Population Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Target Attainment Analyses for Rezafungin for Treatment of Candida Infections

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Christopher M. Rubino, Pharm.D.
Institute for Clinical Pharmacodynamics, Inc.
Schenectady, New York
• Rezafungin is being developed for the prevention and treatment of invasive fungal infections.
• Rezafungin exhibits an exceptionally long half-life (~133 h) which enables the administration of once-weekly dosing regimens [1].
• A pharmacometric approach to dose selection has been utilized throughout the development of rezafungin starting with the first-in-human study and progressing through to the current analysis using Phase 2 data from patients.
• Phase 3 clinical trials for treatment of candidemia or invasive candidiasis using doses informed by pharmacokinetic-pharmacodynamic (PK-PD) approaches and confirmed through Phase 1 and 2 studies are currently ongoing.

OBJECTIVES

• To refine a previously-developed population PK model [1] using PK data from healthy volunteers administered a broad range of doses and PK data obtained from infected patients enrolled in a Phase 2 study.

• To update PK-PD target attainment simulations using the refined population PK model.

METHODS

Population PK Model Refinement

- Data from the two Phase 1 trials used previously to develop the population pharmacokinetic (PK) model were pooled with data from an additional Phase 1 trial and data from Part A of the Phase 2 STRIVE trial in patients with candidemia and/or invasive candidiasis.

- The population PK model was refined using NONMEM Version 7.2.

- The ability of covariates such as body size, age, sex, albumin, creatinine clearance, and infection status to explain a portion of the interindividual variability on select PK parameters was explored using stepwise forward selection ($\alpha = 0.01$) and backward elimination ($\alpha = 0.001$).

- The final model was qualified using traditional goodness-of-fit plots and a prediction-corrected visual prediction check.

- The impact of identified covariate relationships on drug exposure was explored using model-based simulations.
METHODS

PK-PD Target Attainment Analyses

2. Pfaller MA, et al. Abstract 2400. IDWeek 2018
Rezafungin PK-PD Targets
Exposure Shape Matters

Results

Refined Population PK Model

- Robust dataset
- No change to structural model
- Several covariate relationships apparent
- All parameters estimated with high precision
- Very little shrinkage in IIV estimates
- Traditional GOF plots showed excellent fit to data on both individual and population basis
RESULTS

Visual Predictive Check

STRIVE Patients

- Prediction-Corrected Plasma Conc (mg/L)
- Time Since Last Dose (h)

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- Prediction-Corrected Plasma Conc (mg/L)
- Time Since Last Dose (h)
RESULTS

Impact of Covariates

Change Relative to Reference Week 1 AUC$_{0–168}$ (%)

Reference Population: Infected, Male, BSA = 1.83 m$^2$, Alb = 2.8 g/dL
Dashed lines and whiskers represent 5th and 95th percentiles
PK-PD Target Attainment by MIC

Week 1

Probability of PK-PD Target Attainment (%)

Relative Frequency of MIC Distribution (%)

MIC (µg/mL)

0.008 0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8

C. albicans  Net Fungal Stasis^a
C. glabrata  1-log_{10} CFU Reduction^b

^aStasis targets of 20.5 and 0.50 for C. albicans and C. glabrata, respectively

^b1-log_{10} CFU Reduction targets of 37.2 and 2.94 for C. albicans and C. glabrata, respectively

Pfaller MA, et al. Abstract 2400. IDWeek 2018
CONCLUSION

• The population PK model robustly described rezafungin PK in healthy subjects and infected patients.

• Several statistically significant covariate relationships were identified but none appear to be clinically relevant in infected patients.

• PK-PD target attainment analyses indicate strong probabilities of achieving pre-clinical PK-PD targets across the range of MIC values observed in an international surveillance program.

• These data support the chosen dose regimen of 400 mg on Week 1 followed by 200 mg once weekly for the treatment of patients with candidemia or invasive candidiasis.
Thank you for your attention.