Safety and Pharmacokinetics of Single and Multiple Doses of CD101 IV: Results from Two Phase 1 Dose-Escalation Studies

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INTRODUCTION AND PURPOSE

- CD101 IV is a novel echinocandin being developed for treatment of invasive fungal infections as a once-weekly, intravenous therapy that provides high plasma exposure
- CD101 has potent in vitro activity and was safe and efficacious in animal models of candidiasis and aspergillosis,[1-2] as well as vulvovaginal candidiasis[3]
- CD101 IV safely achieves high plasma exposures[4] that are advantageous for front-loading drug exposure (maximizing drug effect early to benefit efficacy)[5] and its long-half life enables weekly dosing
- Two Phase 1 studies[6] were conducted to determine the safety, tolerability, and PK profile of single- and multiple-ascending doses of CD101 administered intravenously (IV) in healthy adults.

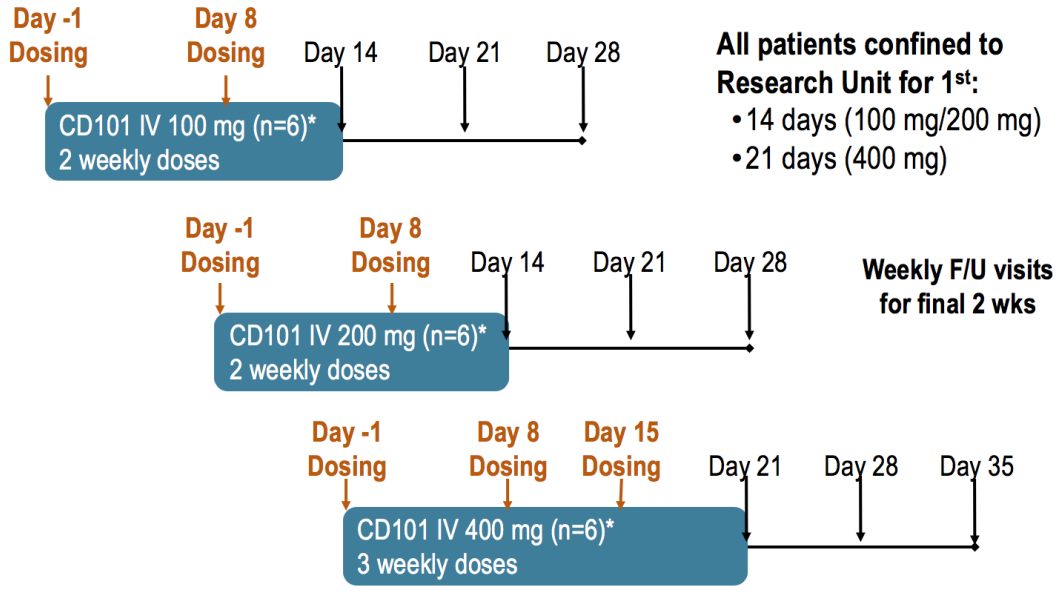
METHODS

- Randomized, double-blind, placebo-controlled, single-center, dose-escalation trials that studied CD101 or placebo infused IV over 1 h

Single-Ascending Dose Subjects and Treatments

Treatment	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Totals
CD101 IV	50 mg n = 6	100 mg n = 6	200 mg n = 6	400 mg n = 6	24
Placebo	n = 2	n = 2	n = 2	n = 2	8

Multiple-Ascending Dose Study Design



*Each dosing cohort included a Placebo group (n=2 per cohort)

Safety Assessments

- Adverse events (AEs), serious AEs (SAEs): long follow-up after last dose (up to 21 d) for monitoring of potential delayed safety events
- ECGs and urinalysis (UA), hematology and serum chemistry
- Additional assessments at weekly visits for 21 d after last dose

PK Evaluation

- Plasma and urine sampling after dosing and for 3 wks after the last dose; CD101 concentrations analyzed by LC-MS/MS method
- PK parameters calculated using non-compartmental methods with validated software (Phoenix® WinNonlin®, Version 6.3)

RESULTS

- All subjects in both studies were included in safety and PK analyses, with one withdrawal (100 mg group, single-ascending dose study) due to a family emergency

Disposition and Predominant Baseline Characteristics by Study

	Single-ascending dose (N=32)	Multiple-ascending dose (N=24)
Age, mean±SD	43.2±7.9 years	42.8±9.4 years
Male, n (%)	17 (53)	12 (50)
Hispanic or Latino, n (%)	30 (94)	18 (75)
White, n (%)	31 (97)	21 (88)
BMI, mean±SD	28.1±2.6 kg/m^2	27.2±2.9 kg/m^2

RESULTS (cont'd)

Safety

- No SAEs, severe AEs, study withdrawals due to AE, or deaths
- No dose-response trends in treatment-emergent AEs (TEAEs) or TEAEs related to study drug across single-ascending dose cohorts
- Relatively higher incidence of TEAEs with 400 mg x 3 doses
  - Mild transient infusion reactions, in 3/6 subjects with the third dose of 400 mg and 1/6 subjects with the second dose of 100 mg, resolved within minutes of infusion without sequelae or interruption/discontinuation of infusion

No. of Subjects w/TEAEs Following Single-/Multiple- Ascending Doses of CD101

TEAE	CD101 IV dose (mg)				Placebo	CD101 IV dose (mg)			Placebo
	50	100	200	400		100 x3	200 x3	400 x3	
All	3 of 6	0 of 6	3 of 6	1 of 6	5 of 8	3 of 6	2 of 6	4 of 6	2 of 6
Mild, n	3	0	2	0	2	3	1	2	1
Moderate, n	0	0	1	1	3	0	1	2	1

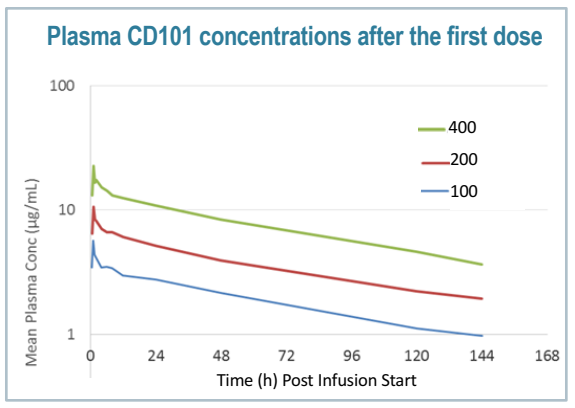
Laboratory Values

- No clinically significant trends in vital signs, physical exam, ECG, or laboratory abnormalities (hematology, chemistry, or UA)
- Trends in mean values and changes from baseline were similar between CD101 IV and placebo groups

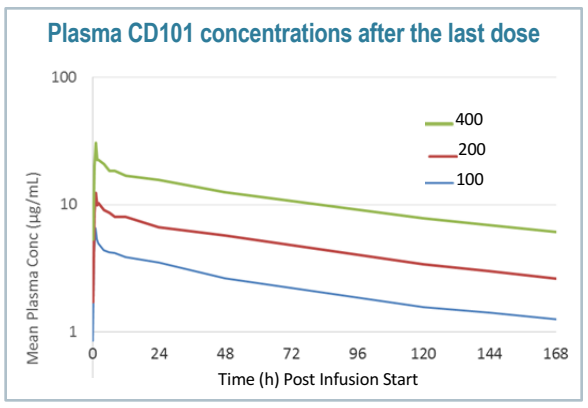
Pharmacokinetics

- In both studies, AUC and C_{max} increased proportionally with dose; total CL was low and comparable across dose levels
- Single-ascending dose PK was consistent with that of the first dose in the multiple-ascending-dose study for each dose cohort (Figures)

Plasma CD101 concentrations after the first dose



Plasma CD101 concentrations after the last dose



- Minor accumulation; ≤0.26% of the CD101 IV dose excreted in urine
- Mean $t_{1/2}$ on Days 8 or 15 (range, 150-154 h) double that of Day 1 (range, 78-85 h); total body CL on Day 1 double that of Days 8 and 15
- Higher $t_{1/2}$ and lower CL values reflect longer PK sampling interval (480 h) following last dose (Day 8 or 15) than for the first (144 h)
- Mean V_z similar for all 3 cohorts (range, 26-32 L)

CONCLUSIONS

- These two Phase 1 studies established the safety and PK profile of single- and multiple- ascending doses of CD101 IV in healthy subjects
  - CD101 IV up to 400 mg once weekly x 3 consecutive weeks was safe and well tolerated
  - Overall incidences of AEs similar between CD101 IV groups and placebo
  - No clinically significant trends in vital signs, physical exam, or lab findings
  - CD101 IV demonstrated dose-proportional PK with a long half-life, plasma concentrations through 480 hours after the last dose and minor accumulation
- These data support the continued development of CD101 IV for treatment of candidemia and invasive candidiasis in the inpatient and outpatient settings

REFERENCES

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2. ICAAC 2015 Poster F-748.
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5. ICAAC 2015 Posters F-753, F-754.
6. NCT02516904; NCT02551549

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