC-3781, a pleuromutilin antimicrobial agent with activity against Gram-positive pathogens, including methicillin-resistant *S. aureus* (MRSA), is being developed for the treatment of patients with acute bacterial infections including skin and skin-structure infections (ABSSSI). Data from a Phase 2 study in patients with ABSSSI were used to refine a previous PPK model and explore potential predictors of pharmacokinetic (PK) variability.

Methods: A previously-derived PPK model based on data from 3 Phase 1 studies (ICAAC 2010, abstract A1-018) was applied to sparse sampling data from a Phase 2 ABSSSI study. Alterations to the structural model were made based on the fit of the model. Covariate analyses were conducted to identify covariates (e.g., body size, renal function, age) associated with interindividual variability in PK. All PPK analyses were conducted using Monte Carlo parametric expectation maximization implemented in S-ADAPT 1.5.6.

Results: The PPK dataset contained 1,167 concentrations from 129 patients; 95% of patients had 5 or more PK samples (median: 11). The previous PPK model (3-compartment model with 1st order elimination and non-linear protein binding) provided an acceptable and unbiased fit to the data from the 129 patients (r^2 of 0.892). PPK parameters were all estimated with acceptable precision; individual clearance values were particularly well estimated (median individual precision of 9.15%) and had an interindividual variability of 18%. Graphical covariate evaluations showed no relationships between PK and age or renal function but modest relationships between body size and clearance and volume of distribution, which were not statistically significant when included into the PPK model.

Conclusions: The previously-derived PPK model for BC-3781 fit the Phase 2 data well and provided reliable estimates of drug exposure. None of the covariate relationships evaluated were statistically significant. This PPK model will be useful for subsequent PK-PD analyses and simulations conducted to support Phase 3 dose selection.

INTRODUCTION

Population (PK) and pharmacokinetic-pharmacodynamic (PK-PD) analyses are an integral part of the BC-3781 drug development plan. These analyses build upon a population PK model developed from Phase 1 data [1].

The objectives of these analyses were to modify the existing population PK model for BC-3781 in order to characterize BC-3781 plasma exposure in the patients with acute bacterial skin and skin structure infection (ABSSSI) enrolled in a Phase 2 study, assess the impact of subject demographic and disease characteristics on interindividual variability for selected PK parameters, and generate individual predicted BC-3781 plasma concentration time profiles and calculated exposure measures for use in subsequent PK-PD analyses for efficacy [2].

MATERIALS & METHODS

PK Data Collection and Assay:

- Data were obtained from a Phase 2 clinical study in patients with ABSSSI.
- Patients were randomized to receive 1 of 2 doses of BC-3781 (100 mg q12h or 150 mg q12h) or vancomycin 1 g q12h (adjusted individually according to institution guidelines) for 5 to 14 days.
- Sparse plasma PK samples were obtained from each patient on Days 1, 5, and the final treatment day.
 - Three samples were drawn on each PK day.
 - The PK sampling strategy was selected using optimal sampling theory.

- Only those patients randomized to BC-3781 were included in the population PK analysis.

Population PK Model Development:

- Candidate PK models were fit to the BC-3781 plasma concentration-time data using Monte Carlo parametric expectation maximization as implemented in the open-source software program S-ADAPT [3].
- Given previous population PK analyses for BC-3781 [1], model development focused on three-compartment models, with zero-order input and first-order elimination.
- In addition to a model incorporating saturable protein binding, a model was attempted in which total drug concentrations were used.

Covariate Exploration:

- Several demographic and disease characteristics were evaluated for their impact on the primary PK parameters.
- Covariate exploration involved graphical examination of plots of PK parameters versus demographic and disease characteristics, followed by creation of statistical models, which were used as the basis for the development of the covariate model using S-ADAPT.

PK Exposures and Secondary PK Parameters:

- PK exposure and secondary PK parameter estimates were calculated for each patient by simulating a concentration-time profile using the final population PK model.
- Secondary PK parameters were obtained by applying non-compartmental analysis methods to the simulated profiles.

RESULTS

Analysis Data:

- The PK population consisted of 141 patients from the Phase 2 study who received BC-3781.
- Twelve subjects were removed for consistent, irreconcilable issues with sample documentation (n=11) or insufficient samples (n=1).
- The final analysis dataset contained 129 patients and 1167 samples. Sixty-four received 100 mg and 65 received 150 mg twice daily.
- Demographic characteristics were relatively consistent between the two dose groups.

RESULTS (Continued)

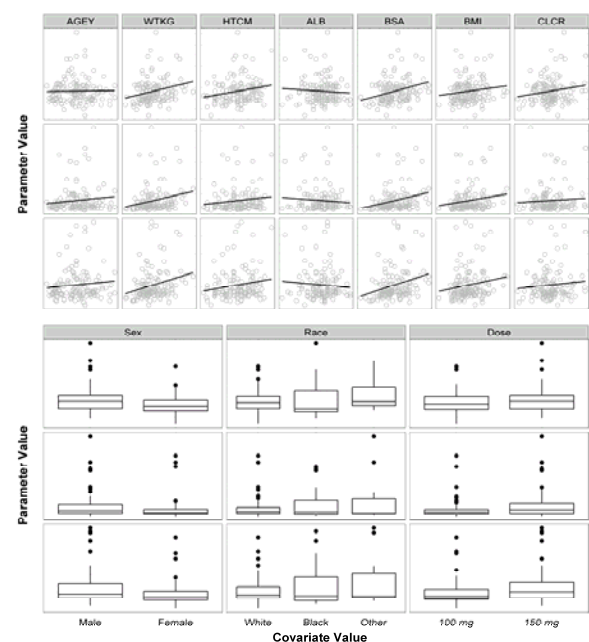
Structural Model Development:

- The final model from the Phase 1 analysis, which included nonlinear protein binding, was deemed most appropriate.
- Simplification of the model resulted in a significant worsening in the fit.

Covariate Exploration:

- The covariate screening plots (Figure 1) revealed that no strong relationships between patient descriptors and primary PK parameters were evident.
- Several models were attempted in S-ADAPT to test their statistical significance; none of these models met the statistical criteria for inclusion of covariate relationships.

Figure 1. Covariate Screening Plots



Final Population PK Model:

- Excellent fits to the data (Figure 2) were obtained.
- Precision of the mean PK parameters was universally high.
- The magnitude of interindividual variability was relatively low (<20% for CLtu) with the exception of Vcu, which was quite variable (CV of 139%), likely due to the fact that the PK sampling scheme was designed to maximize the ability to estimate clearance while sacrificing the ability to estimate volume parameters.
- Intraindividual variability was modest (approximately 22%).
- Individual %CV estimates for clearance were relatively low (Figure 3) indicating that the precision of the individual estimates of clearance and, by inference, AUC, are high.

Exposure Estimates and Secondary PK Parameters:

- Summary statistics for Day 1 PK exposure estimates and half-life are provided in Table 1.
- While the medians differ as expected between groups, there was a modest degree of overlap in AUC_{0-24} values between the 100 and 150 mg dose levels.

Figure 2. Goodness-of-fit plots for the final population PK model

