EFFECT OF MODERATE HEPATIC IMPAIRMENT ON THE SAFETY AND PHARMACOKINETICS OF REZAFUNGIN

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VO, TS, and SF are employees and shareholders of Cidara, and AJ is a consultant of Cidara.

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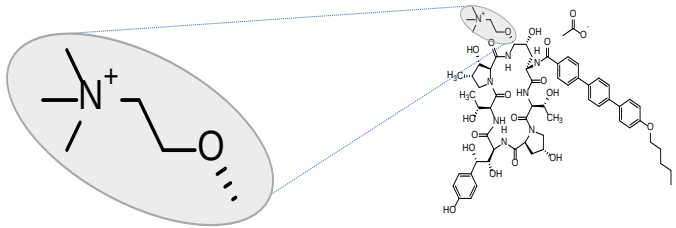
Introduction - Rezafungin

- Novel echinocandin antifungal that inhibits the synthesis of 1,3-β-D-glucan
- In Phase 3 development for treatment candidemia and invasive candidiasis and for prevention of IFD caused by *Candida* and *Aspergillus* spp. and *Pneumocystis jirovecii*

REZAFUNGIN



Structural modification designed to yield improved chemical & biological properties

- Mass balance studies have demonstrated that elimination of rezafungin is primarily in the feces as unchanged rezafungin
- An open-label, single-dose study was conducted to investigate the safety, tolerability, and PK of rezafungin in subjects with hepatic impairment and healthy subjects

IFD=invasive fungal disease; PK=pharmacokinetics.

Study Design

- Open-label study to investigate the safety, tolerability, and PK of rezafungin

Subjects	N	Treatment
Moderate hepatic impairment (Child-Pugh Class B)	8	Single rezafungin 400-mg, 1-hr IV infusion
Normal hepatic function*	8	

*matched for **age** (within ± 10 years of mean for hepatic impaired group); **sex** (similar M:F ratios); and **BMI** (within ± 20% of mean for hepatic impaired group)

Plasma Sampling	Collection Schedule
Rezafungin PK	at end of infusion and 1.5, 3, 6, 8, 12, 24, 48, 96, 168, and 336 h post-dose
Rezafungin protein binding	prior to dosing (spiked), at 45 min post start of infusion, and at 72 h post infusion

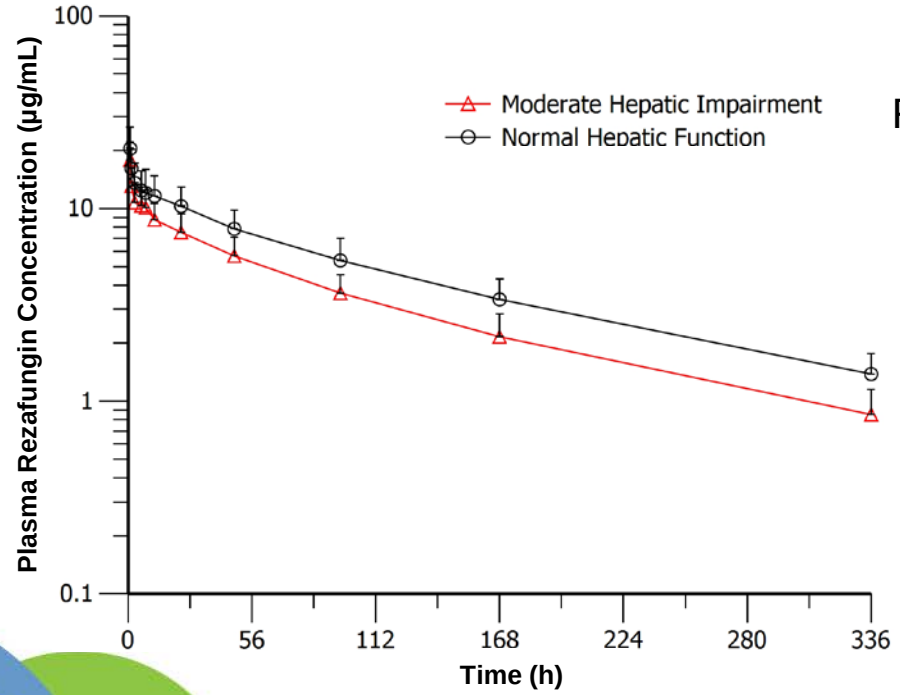
- Vital signs, physical examinations, 12-lead ECGs, clinical laboratory assessments, AEs, and concomitant medication usage were evaluated for all subjects through the Day 32 Follow-up visit

AE=adverse event; BMI=body mass index; ECG=electrocardigram.

Results

- Sixteen subjects (4 male and 4 females/group) were enrolled and completed the study

Mean (+SD) Plasma Rezafungin Concentration-Time Profiles After Single 400-mg IV Infusion of Rezafungin



Rezafungin concentrations

- were similar between groups
- declined in multi-exponential manner
- were >20-fold above detection limits (50 ng/mL) at the last collection time of 2 weeks post dose

Results

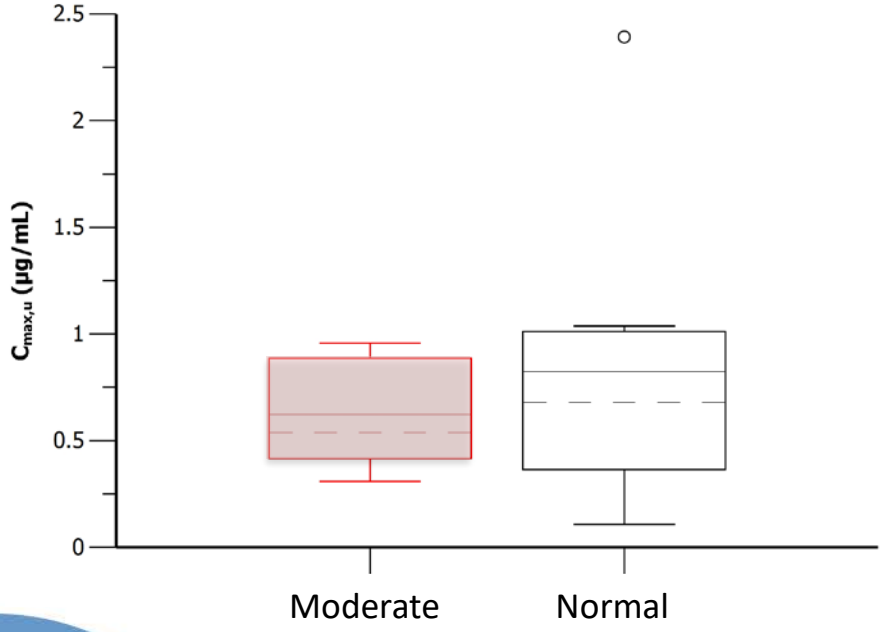
Plasma Rezafungin PK in Subjects with Moderate Hepatic Impairment or Normal Hepatic Function After a Single Dose of IV Rezafungin 400 mg

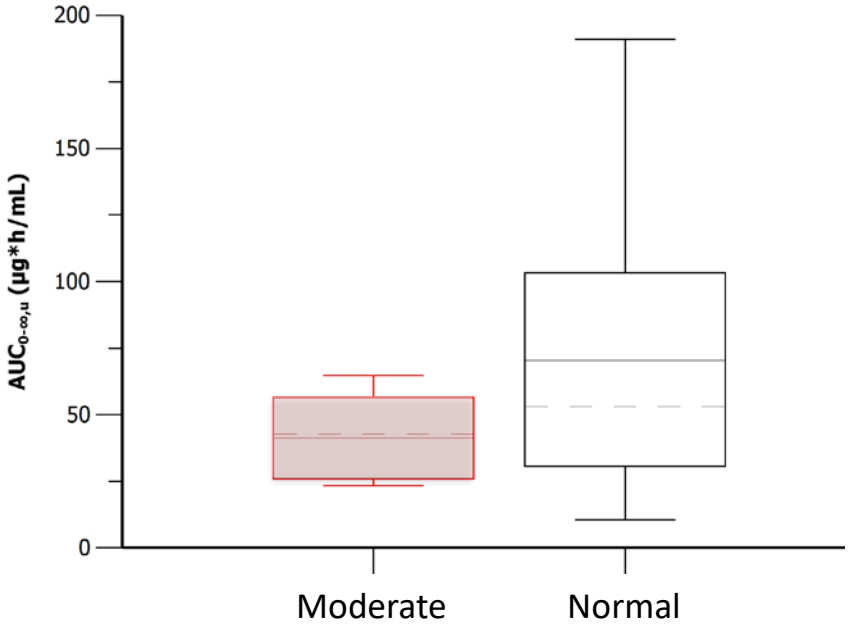
Group	Statistic	C_{max} (µg/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (µg•h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_z (L)
Moderate Hepatic Impairment	Mean	17.9	1	1210	110.27	0.353	55.1
	SD	4.23	(1.00-1.00)	329	11.81	0.0919	10.8
Normal Hepatic Function	Mean	20.6	1	1780	123.1	0.237	42.3
	SD	5.88	(1.00-1.50)	456	18.91	0.0559	12.9

N=8 per group.
[a]Median (Min – Max) are reported for t_{max}

Results

Plasma Rezafungin Unbound C_{max} and $AUC_{0-\infty}$ in Subjects with Moderate Hepatic Impairment or Normal Hepatic Function After a Single Dose of IV Rezafungin 400 mg





Results- Safety

Treatment Emergent AE Severity in Subjects with Moderate Hepatic Impairment or Normal Hepatic Function After a Single Dose of IV Rezafungin 400 mg

Adverse Event[a]	Moderate Hepatic Impaired N=8 n (%)			Normal Hepatic Function N = 8 n (%)		
	Adverse Event Severity					
	Mild	Moderate	Severe	Mild	Moderate	Severe
At least one TEAE	3 (37.5%)	0	0	1 (12.5%)	0	0
Nausea	1 (12.5%)	0	0	0	0	0
Headache	1 (12.5%)	0	0	0	0	0
Pain	1 (12.5%)	0	0	0	0	0
Infusion site extravasation	1 (12.5%)	0	0	1 (12.5%)	0	0

[a]Adverse events are coded using MedDRA version 22.1

AE=adverse event; TEAE=treatment-emergent AE.

Conclusions

- Systemic exposure of rezafungin, though modestly reduced in subjects with moderate hepatic impairment, remained within the range observed in subjects with normal hepatic function
- Importantly, these minor differences are not indicative of reduced drug clearance that can be associated with hepatic impairment and are likely to reflect variability between small groups of subjects
- This study demonstrated that dose adjustment of rezafungin is not warranted in subjects with moderate hepatic impairment, and that it was safe to study subjects with severe hepatic impairment (ongoing)
- Rezafungin was safe and well tolerated in subjects with moderate hepatic impairment