Development of VL-2397 as an Antifungal Drug Candidate to Treat Invasive Fungal Infections
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Safe Harbor

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# VL-2397 for Invasive Fungal Infections

| PRODUCT CANDIDATE | Antifungal compound with a novel mechanism of action  
<table>
<thead>
<tr>
<th></th>
<th>In-licensed from Astellas Pharma Inc.</th>
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</table>
| TARGET INDICATIONS| Treatment of invasive aspergillosis  
|                   | Treatment of infections caused by other pathogenic fungi |
| DEVELOPMENT STATUS| QIDP, Fast Track and orphan designations for treatment of invasive pulmonary aspergillosis  
|                   | Dosing completed in Phase 1 trial in healthy volunteers; Phase 2 in invasive aspergillosis planned to be initiated in 4Q 2017 |
Invasive Aspergillosis (IA)

- More than 200,000 diagnoses of IA annually worldwide\(^1\)
  - Predominantly occurs in immunocompromised patients

- High unmet medical need
  - \(~50\%\) mortality in high risk groups\(^2\)
  - Potential drug interactions, toxicity with current antifungals
  - Increasing resistance
  - Adverse events and drug intolerance to existing antifungals

- Only 1 new therapy class introduced in past 30 years

Sources: \(^1\) Brown, SciTranslMed, 2012; \(^2\) Baddley, CID, 2010
VL-2397 Characteristics

- Resembles the siderophore ferrichrome
- Isolated from fungus *Acremonium persicinium*
  - Produced by fungal fermentation
  - Amino Acid Sequence: Phe-Leu-Asn-Orn-Orn-Orn • (Al$^{3+}$)
- Aluminum (Al$^{3+}$) is chelated by hydroximated ornithines
## Spectrum of In Vitro Antifungal Activity

### Susceptible fungal pathogens (MIC ≤ 2)

<table>
<thead>
<tr>
<th>Fungal Species</th>
<th>Affected Patient Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspergillus species</strong></td>
<td>A. fumigatus, A. terreus, A. flavus, A. nidulans</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressed, older patients</td>
</tr>
<tr>
<td><strong>Candida species</strong></td>
<td>C. glabrata, C. kefyr</td>
</tr>
<tr>
<td></td>
<td>UTI, intra-abdominal infections, MDR infections</td>
</tr>
<tr>
<td><strong>Other yeast species</strong></td>
<td>Cryptococcus neoformans, Trichosporon asahii</td>
</tr>
<tr>
<td></td>
<td>HIV, Africa, South East Asia</td>
</tr>
</tbody>
</table>

Assayed in inactivated human serum-containing media
MIC, minimal inhibitory concentration
VL-2397: A Novel Mechanism of Antifungal Action

- **VL-2397** represents a potentially new class of antifungal agents.
- **Active transport into** *A. fumigatus* occurs via **Sit1**
  - Mammalian cells lack **Sit1** transporter.
- **Activity results from effect on an intracellular target**

Plasma Membrane

- **Azoles:**
  - Ergosterol synthesis inhibitor
- **Polyenes:**
  - Ergosterol binding; membrane disruption

**Cell Wall**

- **Echinocandins:**
  - β-glucan synthesis inhibitor

**Intracellular Target**

- **Sit1**
- **VL-2397**

Adapted from Denning Science 2015
### VL-2397 Antifungal Activity Dependence on Siderophore Iron Transporter 1 (Sit1)

<table>
<thead>
<tr>
<th>A. fumigatus Strain</th>
<th>Property</th>
<th>VL-2397 CSLI MIC (mg/mL)</th>
<th>Voriconazole CSLI MIC (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP1305</td>
<td>Parent wild type strain</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>RSV-1</td>
<td>UV-induced Sit1 mutant</td>
<td>&gt;16</td>
<td>0.25</td>
</tr>
<tr>
<td>RSS</td>
<td>RSV-1 with Sit1 plasmid</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>RSP</td>
<td>RSV-1 with empty plasmid</td>
<td>&gt;16</td>
<td>0.25</td>
</tr>
</tbody>
</table>

- **RSV-1**: UV-induced nonfunctional Sit1 mutant (C1437A)
  - Lacks VL-2397 uptake
  - Insensitive to VL-2397 antifungal activity

- **RSS**: Sit1 transformation of RSV-1
  - Restores VL-2397 uptake
  - Restores sensitivity to VL-2397
Murine Invasive Pulmonary Aspergillosis (IPA) Survival Model

-4  0  5  10 (day)

Days -4, +1: Neutropenic mice (cyclophosphamide 200 mg/kg ip)

Day 0: Intratracheal infection with *A. fumigatus* (azole-sensitive or azole-resistant)

Antifungal treatment

Mice dosed on Days +1, +2, +3 VL-2397 (sc) BID, PSCZ (po) BID, N=10/dose

Mouse: Male ICR (5wk)
Organism: *A. fumigatus* 20030 3.83 × 10^6 conidia/mouse
*A. fumigatus* 25001 (azole resistant) 2.0×10^6 conidia/mouse
VL-2397 Efficacy in Murine IPA Survival Model

- All untreated infected mice died by day 5
- VL-2397 1mg/kg BID yielded 30% survival
- VL-2397 2 mg/kg BID and Posaconazole 10mg/kg BID yielded 40% survival
- VL-2397 (4 and 8 mg/kg BID) yielded 100% survival

Source: Nakamura et al. Poster F-1591 at ICAAC 2014
VL-2397 Reduction in Lung Fungal Burden in Murine IPA Model

- Dosed for 2 days BID, lungs harvested day 3, N=5/treatment group
- VL-2397 yielded a dose dependent reduction in lung fungal burden (LFB)
- VL-2397 at 4 and 8 mg/kg BID yielded 1.4 and 1.5 log reduction in LFB
- Posaconazole yielded a 0.3 log reduction in LFB

Source: Nakamura et al. Poster F-1591 at ICAAC 2014
Comparison of VL-2397 with posaconazole for the treatment of IPA model of azole-resistant *A. fumigatus* 25001

- All control and posaconazole-treated mice died by Day 6
- VL-2397 at 4 and 8 mg/kg BID yielded 100% survival to day 10

Source: Nakamura et al. Poster F-1591 at ICAAC 2014
Identification of VL-2397 Major Serum Binding Protein

*In Vitro* Bound Fraction Ratios (%) of $[^{14}C]VL-2397$ to Human Plasma Proteins

<table>
<thead>
<tr>
<th>Serum Protein</th>
<th>1μg/mL</th>
<th>10μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human serum albumin</td>
<td>31.0±0.7</td>
<td>9.4±0.5</td>
</tr>
<tr>
<td>$\alpha_1$-Acid glycoprotein</td>
<td>5.4±1.4</td>
<td>4.9±0.3</td>
</tr>
<tr>
<td>IgG</td>
<td>2.7±0.3</td>
<td>0.5±0.8</td>
</tr>
<tr>
<td>LDL</td>
<td>4.6±0.3</td>
<td>3.4±0.4</td>
</tr>
<tr>
<td>HDL</td>
<td>6.4±0.3</td>
<td>5.2±0.6</td>
</tr>
<tr>
<td>Zinc-$\alpha_2$-glycoprotein (ZAG)</td>
<td>99.6±0.02</td>
<td>30.4±0.5</td>
</tr>
</tbody>
</table>

Serum Protein Binding Summary

- Binding of VL-2397 to ZAG is saturable with 99.6% of drug being bound at 1 μg/mL and 30.4% of drug being bound at 10 μg/mL
- Concentration-dependent saturation of ZAG protein binding was consistent with the saturation of human serum protein binding
- Results strongly identified ZAG to be the major VL-2397 serum binding protein
VL-2397 Phase 1 Clinical Trial Design

- First-in-human, randomized, double-blind, placebo controlled study
- Total enrollment 96 healthy subjects-ages 19 to 55
- Drug administered intravenously through peripheral IV catheter or PICC line
- Eight subjects randomized 3:1 for each cohort
  - Seven single ascending dose (SAD) cohorts: 3mg → 1200 mg
  - Three 7-day multiple ascending dose (MAD) cohorts: 300, 600 and 1200mg
  - 28-day MAD cohort: 300 mg/8hr/7days; 600 mg/day for 21 days
- Safety review committee (SRC) reviewed cohort-specific safety data prior to advice on dose escalation
- Clinical Endpoints: Safety and Pharmacokinetic Parameters
VL-2397 Phase 1 Safety Summary

- The SRC did not identify any overall concerns with the safety profile
- All cohorts were fully enrolled and all subjects completed safety follow up
- No grade 4 adverse events or serious adverse events related to drug were observed
- Most common AEs primarily related to infusion sites
  - No differences between active and placebo groups
  - Replacement of IV peripheral catheter with PICC for Cohort 11 reduced infusion site AEs
- The safety and tolerability profile across all doses and dosing regimens support further clinical evaluation in IA patients

Poster Presentation Friday-192 “Phase 1 Safety and Pharmacokinetics Study of VL-2397, a Novel Antifungal Agent”
VL-2397 300 mg Dose PK Profile

Summary:
- Concentration curves for each subject receiving one or more 300-mg dose
- Peak concentrations are all very similar
- Supports lack of VL-2397 accumulation after seven daily infusions of 300 mg at 24-hour or 8-hour intervals

Occasion 1 is Day 1
Occasion 2 is Day 8
Cohort 5 received a single 300 mg dose
Cohort 8 received 300 mg q24h
Cohort 11 received 300 mg q8h
Summary:

- Concentration curves for each subject receiving one or more 600-mg dose are very similar within and across cohorts.
- Occasion 1 is Day 1 (Cohorts 6 and 9)
  - Occasion 2 is Day 7 (Cohort 9)
  - Occasion 3 is Day 28 (Cohort 11)
Phase 1 PK Summary

- **Low AUC\textsubscript{24} and C\textsubscript{max} variability within, across cohorts**
  - Reproducible drug concentrations among subjects receiving the same doses once or multiple administrations

- **Nonlinear proportional increase in AUC\textsubscript{24} and C\textsubscript{max}**
  - Drug is being cleared during increased infusion timeframe
  - No apparent drug accumulation with multiple doses

- **Long circulation half-life of bound drug**
  - Slow clearance phase due to serum protein binding
FRIDAY – 190
L.L. Kovanda, S.M. Sullivan, L.R. Smith, P. Bonate, W.W. Hope
“Population Pharmacokinetic Modeling of VL-2397, a Novel Systemic Antifungal Agent: Analysis of a Single and Multiple Dose Phase 1 Study”

FRIDAY – 192
“Phase 1 Safety and Pharmacokinetics Study of VL-2397, a Novel Antifungal Agent”

SATURDAY – 235
S.M. Sullivan, I. Nakamura, M. Ohbuchi, S. Matsumoto, L. Smith
“Characterization of Potential Drug Interactions and Off-Target Activities of VL-2397, a Novel Antifungal Agent against Invasive Aspergillosis”

SATURDAY – 239
“The Novel Antifungal VL-2397 Demonstrates Efficacy in an In Vivo Model of Invasive Candidiasis Caused by Wild-Type and Multi-Drug Resistant Candida glabrata”
Invasive aspergillosis (IA) is the initial focus of the VL-2397 development program

VL-2397 antifungal activity dependent on Sit1

In vivo proof of concept demonstrated in azole sensitive and azole resistant murine IPA models

Phase 1 clinical trial showed
- VL-2397 is well tolerated up to 1200 mg dose
- No accumulation observed up for 7 day daily dose of 1200 mg or 600 mg daily dose administered for 21 days

VL-2397 appears to be safe and well tolerated with favorable plasma PK profiles in healthy subjects

Phase 2 trial in IA planned for initiation in 4Q2017
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