Friday-192

Phase 1 Safety and Pharmacokinetics Study of VL-2397, a Novel Antifungal Agent

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ASM Microbe 2017
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Corrected Abstract

Background: VL-2397 is an antifungal drug with a novel mechanism of action. Given its rapid fungicidal activity in preclinical models and *in vitro* activity against azole-resistant fungal species, VL-2397 is being developed to treat infections caused by pathogenic fungi, including invasive aspergillosis (IA). We report the results of a Phase 1, first-in-human, randomized, double-blind, placebo-controlled study to assess safety, tolerability, and pharmacokinetics (PK) of intravenous (IV) VL-2397 in healthy male and female volunteers 18 to 55 years of age.

Methods: The single ascending dose (SAD) part of the study enrolled 7 cohorts and the multiple ascending dose (MAD) part of the study enrolled 4 cohorts, each with 8 subjects. Subjects were randomized in a 3:1 ratio per cohort to receive IV infusion(s) of either VL-2397 (active) or vehicle alone (placebo). SAD Cohorts 1-7 received single doses of 3, 10, 30, 100, 300, 600, and 1200 mg, respectively. MAD Cohorts 8-10 received 7 daily doses of 300, 600, and 1200 mg, respectively. MAD Cohort 11 received a 300-mg dose every 8 hours for 7 days followed by a 600 mg daily dose for 21 days. A safety committee reviewed the safety data throughout the trial. Serial plasma samples were assessed for PK.

Results: All cohorts were fully enrolled and all subjects completed the safety follow-up. The most common related adverse events were infusion site reactions. Dosing was discontinued in two subjects receiving the 1200-mg dose (Cohort 10), one due to a grade 1* creatinine increase and the other due to a grade 3 generalized rash. No grade 4 adverse events or serious adverse events related to drug were observed. Variability in plasma concentrations of total VL-2397 drug was low between subjects in each cohort. The C_{max} plasma VL-2397 concentrations for all doses were achieved at the end of infusion and increased in a dose-dependent but not dose-proportional fashion between cohorts. No apparent accumulation of VL-2397 was observed in the MAD cohorts. Based on an apparent rapid drug clearance from plasma with once-a-day dosing, when dose frequency was increased to every 8 hours for 7 days, the sustained VL-2397 levels in human plasma were observed to exceed the minimal inhibitory concentration (1 µg/mL) for *Aspergillus fumigatus* in RPMI 1640 medium.

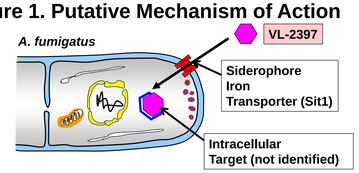
Conclusions: The safety and tolerability of VL-2397, combined with consistency in PK parameters and lack of drug accumulation following escalating single and multiple IV doses in healthy volunteers, support further clinical evaluation of VL-2397 in subjects with IA.

* Corrected from Grade 2 in original abstract

Introduction

- VL-2397 is a natural compound with a novel antifungal mechanism of action being developed for the treatment of invasive fungal infections, in particular as a potential frontline treatment for invasive aspergillosis (IA).
- VL-2397 has demonstrated rapid fungal cell kill activity in preclinical models with activity against azole-resistant fungi.
- VL-2397 enters the fungal cell through a membrane-bound transporter called siderophore iron transporter 1 (Sit 1) used by fungi to acquire iron from the environment[1]. Since mammalian cells lack Sit 1[2], VL-2397 is not expected to enter human cells, allowing for a potentially favorable therapeutic window.
- A Phase 1 trial was conducted to evaluate safety, tolerability, and pharmacokinetics (PK) of single and multiple doses of VL-2397 administered in healthy adult volunteers 18 to 55 years of age.

Figure 1. Putative Mechanism of Action



Methods

Trial Design:

- A first-in-human, randomized, dose-escalation, double-blind, placebo-controlled study involving seven SAD cohorts followed by three 7-day MAD cohorts, and a final 28-day MAD cohort.
- Eight male or female adult subjects 18-55 years of age were randomized 3:1 within each cohort to receive either VL-2397 or placebo using a peripheral intravenous (IV) catheter in all but the final cohort when a peripherally inserted central catheter (PICC) was used.
- Investigational products (IP) were active VL-2397 in 5% dextrose (D5W) and placebo (D5W alone) via IV administration.

Table 1. Dosing Regimens

Cohorts		VL-2397 Dose (mg)	Dose Frequency	D5W Volume (mL)	Time of Each Infusion (min)
1	SAD	3	single dose	25	6
2	SAD	10	single dose	83	20
3	SAD	30	single dose	250	60
4	SAD	100	single dose	83	20
5	SAD	300	single dose	250	60
6	SAD	600	single dose	500	120
7	SAD	1200	single dose	1000	240
8	MAD/ 7 days	300	daily for 7 days	250	60
9	MAD/ 7 days	600	daily for 7 days	500	120
10	MAD/ 7 days	1200	daily for 7 days	1000	240
11	MAD/ 28 days – split dosing	300	every 8 hours for 7 days	250	60
		600	every 24 hours for 21 days	500	120

- Subject visit periods consisted of screening, inpatient dosing, and outpatient follow-up completed 10 days after final dose. Dosing initiated on Day 1.

Safety Objectives:

- Assess the safety and tolerability of VL-2397 at varying dose schedules in healthy adults
- Adverse events (AEs) and serious adverse events (SAEs) were collected from initiation of dosing until the final visit and graded as per the Common Terminology Criteria for Adverse Events (v. 4.03)
- Serial complete blood count, chemistries, and urinalyses
  - SAD: Predose and Days 2, 3, 5, and 11
  - MAD (7-day dosing): Predose and Days 2, 5, 9, 11, and 17. Additional creatinine and urinalysis on Days 3-4 and 6-8
  - MAD (28-day dosing): Predose and on Days 2, 8, 15, 22, 30, 32, and 38. Additional creatinine and urinalysis on Days 3-7
- A Safety Review Committee (SRC) reviewed cohort-specific safety data to advise on dose escalation

PK Objectives: Serial plasma PK samples were collected:

SAD:

- Day 1 predose, midway and end of infusion, at 15 min, 30 min, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hrs relative to the end of infusion. Follow-up samples on Days 5 and 11.

MAD (7-day dosing):

- Days 1 and 7 predose, midway and end of infusion, at 15 min, 30 min, 1, 2, 3, 4, 6, 8, 12, and 24 hrs relative to end of infusion; PK samples also collected 36 and 48 hrs after end of Day 7 infusion,
- Days 3-6 predose, and follow-up samples on Days 11 and 17.

MAD (28-day dosing):

- Days 1 and 7 predose and end of infusion, and 3, 7, 8, 11, 15, 16, and 19 hrs relative to the end of the first infusion; PK samples also collected midway through Day 1 infusion,
- Days 2-6, 8-10, 15 and 22 pre-dose,
- Day 28 predose, midway and end of infusion, and 15 min, 30 min, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hrs relative to the end of the infusion. Follow-up PK samples collected on Days 32 and 38.

Results

Enrollment Summary:

- A total of 96 subjects ranging in age from 19 to 55 were enrolled into the 11 cohorts; all subjects completed all study visits
  - 71 men and 25 women
  - 81 white, 11 black and 4 other race
- Cohort 7 infusions were discontinued early due to infusion occlusion alarms resulting from cumulative filtration of drug product. An additional 8 subjects were dosed within Cohort 7 following introduction of an exchangeable filter extension set.

Safety Summary:

- No SAEs or Grade 4 Treatment-Emergent Adverse Events (TEAEs) were observed related to IP at any dose.

Table 2. Subjects with TEAEs Related to IP by Maximum Grade

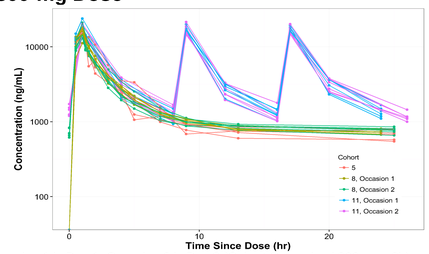
	SAD Cohorts							MAD Cohorts			
Cohort	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Dose (mg)	3	10	30	100	300	600	1200	300	600	1200	900/600*
Dosing Days	1	1	1	1	1	1	1	7	7	7	28
Subjects	8	8	8	8	8	8	16	8	8	8	8
Grade 1	4	1	1	2	2	-	4	8	7	5	1
Grade 2	-	1	1	-	-	-	1	-	1	2	1
Grade 3	-	-	-	-	-	-	-	-	-	1	-
Grade 4	-	-	-	-	-	-	-	-	-	-	-

*300 mg Q8 hours (900 mg total daily dose) x 7 days followed by 600 mg Q24 hours x 21 days

- The most common TEAEs were infusion site reactions.
- Dosing in two subjects was discontinued after dose 2 in Cohort 10 (1200-mg):
  - Grade 3 generalized rash (the only Grade 3 AE and the only systemic rash in the trial).
  - Grade 1 creatinine elevation (the only other AE due to creatinine rise in the trial was in a placebo recipient in Cohort 1).
- Proportion of subjects with TEAEs did not appear to increase with dose.
- The SRC did not identify any overall concerns with the safety profile.

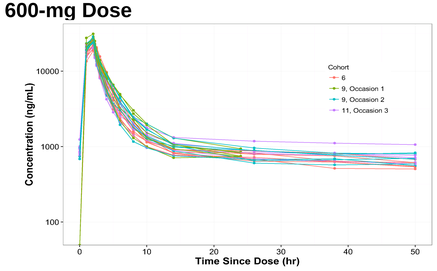
Pharmacokinetics (PK):

Figure 2. 300-mg Dose



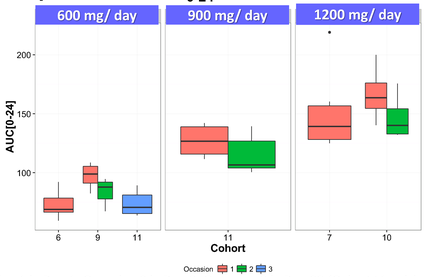
Occasion 1 is Day 1; Occasion 2 is Day 8 (Cohort 11 received 300 mg q8h)

Figure 3. 600-mg Dose



Occasion 1 is Day 1; Occasion 2 is Day 8; Occasion 3 is Day 28 (Cohort 11 only)

Figure 4. Comparison of AUC_{0-24}



Occasion 1 is Day 1; Occasion 2 is Day 8; Occasion 3 is Day 28 (Cohort 11 only)

PK Summary:

- Low variability between subjects within a cohort and between cohorts receiving the same dose
- No apparent accumulation of VL-2397

Conclusions

VL-2397 appears to be safe and well-tolerated with favorable plasma PK profiles in healthy subjects in this Phase 1 trial, supporting its advancement to a Phase 2 trial for the treatment of patients with invasive aspergillosis.

Acknowledgements

Vical wishes to thank our trial subjects, the staff at Celerion, and MicroConstants and our expert consultants Dr. Erin Castelloe, Dr. Haran Schlamm, Dr. Michael Hodges, and Dr. Christopher Rubino.

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