Rezafungin is a novel antifungal of the echinocandin class being developed as a single agent for the prevention and treatment of invasive fungal infections (IFIs) caused by C. albicans, A. fumigatus, and Penicillium species in patients at high risk of infection. Rezafungin exhibits an exceptionally long half-life (~13.3 h) which enables the administration of once-weekly dosing regimens.

**OBJECTIVES**

- To refine a previously-developed population pharmacokinetic (PK) model [2] using data from healthy volunteers administered a broad range of doses and PK data obtained from infected patients
- To update pharmacokinetic/pharmacodynamic (PK-PD) target attainment predictions using the refined population PK model.

**METHODS**

**Population Pharmacokinetic Model**

Data from the two Phase 1 trials used previously to develop the population 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. Parameters was explored using stepwise forward selection (α = 0.001) and backward elimination (α = 0.01) and backward selection. The final model was qualified using traditional goodness-of-fit plots and a prediction-corrected visual predictive check (PC-VPC).

**RESULTS**

**Population Pharmacokinetic Model**

The final population PK model was a four-compartment model with zero order IV input. Covariate analyses indicated that the following variables were statistically significant: Sex and albumin were significant for CL (CLcr). Body weight was a significant factor for Vc. RSA and albumin were significant for Vp1. RSA and infection status were significant for Vp2.

**Clinical relevance of these covariate effects are shown in Figure 1.**

The model provided precise and unbiased fits to the observed data (goodness-of-fit plots not shown).

PC-VPC shows that model-based predictions are capturing the clinical tendency and variability of the observed data used for PK model development.

**Summary data for the Bayesian post hoc PK parameters in subject from the STRIVE trial are provided in Table 3.**

**Figure 1.** Forest plot of covariate effects on rezafungin Week 1 plasma AUC.

**Table 3.** Summary data for the Bayesian post hoc PK parameters in subject from the STRIVE trial.

**Table 2.** Summary data for patients from the STRIVE trial included in the population PK analysis (n = 66).

**Table 2.** Summary data for patients from the STRIVE trial included in the population PK analysis (n = 66).

- **MIC**
- **MIC90**
- **MIC50**
- **MIC40**

**MIC**

- **C. albicans**
  - Mean (SD) Median (Min. – Max)
  - 16.4 (4.38) 16.4 (9.53 – 24.3)
  - 16.4 (24.0 – 13.7)
  - 16.4 (8.97 – 24.3)
  - 16.4 (9.53)

**MIC90**

- **C. albicans**
  - Mean (SD) Median (Min. – Max)
  - 60.2 (49.2) 60.2 (49.2 – 146.3)
  - 60.2 (146.3)
  - 60.2 (49.2)
  - 60.2

**MIC50**

- **C. albicans**
  - Mean (SD) Median (Min. – Max)
  - 16.4 (4.38) 16.4 (9.53 – 24.3)
  - 16.4 (24.0 – 13.7)
  - 16.4 (8.97 – 24.3)
  - 16.4 (9.53)

**CONCLUSIONS**

- The population PK model robustly described rezafungin 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.

**REFERENCES**