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EFFECT OF HEPATIC IMPAIRMENT ON THE SAFETY AND PHARMACOKINETICS OF REZAFUNGIN

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INTRODUCTION

Rezafungin is a novel echinocandin antifungal being developed for treatment of candidemia and invasive candidiasis, and for prevention of invasive fungal diseases among immunosuppressed patients.

In the Phase 2 and Phase 3 treatment trials of rezafungin compared with caspofungin (STRIVE [NCT02734862] and ReSTORE [NCT03667690], respectively), patients with severe hepatic impairment were not included due to lack of caspofungin data in this population.

Rezafungin was previously evaluated in patients with moderate hepatic impairment and showed no meaningful differences in pharmacokinetics (PK) or tolerability. Here we report an open-label, single-dose study on rezafungin in patients with severe hepatic impairment (Child-Pugh class C).

METHODS

To investigate the safety, tolerability, and PK of rezafungin in subjects with severe hepatic impairment, 8 subjects with hepatic impairment and 8 healthy subjects with normal hepatic function matched for age, sex, and body mass index (BMI) were enrolled and received a single 400-mg intravenous 1-hour infusion of rezafungin. Plasma PK sampling was performed at various time points through 336 hours (14 days) postdose. Rezafungin PK parameters were derived using non-compartmental analysis. Safety was assessed throughout the study.

RESULTS

Table 1: Demographic Characteristics (Safety Population)

Characteristic	Severe hepatic impairment (N = 8)	Normal hepatic function (N = 8)
Age, years		
Mean (SD)	58.0 (9.23)	56.6 (4.81)
Median (Min, Max)	61.5 (41, 68)	57.5 (50, 61)
Sex, n (%)		
Male	6 (75.0)	6 (75.0)
Female	2 (25.0)	2 (25.0)
Ethnicity, n (%)		
Hispanic/Latino	2 (25.0)	1 (12.5)
Not Hispanic/Not Latino	6 (75.0)	7 (87.5)
Race, n (%)		
White	7 (87.5)	4 (50.0)
Black or African American	0	4 (50.0)
Asian	0	0
Other	1 (12.5)	0
Weight, kg		
Mean (SD)	87.55 (11.600)	85.11 (9.386)
Median (Min, Max)	87.65 (74.3, 106.3)	84.00 (71.8, 98.0)
Height, cm		
Mean (SD)	171.95 (7.170)	169.40 (4.912)
Median (Min, Max)	173.50 (161.5, 181.5)	168.40 (163.0, 178.0)
Body Mass Index, kg/m^2		
Mean (SD)	29.64 (3.681)	29.66 (3.007)
Median (Min, Max)	30.55 (23.5, 34.4)	29.35 (25.3, 33.6)

Table 2: Plasma Rezafungin PK Parameter Estimates by Hepatic Function After a Single 400-mg IV Infusion of Rezafungin

Group	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg•h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_z (L)
Severely impaired (n=8)	16.6 (2.01)	1250 (224)	120.8 (11.82)	0.33 (0.06)	57.1 (9.89)
Normal (n=8)	23.1 (4.12)	1840 (340)	124.1 (27.51)	0.22 (0.04)	40.0 (10.3)

Data are presented as mean (standard deviation).

PK

Rezafungin PK exposure (C_{max} and AUC) in subjects with hepatic impairment was ~30% lower than that in normal hepatic function (Table 2), while half-life values were generally similar (hepatic impairment: 121 h, normal hepatic function:124 h; Figure 2).

Figure 1: Overlaid Concentration-Time Spaghetti Plots by Hepatic Function After a Single 400-mg IV Infusion of Rezafungin (Linear Scale)

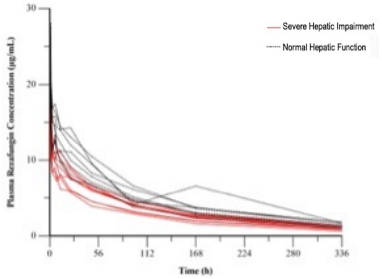
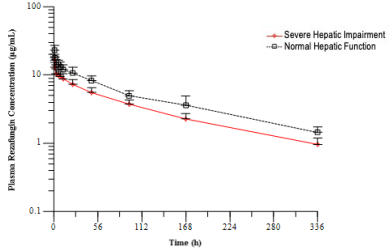


Figure 2: Mean (+SD) Plasma Rezafungin Concentration-Time Profiles by Hepatic Function After a Single 400-mg IV Infusion of Rezafungin (Semi-Logarithmic Scale)



RESULTS

SAFETY

There were no serious AEs or deaths. Three hepatic impairment subjects had one adverse event (AE) each (bronchitis, worsening hepatic encephalopathy, hyponatremia), all moderate in severity. There were no AEs in the subjects with normal hepatic function. No AEs were considered related to rezafungin, and all were resolved or resolving by the end of the study.

CONCLUSIONS

In this Phase 1 clinical trial, rezafungin was well tolerated in subjects with severe hepatic impairment and showed modestly reduced exposure that was generally within the range observed in matched subjects with normal hepatic function.

These differences, though not considered to be clinically significant, are likely attributable to differences in albumin and protein binding levels between the groups.

These findings support no rezafungin dose adjustment in subjects with severe hepatic impairment.

DISCLOSURES / ACKNOWLEDGMENTS

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