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Pharmacokinetics, Safety, and Target Attainment of Single and Multiple Doses of CD101 IV – a Novel, Once-Weekly Echinocandin

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ABSTRACT

Introduction: CD101 is a novel, long-acting echinocandin with activity against *Candida* and *Aspergillus* spp. in development for prevention and treatment of serious fungal infections. CD101 has shown robust efficacy in neutropenic mouse infection models of disseminated candidiasis as well as aspergillosis and an excellent nonclinical safety/toxicology profile. Two randomized, double-blind, placebo-controlled, phase 1, dose-escalation trials were conducted to establish the safety and pharmacokinetics (PK) of single and multiple weekly dosing of CD101 administered intravenously. PK/pharmacodynamic (PD) analyses of these data were conducted to evaluate the probability of achieving therapeutic targets against *Candida*.

Methods: Sequential cohorts of 8 healthy subjects (n=6, CD101; n=2, placebo) received a single dose of CD101 (50, 100, 200, 400 mg) or multiple weekly doses (100 mg x2, 200 mg x2, 400 mg x3) infused intravenously over 1 hour. PK was assessed using plasma and urine samples collected over 21 days. Safety and tolerability were assessed by adverse events (AEs), vital signs, physical exams, electrocardiograms, and safety laboratory values up to 21 days after dosing. Data from these clinical trials were used to develop a population PK model and perform Monte Carlo simulation (n=2000) evaluating a single dose of 400 mg and multiple weekly doses (400 mg x3 or 400 mg x1 followed by 200 mg x2) chosen for an upcoming Phase 2, dose-ranging trial in candidemia. For each dosing regimen, percent probabilities of PK/PD target attainment against *Candida albicans* (R303, human blood isolate) were calculated.

Results: CD101 and placebo groups had similar incidences of AEs. The majority were mild, and all resolved completely. Slightly higher incidences of AEs and mild transient infusion reactions were seen in the group that received CD101 400 mg x 3 weekly doses. There were no clinically significant safety issues in observed or laboratory assessments, and no deaths, serious AEs, severe AEs, or withdrawals due to an AE. CD101 IV demonstrated dose-proportional plasma exposures, low apparent clearance (<0.3 L/h), long half-life ($t_{1/2}$ >80 h), minimal urinary excretion (<1%), and minor accumulation (30% to 55%, multiple-dose study). The percent probability of therapeutic target attainment against *C. albicans* was 100% for both weekly dosing regimens of CD101 (Figure) and >99% for the single dose of CD101 400 mg.

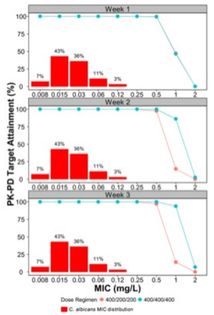


Figure. Probability of achieving therapeutic target against *C. albicans* (R303 clinical isolate) with two CD101 dose regimens (lines) and MIC distribution of *C. albicans* from recent surveillance (columns)

Conclusion: CD101 IV was safe and well tolerated as single and multiple doses up to 400 mg once weekly for up to 3 weeks. Target attainment analyses support the dosing regimens evaluated and suggest these regimens will effectively cover the vast majority of *Candida* likely to be encountered clinically. The high plasma exposures achieved with CD101 IV may improve treatment outcomes compared to other echinocandins, and its long $t_{1/2}$ enables weekly dosing. These findings support the continued development of CD101 IV dosed once weekly as treatment or prophylaxis for invasive fungal infections, delivering PK/PD optimized drug exposures while reducing the resources required for therapeutic drug monitoring.

INTRODUCTION

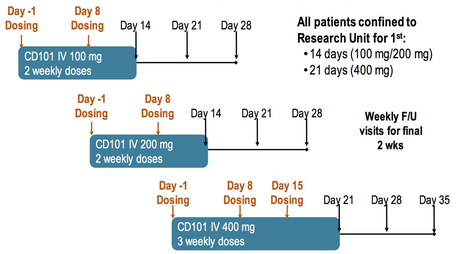
- CD101 is a novel echinocandin in development for prevention and treatment of serious fungal infections.
- CD101 has in vitro activity against *Candida* and *Aspergillus* spp., including azole-resistant strains[1] and has demonstrated safety and efficacy in animal models of candidiasis and aspergillosis,[2,3] as well as in a mouse model of *Pneumocystis* prophylaxis.[4]
- CD101 IV is an intravenous formulation that safely achieves high plasma exposures, which may improve treatment outcomes,[3] and has a long-half life that enables weekly dosing.[5]
- The stability of CD101 supports additional dosage forms, such as subcutaneous and topical formulations, which are also in development.[5-8]
- Two Phase 1 studies were conducted to determine the safety, tolerability, and PK profile of single- and multiple-ascending doses of CD101 administered intravenously (IV) in healthy adults (NCT02516904 and NCT02551549, respectively).

METHODS

Study Design and Treatments

- These were randomized, double-blind, placebo-controlled, single-center, dose-escalation studies in which CD101 or placebo was infused IV over 1 h in the following dosing cohorts.
- In the single-ascending dose study (N=32), subjects were randomized to receive one dose of CD101 50 mg, 100 mg, 200 mg, or 400 mg, or placebo. Details of the multiple-ascending dose study (N=24) are shown below. Both studies randomized 6 CD101 and 2 placebo subjects per cohort.

Multiple-ascending Dose Study Design



METHODS (cont'd)

Safety

- Adverse events (AEs) and serious AEs (SAEs): up to 21 days of follow-up after the last dose allowed monitoring for potential delayed safety events
- ECGs and urinalysis (UA), hematology and serum chemistry

PK

- Plasma and urine sampling after dosing and for 3 weeks 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)
- Percent probabilities of PK/PD target attainment (TA) against *C. albicans* (R303, human blood isolate) with 3 weeks of once-weekly doses of CD101 (400/400/400 mg and 400/200/200 mg)

RESULTS

- All subjects were included in safety and PK analyses; one subject withdrew (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

Safety

- No SAEs, severe AEs, study withdrawals due to an 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 observed in the group receiving 400 mg x 3 doses
  - Transient infusion reactions (in 3/6 subjects with 3rd dose of 400 mg and 1/6 subjects with 2nd dose of 100 mg) resolved within minutes of infusion without sequelae or interruption/discontinuation of infusion

No. of Subjects with TEAEs Following CD101 Treatment by Cohort

	CD101 IV dose (mg)				PBO	CD101 IV dose (mg)			PBO
TEAE	50	100	200	400		100 x2	200 x2	400 x3	
All, n	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	3	0	2	0	2	3	1	2	1
Moderate	0	0	1	1	3	0	1	2	1

PBO = placebo subjects pooled across cohorts; TEAE = treatment-emergent adverse event.

RESULTS (cont'd)

- No clinically significant (CS) 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

Summary of Laboratory Findings[a]

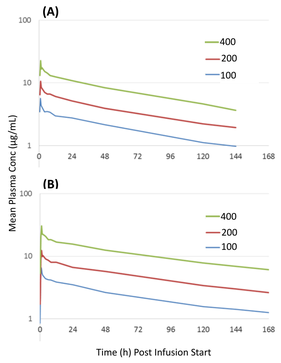
	CD101 IV dose (mg)				PBO	CD101 IV dose (mg)			PBO
Lab Finding[b]	50	100	200	400		100 x2	200 x2	400 x3	
Hematology, n (%)									
Normal	78 (87)	80 (99)	89 (99)	88 (98)	115 (96)	136 (94)	137 (95)	198 (100)	159 (98)
Abnormal- not CS	12 (13)	2 (2)	1 (1)	2 (2)	5 (4)	8 (6)	7 (5)	0	3 (2)
Abnormal- CS	0	0	0	0	0	0	0	0	0
Chemistries, n (%)									
Normal	461 (96)	432 (100)	465 (97)	475 (99)	619 (96.5)	699 (97)	696 (97)	969 (98)	790 (98)
Abnormal- not CS	19 (4)	0	16 (3)	5 (1)	18 (3)	21 (3)	24 (3)	21 (2)	20 (3)
Abnormal- CS	0	0	0	0	2 (0.5)	1[c]	0	0	0

CS = clinically significant, PBO = placebo subjects pooled across cohorts.
[a] Single-ascending dose study: 5 blood draws per subject on Days 2, 4, 7, 14, and 21; multiple-ascending dose study: 8 blood draws per subject in the 100 mg/200 mg dose cohorts (CD101 IV and placebo groups) on Days 2, 4, 7, 9, 11, 14, 21, and 28; 11 blood draws in the 400 mg dose cohort on Days 2, 4, 7, 9, 11, 14, 16, 18, 21, 28, 35.
[b] 3 parameters for hematology (hemoglobin, white blood cell count, platelets) and 15 for chemistry (calcium, chloride, bicarbonate, potassium, albumin, BUN, creatinine, glucose, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, protein, sodium).
[c] Value determined to be Abnormal-CS *a priori* at the start of the study; however, during the study, the lead clinician did not consider the abnormal lab to be clinically significant.

Pharmacokinetics

- Plasma CD101 conc. detectable through 144 h after first dose and 480 h after last dose
- Area under the curve and maximum plasma conc. increased dose-proportionally
- Single-ascending dose PK was consistent with that of the first multiple-ascending dose (Figs)

Plasma CD101 concentrations after the first (A) and last doses (B)



RESULTS (cont'd)

- Total clearance was low and comparable across dose levels (<0.3 L/h)
- ≤0.26% of the CD101 dose was excreted in urine
- Accumulation was 30% to 55% following multiple doses

Summary of CD101 PK Values

PK parameter	Mean (range)
Volume of distribution (V_d)	26-32 L
Clearance (Cl)	
Day 1	0.2463-0.2640 L/h
Days 8 and 15[a]	0.1202-0.1468 L/h
Half-life ($t_{1/2}$)	
Day 1	78-85 h
Days 8 and 15[a]	150-154 h

[a]Higher $t_{1/2}$ and lower CL values reflect the longer PK sampling interval (480 h) following the last dose (Day 8 or 15) than for the first (144 h).

- The probability of CD101 therapeutic TA against *C. albicans* was >99% with a single dose of CD101 400 mg (abstract Fig, top panel) and 100% after 3 weeks of once-weekly CD101 (400/400/400 mg and 400/200/200 mg, bottom panels).

CONCLUSIONS

- These two Phase 1 studies established the safety and PK of single- and multiple- ascending doses of CD101 IV in healthy adults.
  - Safe and well tolerated at doses up to 400 mg once weekly x 3 consecutive weeks
  - No CS trends in vital signs, physical exam, or labs
  - Dose-proportional PK with a long half-life, plasma concentrations through 480 hours after the last dose and minor accumulation
- The probability of therapeutic TA against Candida was 99% with a single dose and 100% after 3 weeks of once-weekly CD101.
- These data support the continued development of CD101 IV for prevention and treatment of serious fungal infections in the inpatient and outpatient settings.

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