

Pharmacokinetics, Excretion, and Mass Balance of [¹⁴C]-Rezafungin Following Intravenous (IV) Administration in Healthy Adults

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INTRODUCTION

- Rezafungin is a once-weekly novel echinocandin antifungal currently in ongoing Ph3 clinical development (ReSTORE trial [NCT03667690] in treatment of candidemia and invasive candidiasis and reSPECT trial [NCT04368559] in prophylaxis against invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp.
- Rezafungin's distinctive pharmacokinetics (PK) allow for once-weekly dosing and high, front-loaded drug exposures
- Rezafungin has demonstrated extensive distribution and penetration to sites of infection with greater antifungal efficacy *in vivo* compared with current echinocandins[1]
- Nonclinical ADME studies[2] show rezafungin is primarily excreted unchanged in feces, with urine as a minor route. This study was conducted to characterize the mass balance, excretion, and PK of [¹⁴C]-rezafungin in human

METHODS

Subjects (N=9; male) received a single IV 400-mg rezafungin infusion containing 200 μ Ci of [¹⁴C]-rezafungin. Blood, urine, and feces were collected over 60 days; subjects were initially confined in the clinical research unit (CRU) for 17 days postdose and returned for two follow-up visits (days 29 and 60). Combusted whole blood, plasma, urine, and fecal samples were analyzed by liquid scintillation counting. During periods that subjects were away from the CRU, recovery of radioactivity was estimated by linear interpolation. Rezafungin concentration was measured by LC-MS/MS.

Metabolite Profiling. Plasma samples were pooled across subjects to produce inter-subject time point pools. Urine and fecal samples were pooled by subject across various time points up through 408 and 672 hours postdose, respectively. Selected plasma, urine, and fecal samples were profiled for rezafungin and metabolites by LC with radiochemical and high-resolution mass spectrometry detection; metabolites were identified by chromatography with known standards and/or by LC-MS/MS structure elucidation.

RESULTS

Rezafungin exhibited a long plasma half-life. Mean blood-to-plasma concentration ratios ranged from 0.860 to 1.02 through the last collection time point (day 60), which indicated low association of radioactivity with blood cells.

Fig 1. Mean Concentration-Time Profiles for Whole Blood/Plasma Radioactivity and Plasma Rezafungin

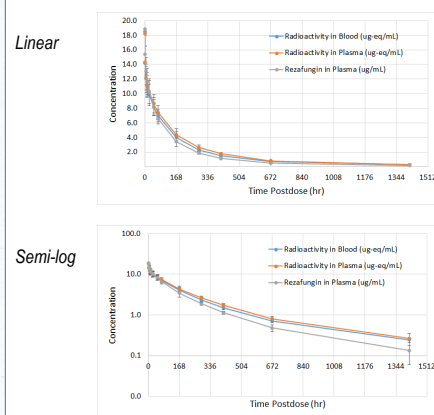


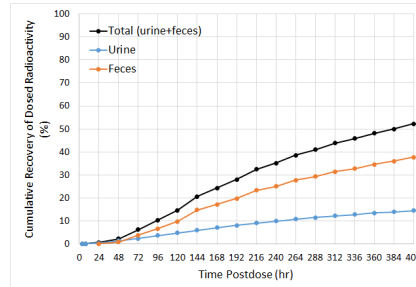
Table 1. Mean (SD) PK Parameters for Rezafungin, Plasma Total Radioactivity, and Whole Blood Total Radioactivity

Parameter	Plasma Rezafungin	Plasma Total Radioactivity	Whole Blood Total Radioactivity
AUC _{0-∞} (ug.hr/mL or ug-eq.hr/mL)	2050 (137)	2600 (163)	2390 (175)
AUC ₀₋₆₀ (ug.hr/mL or ug-eq.hr/mL)	2110 (141)	2750 (182)	2450 (200)
C _{max} (ug/mL)	18.9 (2.50)	18.2 (2.28)	18.5 (2.24)
t _{1/2} (hr)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
t _{1/2} (hr)	341 (42.8)	387 (44.8)	408 (39.7)
CL (L/hr)	0.180 (0.131)	NA	NA
V _Z (L)	88.6 (12.0)	NA	NA

RESULTS (cont'd)

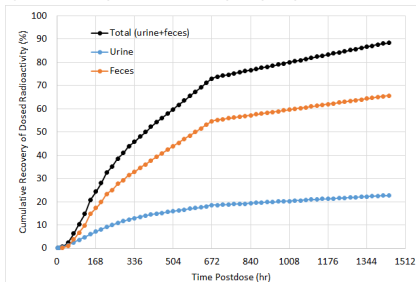
Rezafungin was mainly excreted unchanged in feces. Cumulative recovery of radioactivity from excreta collected through the first 17 days was 52.3% (37.8% in feces, 14.5% in urine) indicating the slow elimination of rezafungin.

Fig 2. Recovery of Radioactivity – first 17 Days Postdose (%)



Based on linear interpolation, by day 60, overall recovery of the administered dose was estimated to be 88.3% (65.6% in feces, 22.7% in urine).

Fig 3. Recovery of Radioactivity – by Day 60 Postdose (%)

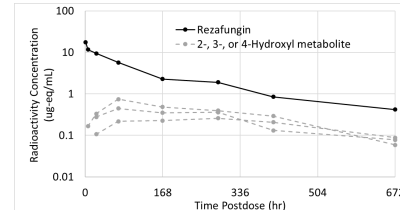


RESULTS (cont'd)

As similarly found in animals², rezafungin was the predominant compound measured in plasma and feces across all collected time points. In the urine, low level, inactive, oxidative metabolites were identified as 2-, 3-, or 4-hydroxypentyl rezafungin, and desmethyl-rezafungin.

Rezafungin accounts for ~77% of total plasma radioactivity AUC, and metabolites accounted for less than 10% of the total plasma radioactivity AUC exposure.

Fig 4. Radioactivity Concentration (semi-log) -Time Profile in Plasma



CONCLUSIONS

Results from this human excretion balance, metabolism, and PK study are consistent with nonclinical results, which showed fecal excretion as the major route of elimination of [¹⁴C]-rezafungin. Overall, rezafungin underwent minimal metabolism and slow elimination after IV administration.

REFERENCES

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- Ong V, et al. Absorption, Distribution, and Excretion of [¹⁴C]Rezafungin after Single-Dose Intravenous (IV) Administration in Rats and Monkeys[†], 29th European Congress of Clinical Microbiology & Infectious Diseases, 2019.

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