Poster No. SATURDAY-AAR-736

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

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INTRODUCTION

- 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 *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].

OBJECTIVES

- To refine a previously-developed population pharmacokinetic (PK) model [2] 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; and
- To update pharmacokinetic-pharmacodynamic (PK-PD) target attainment simulations 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.

CD101.IV.1.01	Single intravenous (IV) doses ranging from 50 – 400 mg
CD101.IV.1.02	Multiple weekly IV doses ranging from 100 – 400 mg
CD101.IV.1.06	Single IV doses ranging from 600 – 1400 mg
CD101.IV.2.03 (STRIVE)	Treatment Arm 1: 400 mg once-weekly x 2 weeks, with 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 ($\alpha = 0.01$) and backward elimination ($\alpha = 0.001$).
- The final model was qualified using traditional goodness-of-fit plots and a prediction-corrected visual prediction check (PC-VPC).
- The impact of identified covariate relationships on drug exposure was explored using model-based simulations.

Table 1. Rezafungin MIC distributions for *C. albicans* and *C. glabrata* based on isolates collected in the international SENTRY Antifungal Surveillance Program

Pathogen (N)	No. of occurrences by MIC (µg/mL) (cumulative % inhibited)[a]										
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	MIC_{50}	MIC_{90}
C. albicans (267)	12 (4.5)	83 (35.6)	96 (71.5)	66 (96.3)	10 (100)	–	–	–	–	0.03	0.06
C. glabrata (121)	–	–	33 (27.3)	60 (76.9)	20 (93.4)	2 (95.0)	3 (97.5)	2 (99.2)	1 (100)	0.03	0.25

a. Based on data for clinical *C. albicans* and *C. glabrata* isolates described in reference [5]. Shaded cells represent the MIC values up to and including the MIC_{90}.

METHODS

Pharmacokinetic-Pharmacodynamic Target Attainment Analyses

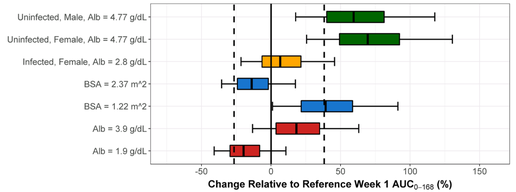
- PK-PD targets for efficacy were determined using neutropenic murine (CD-1 mice) disseminated candidiasis models [3].
- Using the above-described population PK model, free-drug plasma concentration-time profiles were generated for 2,000 simulated subjects following administration of rezafungin 400 mg on Week 1, then 400 or 200 mg once-weekly thereafter.
  - Each patient's albumin, sex, and weight were randomly selected from the STRIVE trial database using a bootstrap technique.
  - A protein binding estimate for rezafungin for humans of 97.4% was used [4].
- Weekly free-drug plasma area under the concentration-time curve (AUC) values were calculated for each subject following administration of the rezafungin dosing regimens.
- The free-drug plasma $AUC_{0\text{-}168}$ values were then divided by minimum inhibitory concentration (MIC) values (CLSI M27 Ed4) ranging from 0.008 to 2 µg/mL. In a second analysis, MIC values were randomly assigned based on the rezafungin MIC distributions for *C. albicans and C. glabrata* from the JMI 2017 SENTRY Antifungal Surveillance Program [5] shown in **Table 1**.
- Percent probabilities of PK-PD target attainment for Week 1 were calculated for each pathogen and PK-PD endpoint combination.

RESULTS

Population Pharmacokinetic Model

- The final population PK model was a linear, four-compartment model with zero order IV input.
- Covariate analyses indicated that the following relationships were statistically significant:
  - Sex and albumin were significant for clearance (CL).
  - Body surface area (BSA) and infection status were significant for Vc.
  - BSA and albumin were significant for Vp1.
  - BSA 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-VPCs show that model-based predictions are capturing the central tendency and variability of the observed data used for PK model development (**Figure 2**).
- Summary statistics for the Bayesian post-hoc PK parameters in subject from the STRIVE trial are provided in **Table 2**.

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



RESULTS

Figure 2. Prediction-corrected visual predictive check plots for the final population PK model

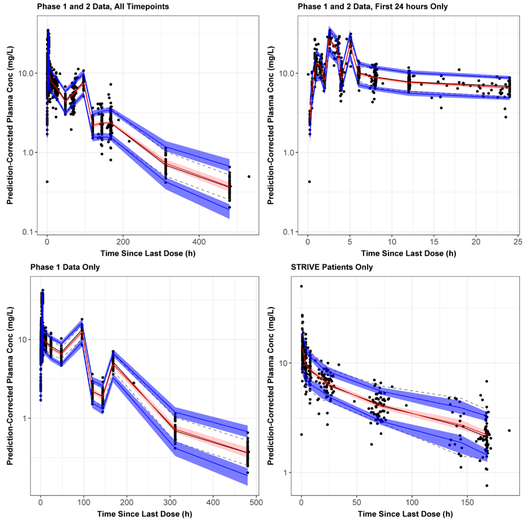


Table 2. Summary statistics for patients from the STRIVE trial included in the population PK analysis (n = 68)

Parameter	Mean (SD)	Median (Min. – Max)
$AUC_{0\text{-}\tau}$ (mg*h/L)[a]	709 (184)	673 (456 - 1060)
C_{max} (mg/L)[a]	16.4 (4.38)	16.4 (9.53 - 24.3)
C_{min} (mg/L)[a]	2.07 (0.659)	1.90 (1.19 - 3.30)
CL (L/h)	0.365 (0.128)	0.345 (0.188 - 0.573)
Vss (L)	61.0 (26.3)	52.7 (31.5 - 111)

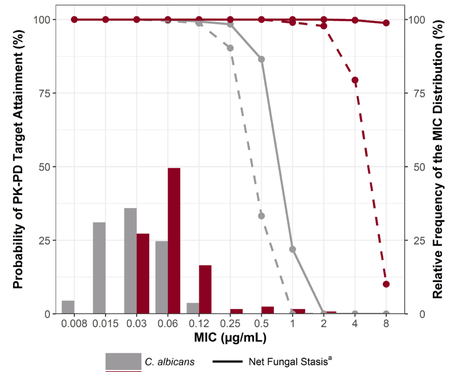
a. Rezafungin exposure calculated after first dose

Pharmacokinetic-Pharmacodynamic Target Attainment Analyses

- Summary statistics for the simulated PK parameters in subject from the STRIVE trial are provided in **Table 2**.
- Week 1 percent probabilities of PK-PD target attainment by MIC for *C. albicans* and *C. glabrata* are shown in **Figure 3**.
- Regardless of fungal reduction endpoint (stasis or 1-log_{10} CFU reduction), percent probabilities of PK-PD target attainment of 100% were achieved at the MIC_{90} for *C. albicans* and *C. glabrata* (0.06 and 0.25 µg/mL, respectively).
- Percent probabilities of PK-PD target attainment of >90% were achieved at or above the MIC_{100} values for *C. albicans* and *C. glabrata* (0.25 and 2 µg/mL, respectively).

RESULTS

Figure 3. Week 1 percent probabilities of PK-PD target attainment by MIC



[a]Stasis targets of 20.5 and 0.50 for *C. albicans* and *C. glabrata*, respectively [3]

[b]1-log_{10} CFU Reduction targets of 37.2 and 2.94 for *C. albicans* and *C. glabrata*, respectively [3]

CONCLUSIONS

- 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.

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American Society for Microbiology Microbe 2019, San Francisco, CA. June 20-24, 2019