Pharmacodynamic (PD) evaluation of Rezafungin (CD101) against *Candida auris* in the persistently neutropenic murine model of disseminated candidiasis

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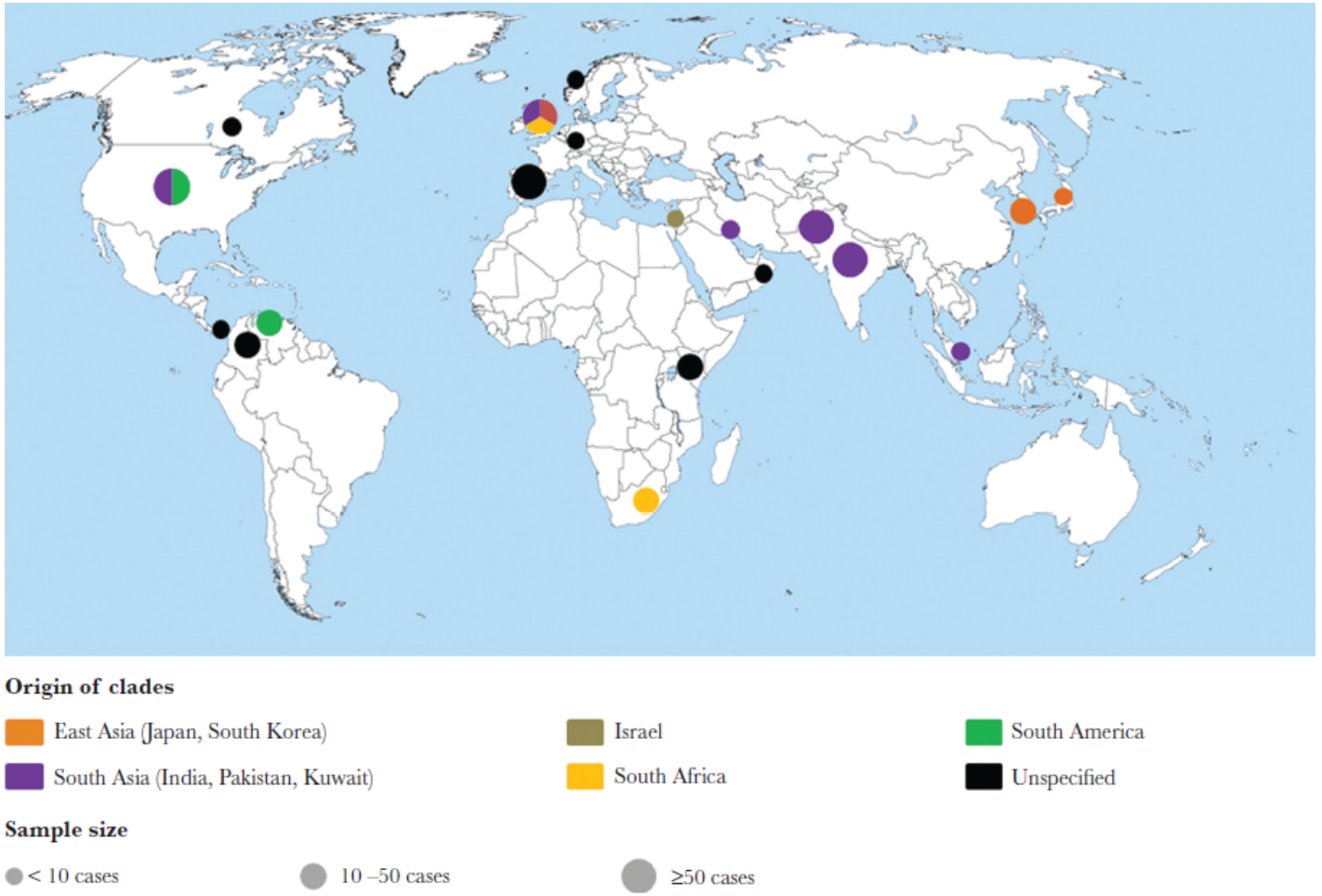
Transparency Declaration

- This study was supported by funding from Cidara Therapeutics, Inc.

Candida auris - Background

- Global emerging pathogen
- Mortality rate 40-60%
- Environmental persistence and interhuman transmission
- Drug-resistance and multi-drug resistance is typical
  - Fluconazole resistance >90%
  - Amphotericin B resistance 30-50%
  - Echinocandin resistance 5-10%



Lamoth F & Kontoyiannis DP. J Infec Dis 2018

Rezafungin (CD101)

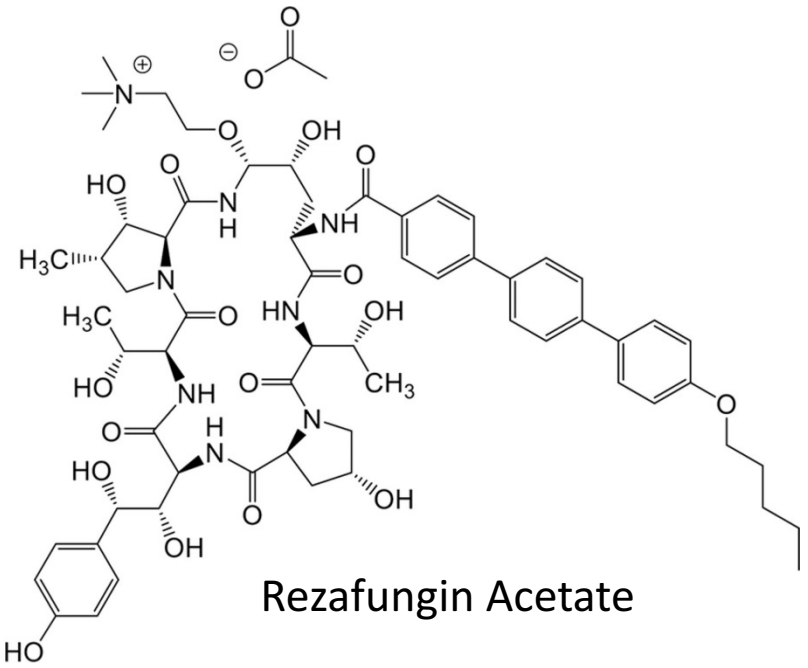
- Novel echinocandin with toxicological and pharmacokinetic advantages including a prolonged terminal half-life of 130-hours in humans
- Developed for extended interval dosing (i.e. once-weekly intravenous infusions)
- Echinocandin PK/PD studies have

  demonstrated the importance of both

  AUC/MIC and Cmax/MIC

  - Rezafungin pharmacological properties

    allow for maximizing both PD indices



Rezafungin Acetate

Lepak AJ et al, AAC 2018
Lakota EA at al, AAC 2018

Previous Rezafungin Murine PK/PD Target Studies

Lepak AJ, et al. Antimicrob Agents Chemother 2018;62:e02154-17

	C. albicans			*C. glabrata*			*C. parapsilosis*	
	Stasis	**1-log kill**		**Stasis**	**1-log kill**		**Stasis**	**1-log kill**
24h fAUC/MIC*	2.89	5.14		0.20	0.66		~3	NA

*PD targets are numerically lower (especially notable for *C. glabrata*) than comparator echinocandins

Current Study

<u>Aim:</u> Determine the pharmacodynamic target for treatment of disseminated *C. auris* infection in the neutropenic murine model of invasive candidiasis

<u>Methods</u>

Strains:

- 4 *C. auris* strains (one FKS mutant strain)

Susceptibility testing:

- MICs by CLSI methods

Murine PK:

- Plasma PK from groups of mice after IP administration of rezafungin at 1, 4, 16, and 64 mg/kg
- Non-compartmental model

Infection Model and Analysis:

- 6-week old Swiss/ICR female mice (23-27g)
- Neutropenia by cyclophosphamide injection at day -4, -1, +2 and +4
- Inoculum of 5.99±0.29 $\log_{10}$ CFU/mL injected into tail vein, 2-hours later first dose of drug is administered
- Rezafungin dose (1, 4, 16 or 64 mg/kg) IP on day 0, 3, 6 to mimic once-weekly dosing in humans
- Infectious burden enumerated from kidneys on day 7 by CFU counts
- Treatment data and AUC/MIC evaluated by sigmoid Emax model (Hill equation)
- Static and 1-log kill target exposures were determined

Strains and *in vitro* Susceptibility Testing

Strain	Country of Origin	Log_{10} growth in Untreated Controls (CFU/kidneys)	In vitro Susceptibility Results (mg/L)			
			Rezafungin	Fluconazole	Micafungin	Amphotericin B
B11220	Japan	3.06	**0.06**	4	0.125	0.38
B11785	Colombia	3.43	**0.125**	8	0.5	1.5
B11799	Colombia	3.67	**0.25**	16	2	0.5
B11211*	India	3.17	**2**	256	4	1.5

* *FKS1_HS1_S639F*

Murine Pharmacokinetics

Plasma concentrations of rezafungin (CD101) in mice following single IP doses. Each symbol is the mean and standard deviation for three mice. Cmax, peak concentration, AUC, area under concentration-time curve from zero to infinity, T1/2, terminal elimination half-life

Treatment Studies

Rezafungin dose-response curves against *C. auris* (left). Relationship between total- (red) and free- (blue) drug AUC/MIC and therapeutic effect (right). Groups of mice were treated with one of four rezafungin dosing regimens administered every three days over the 7 day experimental period. Infectious burden was enumerated from kidney homogenates and compared to the burden at time point zero (dashed line). Points above the dashed horizontal line represent net increase in burden over time and those below the line represent a net decrease. PD parameters are also shown in the figure on the right including regression analysis.

PD Target Exposures Associate with Net Stasis and 1-log kill Endpoints

Strain	MIC (mg/L)	Static Dose (mg/kg)	Stasis Ave 24 h AUC/MIC	Stasis Ave 24 h fAUC/MIC	1 log kill dose (mg/kg)	1 log kill Ave 24 h AUC/MIC	1 log kill Ave 24 h fAUC/MIC
B11220	0.06	0.87	144.78	1.16	6.99	987.68	7.90
B11785	0.125	6.09	421.39	3.4	10.65	685.80	5.49
B11799	0.25	8.76	288.72	2.3	16.17	488.81	3.91
B11211	2	23.04	82.95	0.66	NA*		
Mean		**9.69**	**234.46**	**1.88**	**11.27**	**720.76**	**5.77**
Median		**7.43**	**216.75**	**1.73**	**10.65**	**685.80**	**5.49**
Std Dev		**9.48**	**151.53**	**1.21**	**4.62**	**251.26**	**2.01**

*NA, not achieved

Human Exposure

- Translating PK/PD targets to humans
  - Rezafungin 400 mg IV once weekly in humans
    - Total $AUC_{0\text{-}168}$ 1840 mg*h/L, 2.6% free drug ---> 47.84 mg*h/L free AUC or average 24 h free drug AUC of about 7 mg*h/L
    - Using human free drug PK estimates and stasis PD targets yields an MIC ceiling estimate of 2-4 mg/L, for 1-log kill target the MIC ceiling estimate would be 1-2 mg/L

Conclusions

- Rezafungin demonstrated *in vivo* potency against *C. auris* in the neutropenic disseminated candidiasis model using an extended interval dosing regimen to mirror human dosing regimens
  - Efficacy was demonstrated against a highly resistant strain (B11211) with known *FKS1* mutation
- PK/PD target exposures of free drug 24 h AUC/MIC of 2 and 6 led to stasis and 1-log kill, respectively
- Rezafungin is a valuable addition to the antifungal armamentarium, with PK advantages that permit achievement of optimal PK/PD drug exposures in extended-interval dosing regimens and against strains with elevated echinocandin MICs