Pharmacokinetic-Pharmacodynamic Analyses to Provide Rezafungin Prophylaxis Dose Selections: Support for Invasive Fungal Infections in Blood and Bone Marrow Transplant Patients

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INTRODUCTION

Rezafungin is a novel antifungal of the echinocandin class being developed as a single agent for the prevention of invasive fungal infections (IFIs) caused by Candida, Aspergillus, and Pneumocystis species in patients at high risk of infection.

Rezafungin exhibits an exceptionally long half-life (~133 h) which enables the administration of once-weekly dosing regimens [1].

Treatment efficacy in a mouse Pneumocystis model is achieved at a human equivalent dose of <50 mg once-weekly [2].

A dose of 400 mg, followed by 200 mg once-weekly achieved >90% target attainment for treatment of Candida [3].

Although lower doses of rezafungin might be useful for prevention of Pneumocystis and Candida infections, prevention of invasive aspergillosis in immunosuppressed populations is often considered more challenging.

OBJECTIVES

- Pharmacokinetic-pharmacodynamic simulations were performed, at the dosing regimen for treatment of Candida, to evaluate the appropriateness of rezafungin for prophylaxis against A. fumigatus among blood and bone marrow transplant (BMT) patients.

METHODS

Population Pharmacokinetic Model
- 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 the Phase 2 STRIVE trial data in patients with candidemia and/or invasive candidiasis.
- CD101.IV.1.01 Evaluated single intravenous (IV) doses ranging from 50–400 mg
- CD101.IV.1.02 Evaluated multiple weekly IV doses ranging from 100–400 mg
- CD101.IV.1.06 Evaluated single IV doses ranging from 600–1400 mg
- CD101.IV.2.03 Treatment Arm 1: 400 mg once-weekly x 2 weeks, optional additional weekly doses
- Treatment Arm 2: 400 mg once-weekly x 1 week, followed by 200 mg once-weekly x 1 week, optional additional weekly doses
- 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 (α = 0.01) and backward elimination (α = 0.001).

RESULTS

Monte Carlo Simulations
- Baseline demographic data were available from 100 patients who underwent a BMT at Stanford Medical Center.
- Using this dataset and the developed population PK model, a Monte Carlo simulation (n=2,000) was conducted to simulate expected rezafungin concentration-time profiles in BMT patients following administration of rezafungin 400 mg IV on Week 1 then 200 mg IV weekly x11.
- A human plasma protein binding estimate of 97.4% was used (4).

Population Pharmacokinetic Model
- The final population PK model was a linear, four-compartment model with zero order IV input.
- The model provided precise and unbiased fits to the observed data (Figure 1).

Figure 1. Observed versus model predicted rezafungin concentrations.

Population Pharmacokinetic Model
- Following administration of rezafungin 400 mg IV on Week 1 then 200 mg IV weekly x11, free-drug plasma concentration-time profiles for Week 1, 2, and 12 relative to the A. fumigatus MEC_{90} (0.03 mg/L) are displayed in Figure 3.
- As shown in Table 4, through Week 12, >90% of simulated patients had rezafungin free-drug concentrations above the MEC_{90} value for the entire dosing interval (one week).

CONCLUSIONS

- These data provide support for a weekly rezafungin dosing regimen for the prevention of A. fumigatus infections among BMT patients.
- The effectiveness of antifungal prophylactic regimens are frequently limited due to pill burden, adherence, safety, tolerability, and drug interactions.
- In addition to the excellent safety, tolerability, and lack of drug interactions exhibited by echinocandin agents, rezafungin’s favorable PK profile presents the opportunity to mitigate the typical challenges faced when administering IPI prophylaxis in BMT patients.

REFERENCES


Figure 2. Forest plot of covariate effects on rezafungin Week 1 plasma AUC.

Table 1. Rezafungin MEC distributions for A. fumigatus based on isolates collected in the international SENTRY Antifungal Surveillance Program.

Table 2. Summary statistics for patient demographics.

Table 3. Summary statistics for simulated plasma weekly AUC.

Table 4. Percent probability of achieving free-drug plasma concentrations above select MEC values for the entire dosing period (57-MEC_{100}).