Population Pharmacokinetic Analyses for Rezafungin (CD101) Efficacy Using Phase 1 Data

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Running title: Rezafungin (CD101) Population Pharmacokinetic Model

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Rezafungin (CD101) is a novel echinocandin antifungal agent currently in clinical development for the treatment of candidemia and invasive candidiasis. Rezafungin has potent in vitro activity against Candida albicans and Candida glabrata, including azole- and echinocandin-resistant isolates. The objective of this analysis was to develop a population pharmacokinetic (PK) model to characterize the disposition of rezafungin in plasma following intravenous (IV) administration. Data from two Phase 1 studies, a single-ascending-dose study and a multiple-ascending-dose study, were available. Candidate population PK models were fit to the pooled data using the Monte Carlo parametric expectation maximization algorithm in S-ADAPT. The data were best described using a linear four-compartment model with zero-order drug input via IV infusion and first-order elimination. In order to account for the relationships between the structural PK parameters and subject body weight, all parameters in the model were scaled to subject body weight using standard allometric coefficients (a power of 0.75 for the clearance terms and 1.0 for the volume terms). The final model fit the observed data with very little bias and excellent precision. The prediction-corrected visual predictive check demonstrated that the final model could accurately simulate both the central tendency and the variability of observed rezafungin plasma concentrations. Given this, the final rezafungin population PK model is expected to provide reliable simulated concentration-
time profiles across a population and can provide dose selection decision support for future clinical studies.
INTRODUCTION

Historically, *Candida albicans* has been the predominant pathogen in candidemia and invasive candidiasis infections [1]. Despite this, *Candida glabrata* is now emerging as a greater concern for clinicians due to a recent increase in prevalence among candidemia and invasive candidiasis infections and the pathogen’s natural predisposition for expressing azole- and echinocandin-resistance mutations [2, 3]. Accordingly, the incidence of infections due to *C. glabrata* has not only increased more than 4-fold over the past 20 years [4] but also has been accompanied by increased prevalence of bloodstream infections due to resistant *C. glabrata* isolates [5, 6]. Rezafungin (CD101) is a novel echinocandin antifungal agent currently in development for the treatment and prevention of candidemia and invasive candidiasis. Rezafungin has potent *in vitro* activity against *C. albicans* and *C. glabrata*, including azole- and echinocandin-resistant isolates. In addition, rezafungin has shown *in vivo* activity against a range of *C. albicans* and *C. glabrata* isolates including, importantly, an echinocandin-resistant *C. glabrata* isolate [7].

One of the unique features of rezafungin is its long half-life. Analyses of Phase 1 single- and multiple-ascending-dose studies showed that the rezafungin half-life in humans was approximately 133 hours (5.5 days) [8]. This value far exceeds those reported for other echinocandins, which have terminal half-lives ranging from 9 to 52 hours [9, 10, 11]. The rezafungin maximum concentration, area
under the concentration-time curve (AUC), and half-life were shown to be dose proportional up to 400 mg, the highest dose evaluated in the studies [8]. Given rezafungin’s long half-life, it is being evaluated in clinical studies using dosing regimens with a once-weekly dosing frequency. The aforementioned analyses of Phase 1 data found minor accumulation (30-55%) of rezafungin following weekly dosing. Moreover, no safety signals were noted in these studies. Of the 42 patients evaluated, only 4 experienced moderate treatment-related adverse events. No serious or severe adverse events were observed in either study.

As the prior analyses performed were conducted using non-compartmental techniques, a quantitative model describing the time course and variability of rezafungin concentrations in humans was desired to facilitate Monte Carlo simulations to aid in dosing regimen selection for future clinical studies. Our objective was to develop a population pharmacokinetic (PK) model to characterize the disposition of rezafungin in plasma following intravenous (IV) administration.

RESULTS

Pharmacokinetic Analysis Dataset

The final dataset consisted of 840 rezafungin samples collected from 42 healthy subjects across two studies. All concentrations were above the lower limit of quantification. No outliers were identified during the population PK analysis. Out
of the 485 samples collected from subjects in the multiple-ascending-dose study, 257 (53.0%) were collected after administration of multiple rezafungin infusions. Table 1 presents demographic and select laboratory measures for the subjects in the analysis dataset. The majority of subjects were Caucasian (90.4%) and male (52.3%). Subjects ranged in age from 22 to 54 years. The mean (min, max) weight observed was 76.2 (57.1, 102) kg. The typical subject was overweight, as indicated by a mean body mass index (BMI) of 27.7 kg/m². All subjects had normal renal function (minimum creatinine clearance of 80 mL/min/1.73 m²).

Population Pharmacokinetic Model Development

Linear two-, three-, and four-compartment models were evaluated during structural model development. Goodness-of-fit plots for the three- and four-compartment models are displayed in Supplemental Figure 1 and Supplemental Figure 2, respectively. The addition of a fourth compartment resulted in less biased residual versus time since last dose plots and a 55 unit decrease in the objective function. Given these findings, a linear four-compartment model with zero-order drug input via the IV infusion and first-order elimination was selected as the base structural model. Results of the graphical exploration of the continuous covariates versus individual model parameter estimates are displayed in Figure 1. The strongest relationship found (correlation coefficient = 0.622) was between weight and the volume of the first peripheral compartment (V2). Weight was moderately correlated with all eight model parameters.
(correlation coefficients > 0.230). Weight was selected for testing in the model given its physiologic plausibility, correlation with all model parameters, and widely accepted standard allometric scaling coefficients for both volume and clearance terms. The weight relationship was implemented using a power function centered on 75 kg. The power coefficients were fixed to standard estimates of 0.75 for the clearance terms and 1.0 for the volume terms [12].

Addition of weight to the model decreased the objective function by 8.41 units, a statistically significant decline considering no additional model parameters were estimated. Addition of weight also explained 5% of the inter-individual variability on both total clearance and the central volume of distribution. Given these model improvements, the weight relationships were included in the final model.

Final Population Pharmacokinetic Model

Final population PK parameter estimates and their associated precision for rezafungin are provided in Table 2. The individual- and population-predicted rezafungin concentrations were unbiased and agreed well with the observed data ($r^2 = 0.98$ and 0.96, respectively; Figure 2). There was a lack of bias when residuals were plotted by predicted concentration, time, dose, and study, as displayed in Figure 2. For a typical subject weighing 75 kg, rezafungin clearance was estimated to be 0.187 L/h, while typical 50- and 100-kg subjects were estimated to have rezafungin clearances of 0.138 and 0.232 L/h, respectively.
The prediction-corrected visual predictive check (PC-VPC) plot for the final rezafungin population PK model is provided in Figure 3. The majority of the observed concentrations were contained within the 90% prediction interval. Additionally, the observed median and 90% prediction interval were very similar to the simulated median and 90% prediction interval, suggesting that the final population PK model provided an accurate and unbiased fit of the rezafungin PK data.

**DISCUSSION**

A population PK model was successfully developed to describe rezafungin plasma concentration-time data following IV administration of single and multiple rezafungin doses in healthy volunteers. The final model was a linear four-compartment model with all parameters scaled to subject body weight using standard allometric scaling coefficients. The final model is structurally similar to population PK models for anidulafungin, caspofungin, and micafungin [13, 14, 15]. All three of these models are linear, multi-compartment models with weight as a covariate on clearance. Weight is also a covariate on select volume terms in the anidulafungin and caspofungin models. Linear, multiphasic PK impacted by weight appears to be a consistent characteristic of the echinocandin class, including rezafungin.
During the covariate evaluation step, BMI, body surface area (BSA), and height were also correlated to several model parameters, signaling the consistent impact of body size on rezafungin PK. Although the correlations were not as strong as those observed with body weight, another body size measure may also adequately describe variability in various rezafungin PK parameters. The dataset utilized for this analysis had a limited number of subjects (n=42). In addition, the subjects were fairly homogenous, as evidenced by the low coefficient of variation observed for body weight (15%) relative to those reported previously (21-32%) [15, 16, 17, 18]. The small homogeneous dataset is a limitation of the current analysis. Given this, the model will need to be refined and a formal covariate analysis will be needed once more data are available. The updated covariate analysis will be especially critical once data from special populations (e.g., obese patients) and Phase 2 and 3 studies, which enroll large numbers of patients with greater covariate variability, are available.

The model-predicted mean rezafungin clearance for study subjects was 0.188 L/h, consistent with the clearance values reported from the non-compartmental analysis, which ranged from 0.126 L/h to 0.279 L/h [8]. This is considerably lower than the model-estimated mean clearances for anidulafungin, caspofungin, and micafungin, which range from 0.411 L/h to 1.22 L/h [13, 14, 15]. A lower clearance suggests that higher AUC values can be achieved using the same dose, which is critical given that the ratio of AUC to minimum inhibitory
concentration (MIC) drives efficacy for this agent [19]. Moreover, the model-estimated inter-individual variability on rezafungin clearance (13%) is lower than that of other echinocandins, which range from 28% to 36% [13, 14, 15]. However, the population PK models for anidulafungin, caspofungin, and micafungin were developed using data from infected patients enrolled in Phase 2 and 3 studies. PK in infected patients is often more variable than in healthy volunteers [16, 20], further supporting the need for an updated, formal covariate analysis once Phase 2 data are available.

As shown in Figure 3, simulations conducted using the final model could accurately estimate both the central tendency and the variability of observed rezafungin plasma concentrations. This indicates that both the model population mean and inter-individual variability parameter estimates are reliable. Therefore, the final population PK model is expected to provide dependable simulations of rezafungin concentration-time profiles following administration of rezafungin doses up to 400 mg in subjects with similar demographics to the current dataset. The final model can be utilized to conduct Monte Carlo simulations of various dosing regimens to provide dose selection decision support for future clinical studies.

METHODS
Studies

Data were pooled from two Phase 1 studies (NCT02516904 and NCT02551549) previously described by Sandison et al [8]. The protocols and informed consent were reviewed and approved by an appropriate Institutional Review Board before subject enrollment. The studies were designed and monitored in compliance with the ethical principles of good clinical practice and in accordance with the Declaration of Helsinki.

The first study (NCT2516904) evaluated single IV doses of rezafungin. A total of 32 subjects were enrolled and randomized evenly to one of four cohorts. Within each cohort, six subjects were administered rezafungin and two subjects were administered placebo as a single 60-minute IV infusion. A single rezafungin dose of 50, 100, 200, and 400 mg was administered to Cohorts 1, 2, 3, and 4, respectively. In all cohorts, blood samples for PK evaluations were collected predose and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, and 120 hours after the start of infusion and on Days 7, 14 (±1 day), and 21 (±1 day).

The second study (NCT02551549) evaluated multiple IV doses of rezafungin. A total of 24 subjects were enrolled and randomized evenly to one of three cohorts. Within Cohorts 1 and 2, six subjects were administered once-weekly IV doses of rezafungin 100 and 200 mg, respectively, and two subjects were administered once-weekly IV doses of placebo, infused over 60 minutes on Days...
1 and 8. Within Cohort 3, six subjects were administered once-weekly IV rezafungin doses of 400 mg and two subjects were administered once-weekly IV doses of placebo, infused over 60 minutes on Days 1, 8, and 15. Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, and 120 hours after the start of each infusion and on Days 7, 14 (±1 day), 21 (±1 day), and 35 (±1 day, Cohort 3 only).

**Analytical Methods**

All blood samples were collected using tubes with K2-EDTA. Plasma was collected by centrifugation and stored at -70 °C until analysis. Samples were analyzed using a 100 µL aliquot volume and a protein-precipitation extraction procedure followed by liquid chromatography/tandem mass spectrometry analysis. Rezafungin calibration range was 10.0 ng/mL to 10,000 ng/mL, using d9-CD101 as an internal standard. The range of the assay was extended 10-fold by dilution. An AB-Sciex API 4000 was operated in the selected reaction monitoring mode under optimized conditions for detection of rezafungin and d9-CD101 positive ions formed by electrospray ionization. Excellent inter-assay accuracy and precision, as measured by quality control (QC) samples, was obtained during validation. Across the range of QC samples tested (lower limit of quantitation, LLOQ, through the High QC range), the inter-assay accuracy (% bias from nominal) ranged from 0.3% to 4.3% while the inter-assay precision (% coefficient of variation) ranged from 2.7% to 5%. Dilution QC samples
performed well, with -1.5% bias and an inter-assay precision of 3.4%. Rezafungin was found to be stable through four freeze-thaw cycles, as well as at room temperature for at least 24 hours. Under frozen storage conditions, rezafungin was found to be stable for at least 164 days at either -20 °C or at -70 °C.

**General Data Handling**

The actual dates and times of dose administration and PK sample collection were used in the construction of the population PK data set. Subjects who received placebo were not included in the dataset. An outlier was defined as an aberrant observation that substantially deviated from the rest of the observations within an individual. Any suspected outliers were to be tested, and if justified, excluded from this analysis, given the potential for these observations to negatively impact the convergence and/or parameter estimates [21].

**Population Pharmacokinetic Modeling**

Candidate population PK models were fit to the pooled data using Monte Carlo parametric expectation maximization as implemented in the open-source software program S-ADAPT 1.5.6 [22, 23, 24]. The model selection criteria used to discriminate between candidate PK models included: (i) evaluation of individual and population mean parameter estimates and their precision (standard error of the mean [SEM]), (ii) graphical examination of standard goodness-of-fit plots and plots of the observed versus individual-predicted concentrations, (iii)
reduction in both residual variability and inter-individual variability, and (iv) comparison of objective function for nested models or the Akaike information criterion [25] for either nested or nonnested models.

Inter-individual variability was estimated for each structural population PK model parameter, where possible, by using an exponential-error model. Residual variability was initially described by using an additive plus proportional coefficient of variation (CV) error model. Other models for residual variability were to be explored as necessary. After development of the structural model, relationships between patient-specific covariates and individual post-hoc parameter estimates were evaluated via graphical exploration. Covariates evaluated included age, albumin, creatinine clearance (CLcr), and various measures of body size (weight, height, BMI, and BSA). Covariates with strong relationships were tested in the population PK model.

The final population PK model was qualified by performing a PC-VPC, which examines the agreement between the 5th, 50th, and 95th percentiles of the observed and the individual simulated concentrations across time intervals. This procedure uses the original analysis dataset as a template to simulate PK data for the same number of subjects in 500 new datasets, with each dataset featuring the same study design and data collection scheme. The PC-VPC normalizes both the observed and simulated concentration-time data by the...
median population predictions during each time interval to adjust for the differences due to independent variables in the final population PK model, thus avoiding the need to stratify by single-versus multiple-dose data, dose group, or other significant covariate effects included in the model.
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### Table 1. Summary statistics for demographics and clinical laboratory measures among subjects administered rezafungin

| Variable          | N (%) | Mean (SD) | Median | Minimum | Maximum |
|-------------------|-------|-----------|--------|---------|---------|
| Age (yr)          | 42    | 41.7 (8.95) | 42.5   | 22      | 54      |
| Weight (kg)       | 42    | 76.2 (11.1)  | 75.0   | 57.1    | 102     |
| Height (cm)       | 42    | 166 (8.74)   | 165    | 148     | 187     |
| BSA (m²)          | 42    | 1.84 (0.17)   | 1.81   | 1.51    | 2.22    |
| BMI (kg/m²)       | 42    | 27.7 (2.76)   | 27.8   | 22.4    | 31.9    |
| CLcr (mL/min/1.73 m²) | 42    | 112        | 113    | 79.6    | 153     |
| Albumin (mg/dL)   | 42    | 4.46       | 4.50   | 4.00    | 4.80    |
| Race              |       |            |        |         |         |
| Caucasian         | 38    | (90.4)     |        |         |         |
| Black             | 3     | (7.14)     |        |         |         |
| Other             | 1     | (2.38)     |        |         |         |
| Sex               |       |            |        |         |         |
| Male              | 22    | (52.3)     |        |         |         |
| Female            | 20    | (47.6)     |        |         |         |
Table 2. Rezafungin Population PK model parameter estimates and standard errors

| Parameter | Population mean | Magnitude of IIV (%CV) |
|-----------|-----------------|------------------------|
|           | Final estimate  | %SEM                  | Final estimate | %SEM |
| CL (L/h)  | 0.188           | —                     | 13.0          | 14.6 |
| Vc (L)    | 8.94            | —                     | 28.0          | 15.6 |
| Q2 (L/h)  | 24.4            | —                     | 45.2          | 17.1 |
| V2 (L)    | 12.6            | —                     | 8.81          | 17.0 |
| Q3 (L/h)  | 0.912           | —                     | 84.3          | 17.0 |
| V3 (L)    | 8.75            | —                     | 19.6          | 15.9 |
| Q4 (L/h)  | 0.0739          | —                     | 44.7          | 16.3 |
| V4 (L)    | 27.9            | —                     | 81.3          | 18.0 |
| CL coefficient (L/h/75 kg) | 0.187 | 1.46 | — | — |
| Vc coefficient (L/75 kg) | 8.88 | 3.22 | — | — |
| Q2 coefficient (L/h/75 kg) | 24.3 | 5.42 | — | — |
| V2 coefficient (L/75 kg) | 12.5 | 1.04 | — | — |
| Q3 coefficient (L/h/75 kg) | 0.908 | 10.0 | — | — |
| V3 coefficient (L/75 kg) | 8.70 | 2.35 | — | — |
| Q4 coefficient (L/h/75 kg) | 0.0736 | 5.29 | — | — |
| V4 coefficient (L/75 kg) | 27.7 | 9.70 | — | — |
| SD\(n\) | 0.01            | —                     | —             | —    |
| SD\(s\) | 0.0624          | 4.72                  | —             | —    |

Minimum value of the objective function = -488.108

Abbreviations:
- CL = Total clearance, Vc = Volume of distribution of the central compartment, Q2, Q3, Q4 = Distributional clearances, V2, V3, V4 = Volume of distribution of the peripheral compartments, SD\(n\) = Intercept (additive) term for residual variability model for plasma concentrations, SD\(s\) = Slope (proportional) term for residual variability model, %SEM = Standard error of the mean (percent standard error of the mean), IIV = Inter-individual variability, %CV = Coefficient of variation (percent coefficient of variation)
Figure 1. Scatterplots of individual parameter estimates versus covariate values using the structural population PK model.

Abbreviations:
BMI = Body mass index, BSA = Body surface area, CL = Total clearance, Vc = Volume of distribution of the central compartment, Q2, Q3, Q4 = Distributional clearances, V2, V3, V4 = Volume of distribution of the peripheral compartments, CLCR = creatinine clearance.
Figure 2. Rezafungin plasma goodness-of-fit plots using the final population PK model.
Figure 3. Prediction-corrected comparison of observed and simulated rezafungin plasma concentrations on linear (A and C) and semi-log (B and D) scales up to 24 (A and B) and 480 (C and D) hours post-dose.