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

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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) 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, with each 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 100, 150, 300, 600, and 1200 mg, respectively. MAD Cohorts 8-10 received 7 daily doses of 300, 1200 mg, and 600 mg, respectively. MAD Cohort 11 received a single 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 2 subjects receiving the 1200 mg dose (Cohort 10), one due to a grade 1 skin rash and the other due to a grade 3 generalized rash and the event associated with dose discontinuation. No grade 4 adverse events or serious adverse events related to drug were observed. Variability in plasma concentrations of VL-2397 drug levels was low between subjects in each cohort. The Cmax 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-daily dosing, when dose 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. The most common TEAEs in the trial were in a placebo recipient in Cohort 10. No apparent accumulation of VL-2397 was observed in the MAD cohorts. Based on an apparent rapid drug clearance from plasma with once-daily dosing, when dose 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.

**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 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 (Sit1) used by fungi to acquire iron from the environment. Since mammalian cells lack Sit1, 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 where a peripherally inserted central catheter (PICC) was used.

- Investigational products (IP) were active VL-2397 in 5% dextrose (DSW) and placebo (DSW alone) via IV administration.

**Table 1. Dosing Regimens**

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Dose (mg)</th>
<th>Dose Frequency</th>
<th>DSW Volume (mL)</th>
<th>Time of Each Infusion (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAD Cohorts</td>
<td>1</td>
<td>Single dose</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Single dose</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>Single dose</td>
<td>250</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>Single dose</td>
<td>250</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>300</td>
<td>Single dose</td>
<td>500</td>
<td>250</td>
</tr>
<tr>
<td>6</td>
<td>600</td>
<td>Single dose</td>
<td>500</td>
<td>120</td>
</tr>
<tr>
<td>7</td>
<td>1200</td>
<td>Single dose</td>
<td>1000</td>
<td>240</td>
</tr>
<tr>
<td>MAD Cohorts</td>
<td>8</td>
<td>Daily for 7 days</td>
<td>250</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>7 days</td>
<td>Daily for 7 days</td>
<td>250</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>7 days</td>
<td>Daily for 7 days</td>
<td>250</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>7 days</td>
<td>Daily for 7 days</td>
<td>250</td>
<td>60</td>
</tr>
<tr>
<td>28 days</td>
<td>300</td>
<td>Every 8 hours</td>
<td>500</td>
<td>120</td>
</tr>
<tr>
<td>11 - split dosing</td>
<td>600</td>
<td>Every 24 hours</td>
<td>500</td>
<td>120</td>
</tr>
</tbody>
</table>

- Subject visits consisted of screening, inguinal 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

- VL-2397 PK: Serial plasma PK samples were collected:

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

    - 7-day favored predose, and follow-up samples on Days 11 and 17.

    - MAD (28-days dosing):

      - Days 1 and 7 predose and end of infusion, and 3, 7, 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 11, subjects 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 interchangeable 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**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>SAD Cohorts</th>
<th>MAD Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>100</td>
<td>1000</td>
</tr>
</tbody>
</table>

**Conclusions**

- Low variability between subjects within a cohort and between cohorts receiving the same dose

- No apparent accumulation of VL-2397

**Acknowledgements**

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**References**


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**Figure 2. 300-mg Dose**

**Figure 3. 600-mg Dose**

**Figure 4. Comparison of 2397 (active) or vehicle alone (pH 3.4) vs. Saline 0.9%**