Saturday – LB-057

Safety and Pharmacokinetics of Multiple Doses of CD101 IV: Results From a Phase 1, Dose-Escalation Study

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ABSTRACT

Background: CD101 IV is a novel echinocandin being developed as a high-exposure, once-weekly agent for the treatment and prevention of invasive fungal infections. CD101 has potent in vitro and in vivo activity against a broad range of *Candida* and *Aspergillus* spp. CD101 IV was evaluated in a randomized, double-blind, placebo-controlled, dose-escalation study to establish the safety, tolerability, and pharmacokinetics (PK) of multiple intravenous doses.

Materials/methods: In 3 sequential cohorts of 8 healthy subjects (n=6, active; n=2, placebo), CD101 IV was infused over 1 hr, once weekly (100 mg × 2 doses [Cohort 1], 200 mg × 2 doses [Cohort 2], 400 mg × 3 doses [Cohort 3]), with dose escalation by predefined safety criteria. Extensive plasma and urine sampling over 28 (Cohorts 1 and 2) or 35 days (Cohort 3) was performed for PK analysis. Safety and tolerability was assessed by adverse events (AEs), vital signs, physical exams, electrocardiograms (ECGs), and hematology and clinical chemistry laboratories up to 21 days after dosing.

Results: Subjects (N=24, randomized and completed all assessments) were primarily White (88%), Hispanic or Latino (75%); males and females were equally represented. There were no serious or severe AEs. The majority of AEs were mild; all AEs completely resolved by study completion. There was a higher incidence of AEs and mild, transient infusion reactions in Cohort 3. There were no clinically significant hematology or clinical chemistry laboratory abnormalities at any dose. Additionally, there were no safety issues related to ECGs, vital signs, or physical exam findings. CD101 plasma exposures were dose-proportional. The average C_{max} ranged from 6.49 (Cohort 1, Day 8) to 30.5 µg/mL (Cohort 3, Day 15); corresponding area under the curve ($AUC_{0\text{-}168h}$) values were 390 to 1840 µg•h/mL. Accumulation was minor (30% to 55%, $AUC_{0\text{-}168h}$ ratio of last/first dose). Apparent clearance of CD101 was low (<0.28 L/hour), and its half-life was long ($t_{1/2}$ >80 hr). Excretion in urine was minimal (<1%).

Conclusions: CD101 IV was safe and well tolerated at multiple doses up to 400 mg once weekly for 3 weeks, exhibited long plasma $t_{1/2}$, and maintained plasma exposures that support once-weekly dosing. The overall safety, tolerability, and PK profile of CD101 support continued development as a once-weekly therapy for invasive fungal infections.

INTRODUCTION

- CD101 IV is a novel echinocandin being developed as a high-exposure, once-weekly treatment of invasive fungal infections
- CD101 has potent in vitro activity against *Candida* spp. and *Aspergillus* spp. and has demonstrated safety and efficacy in animal models of candidiasis and aspergillosis (mouse),[1-2] as well as vulvovaginal candidiasis (rat)[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
- The Phase 1 study of single ascending doses of CD101 IV demonstrated safety and tolerability with up to 400 mg and 90% predicted target attainment at MIC=0.5 mg/L[6]
- This multiple-ascending dose study was conducted to determine the safety, tolerability, and PK profile of CD101 IV administered in multiple IV doses to healthy adults.

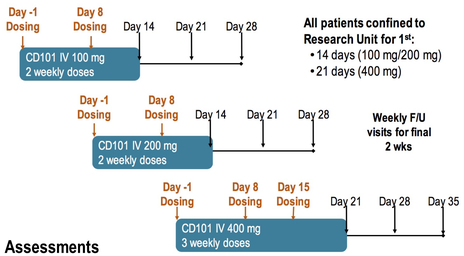
METHODS

Study Design and Treatments

- Double-blind, placebo-controlled, single-center, dose-escalation study of CD101 IV in healthy adults (ages 18-55 years)

Number of Subjects and Doses by Cohort

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

- Long follow-up period (up to 21 days after the last dose) enabled monitoring of potential delayed safety events
  - Adverse event (AE) and serious AE (SAE) monitoring (MedDRA)
  - ECGs and urinalysis (UA), hematology and serum chemistry
  - Additional assessments at weekly visits for 21 days after last dose

PK

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

RESULTS

Disposition and Baseline Characteristics

- 24 subjects (mean±SD age, 42.8±9.4 years) were enrolled and randomized; all completed the study
- Subjects were predominately White (88%) and Hispanic or Latino (75%) and had a mean BMI of 27.2 kg/m^2
- Males and females were equally represented (50% each)

RESULTS (cont'd)

Safety

Adverse Events

- Overall incidences of AEs similar between CD101 IV and placebo
- Treatment-emergent AEs (TEAEs) were generally mild, with relatively higher incidence in the group receiving 400 mg x 3 doses
  - Most common mild TEAE was transient infusion reactions (flushing, feeling hot, nausea, chest tightness), occurring in 3/6 subjects with the third dose of 400 mg and 1/6 subjects with the second dose of 100 mg
    - These reactions resolved within minutes of infusion without sequelae or interruption/discontinuation of infusion
  - The only moderate TEAE occurring in ≥2 subjects was constipation, in 2/6 subjects in the 400 mg group
- No SAEs, severe AEs, study withdrawals due to an AE, or deaths

Overview of Treatment-Emergent Adverse Events

TEAE by Severity	CD101 IV 100 mg	CD101 IV 200 mg	CD101 IV 400 mg	Placebo
No. of subjects with ≥1 TEAE	3 of 6	2 of 6	4 of 6	2 of 6
Mild, n	3	1	2	1
Moderate, n	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

Multiple Ascending Dose Laboratory Summary[a]

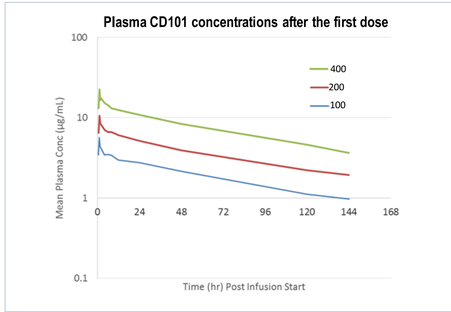
Lab Findings[b]	CD101 IV 100 mg	CD101 IV 200 mg	CD101 IV 400 mg	Placebo
Hematology, n (%)				
Normal	136 (94)	137 (95)	198 (100)	159 (98)
Abnormal- not CS	8 (6)	7 (5)	0	3 (2)
Abnormal- CS	0	0	0	0
Chemistries, n (%)				
Normal	699 (97)	696 (97)	969 (98)	790 (98)
Abnormal- not CS	21 (3)	24 (3)	21 (2)	20 (3)
Abnormal- CS	1[c]	0	0	0

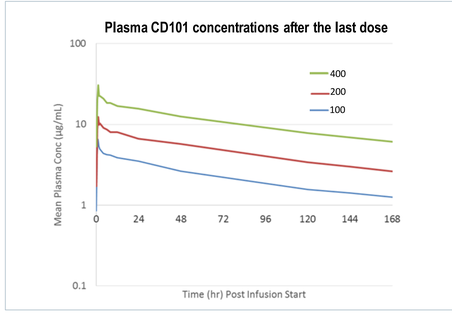
CS = clinically significant.
[a] 8 blood draws in the 100 mg/200 mg dose cohorts (CD101 IV and placebo groups) on Days 2, 4, 7, 9, 11, 14, 21, and 28; 11 blood draws in the 400 mg dose cohort on Days 2, 4, 7, 9, 11, 14, 16, 18, 21, 28, 35.
[b] 3 parameters for hematology (hemoglobin, white blood cell 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

- Plasma CD101 concentrations were detectable in all subjects through 144 hr after the first dose and through 480 hr after the last dose
- C_{max} and AUC increased dose-proportionally with peak plasma concentrations observed at the end of infusion





- Mean $t_{1/2}$ on Days 8 or 15 (range, 150-154 hr) was double that of Day 1 (range, 78-85 hr) 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 hr) following the last dose (Day 8 or 15) than for the first (144 hr)
- Mean V_z (range, 26-32 L) was similar for all 3 cohorts
- Accumulation was minor (C_{max} ratio of last:first dose, 1.14 to 1.34; $AUC_{0\text{-}168}$ ratio of last:first dose, 1.30 to 1.55) (PK Summary Table)
- ≤0.26% of the CD101 IV dose was excreted in urine

RESULTS (cont'd)

Multiple Ascending Dose PK Summary

By Dose and Day		C_{max} (µg/mL)	$AUC_{0\text{-}168\ hr}$ (µg•hr/mL)	Accumulation Ratio C_{max}	Accumulation Ratio $AUC_{0\text{-}168\ hr}$
100 mg	Day 1	5.67	299	-	-
	Day 8	6.49	390	1.14	1.30
200 mg	Day 1	10.6	570	-	-
	Day 8	12.4	813	1.17	1.43
400 mg	Day 1	22.7	1190	-	-
	Day 15	30.5	1840	1.34	1.55

CONCLUSIONS

- This study established the safety and PK profile of multiple ascending doses of CD101 IV in healthy subjects
  - CD101 IV up to 400 mg once weekly for 3 consecutive weeks was safe and well tolerated
  - Overall incidences of AEs were similar between CD101 IV treatment 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
- The results of this study are consistent with the Phase 1, dose-escalation study of CD101 IV administered in a single weekly dose
- These data support the continued development of CD101 IV for treatment of candidemia and invasive candidiasis in the inpatient and outpatient settings

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ACKNOWLEDGEMENTS

Editorial support was provided by Tressa Chung, RPh, CMPP (TMC Medical Communications).