Poster 258

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

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ABSTRACT

Introduction: CD101 IV is a novel echinocandin with activity against *Candida* and *Aspergillus* spp. in development as a high-exposure, once-weekly treatment for candidemia and invasive candidiasis.
Research Questions or Hypothesis: To establish the safety and pharmacokinetics (PK) of single and multiple weekly dosing of CD101 IV.
Study Design: Randomized, double-blind, placebo-controlled, phase 1, dose-escalation trials.
Methods: Sequential cohorts of 8 healthy subjects (n=6, active; n=2, placebo) received single (50, 100, 200, 400 mg) or multiple doses (100 mg ×2, 200 mg ×2, 400 mg ×3) of CD101 IV infused over 1 hour, once weekly. Plasma and urine samples over 21 days were collected for PK assessments. Safety and tolerability were assessed by adverse events (AEs), vital signs, physical exams, electrocardiograms (ECGs), and safety laboratory values up to 21 days after dosing.
Results: Overall incidences of AEs in the CD101 IV and placebo groups were similar. The majority of AEs were mild, and all resolved completely. The 400 mg x 3 dose group of the multiple-dose study had slightly higher incidences of AEs and mild transient infusion reactions. In both studies, there were no clinically significant postbaseline safety laboratory abnormalities; no safety issues related to ECGs, vital signs, or physical exams; and no deaths, serious AEs, severe AEs, or withdrawals due to an AE. CD101 plasma exposures were dose-proportional. CD101 IV demonstrated low apparent clearance (<0.3 L/hour), a long half-life ($t_{1/2}$ >80 h), minimal urinary excretion (<1%), and minor accumulation (30% to 55%, multiple-dose study).
Conclusion: CD101 IV was safe and well tolerated as single and multiple doses up to 400 mg once weekly for up to 3 weeks. CD101 IV demonstrated high plasma exposures that may improve treatment outcomes and a long $t_{1/2}$ that enables weekly dosing. These findings support the continued development of CD101 IV as a once-weekly therapy for treatment of invasive fungal infections.

INTRODUCTION

- 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 against *Candida* spp. and *Aspergillus* spp. and demonstrated safety and efficacy in animal models of candidiasis and aspergillosis,[1-2] as well as vulvovaginal candidiasis[3]
- The pharmacokinetic (PK)/pharmacodynamic profile of CD101 IV is advantageous for front-loading drug exposure (ie, maximizing drug effect early in the course of therapy to benefit efficacy)[4]
- CD101 IV safely achieves high plasma exposures[5] that may improve treatment outcomes and has a long-half life that enables weekly dosing
- 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

- 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

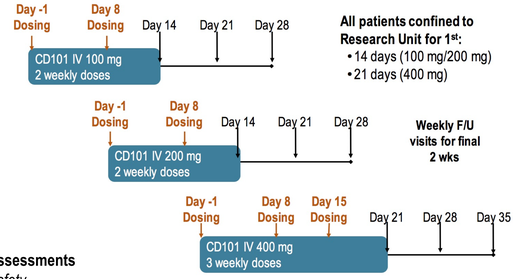
Single-Ascending Dose Subjects and Treatments

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
					32

METHODS (cont'd)

Multiple-Ascending Dose Subjects and Treatments

Treatment	Cohort 1	Cohort 2	Cohort 3	Totals
CD101 IV	100 mg n = 6	200 mg n = 6	400 mg n = 6	18
Placebo	n = 2	n = 2	n = 2	6
				24



Assessments

Safety

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

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)

RESULTS

- All subjects in both studies 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

RESULTS (cont'd)

Safety

Adverse Events

- No SAEs, severe AEs, study withdrawals due to an AE, or deaths in either study
- 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 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 with TEAEs Following Single- and Multiple-Ascending Doses of CD101

	CD101 IV dose (mg)				Placebo	CD101 IV dose (mg)			Placebo
TEAE	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 (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)				Placebo	CD101 IV dose (mg)			Placebo
Lab Finding[b]	50	100	200	400		100 x3	200 x3	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

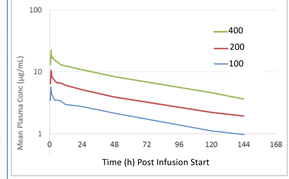
CS = clinically significant.
[a] Single-ascending dose study: 5 blood draws per subject on Days 2, 4, 7, 14, and 21; multiple-ascending dose study: 8 blood draws per subject in the 100 mg/200 mg dose cohorts (CD101 IV and placebo groups) on Days 2, 4, 7, 9, 11, 14, 21, and 28; 11 blood draws in the 400 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.

RESULTS (cont'd)

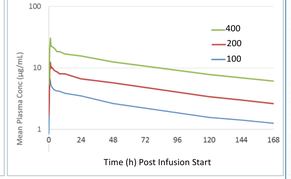
Pharmacokinetics

- In both studies, area under the curve (AUC) and maximum plasma conc. (C_{max}) increased proportionally with dose; total clearance (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



- Plasma CD101 conc. detectable through 144 h after first dose and 480 h after last dose
- Minor accumulation (ratios of last to first dose: C_{max}, 1.14 to 1.34; AUC_{0-168}, 1.30 to 1.55)
- ≤0.26% of the CD101 IV dose excreted in urine
- Mean half-life ($t_{1/2}$) on Days 8 or 15 (range, 150-154 h) was double that of Day 1 (range, 78-85 h) while mean total body CL on Day 1 was double that of Days 8 and 15
  - 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)
- Mean terminal volume of distribution (V_z) was 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 were similar between CD101 IV groups and placebo
  - There were 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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4. ICAAC 2015 Posters F-753, F-754.
5. ICAAC 2015; Posters A-015, A-693, A-694.

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