VL-2397: A Novel Approach to Treat Life-Threatening Invasive Fungal Infections

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Vical at a Glance

- **Small biotechnology company based in San Diego, CA**
- **Platform of DNA delivery technologies**
- **Core competency in vaccines and infectious diseases**
  - ASP0113 vaccine in pivotal Phase 3 study for prevention of CMV reactivation in transplant patients
  - VCL-HB01 vaccine in Phase 2 study for treatment of HSV-2
  - VL-2397 antifungal planned for Phase 2 study in invasive aspergillosis
- **Strategic partnerships with Astellas**

VL-2397 for Invasive Fungal Infections

PRODUCT CANDIDATE	**Antifungal compound with a novel mechanism of action** **In-licensed from Astellas**
TARGET INDICATIONS	**Treatment of invasive aspergillosis (IA)** **Treatment of infections caused by other pathogenic fungi**
DEVELOPMENT STATUS	**QIDP, orphan & Fast Track designations for treatment of IA** **Potential for Limited Use Indication in IA based on successful outcome of a single Phase 2 trial** **Phase 1 trial in healthy volunteers completed** **Phase 2 trial in IA planned to start in 4Q 2017**

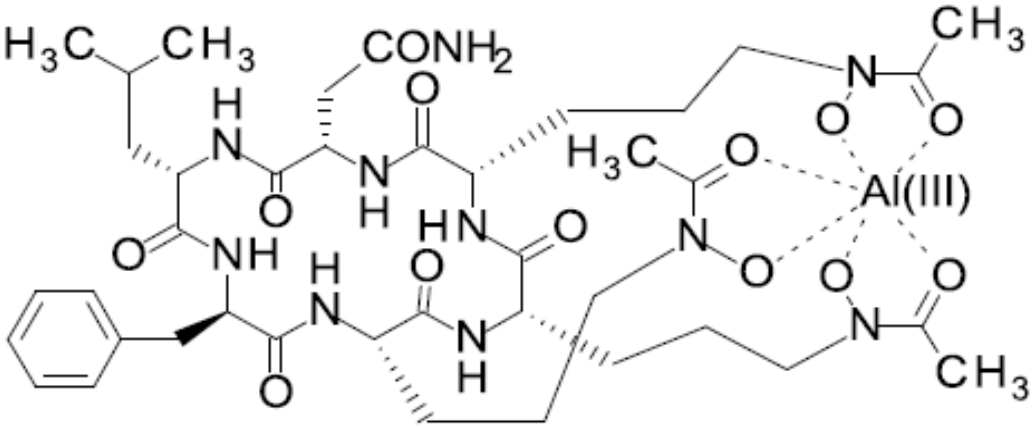
Invasive Aspergillosis

- **More than 200,000 diagnoses annually worldwide[1]**
  - Predominantly occurs in immunocompromised patients
- **Limitations of current antifungals**
  - 20% all-cause mortality at 6 weeks[2]
  - Drug-drug interactions
  - Toxicities, intolerance
  - Lack of coverage against resistant strains
- **Only 1 new therapy class introduced in past 30 years**

[1]Brown, Sci Transl Med, 2012
[2]Maertens, Lancet, 2016

VL-2397 Characteristics

- **Resembles the siderophore ferrichrome**
- **Isolated from fungus *Acremonium persicinum***
  - Produced by fungal fermentation
  - Amino acid sequence: Phe-Leu-Asn-Orn-Orn-Orn • (Al+3)
- **Aluminum (Al3+) chelation by hydroximated ornithines is required for antifungal activity**



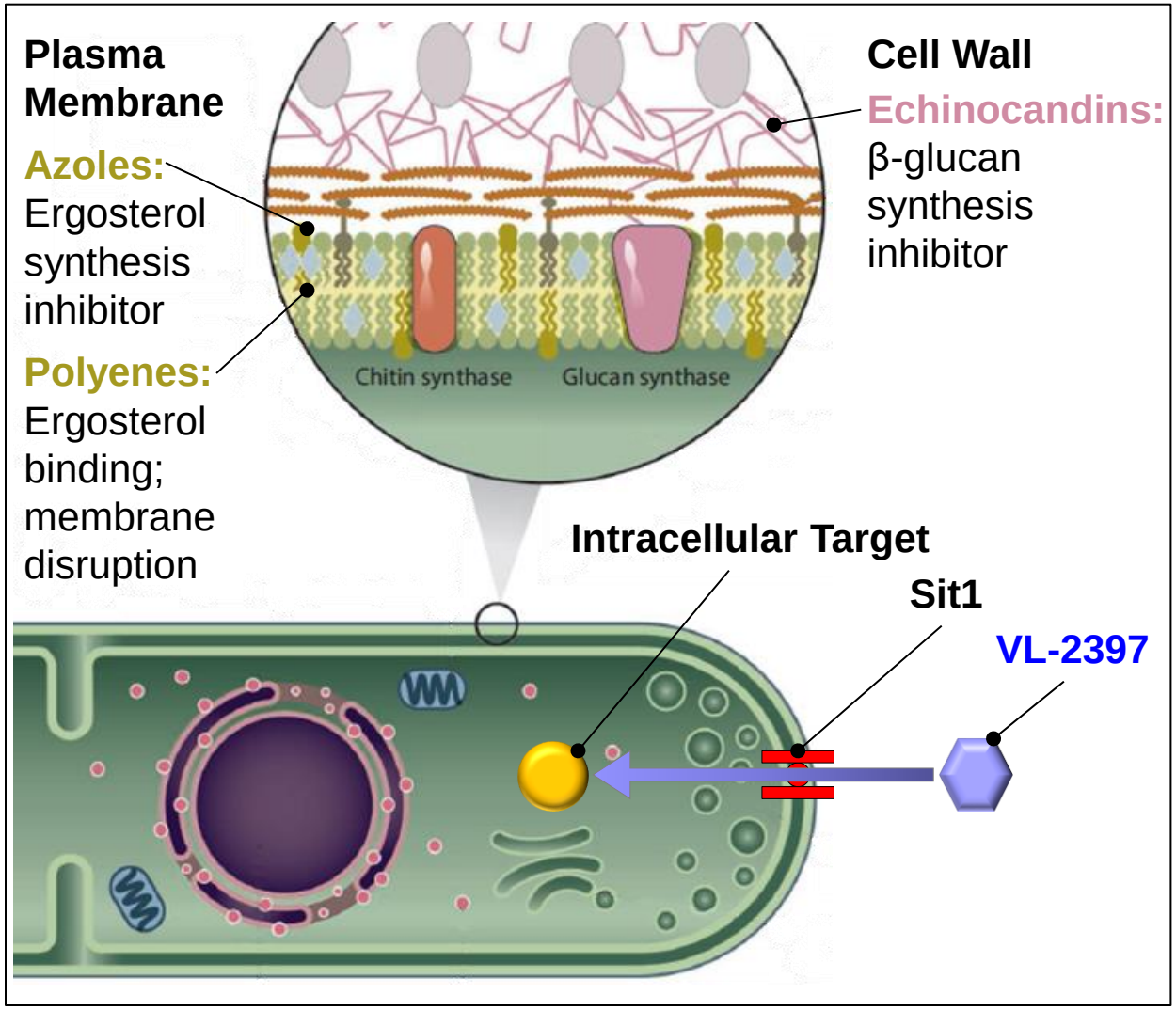
In Vitro Antifungal Activity

Susceptible fungal pathogens (MIC ≤ 2)

Fungal Species		Affected Patient Populations
***Aspergillus* species**	*A. fumigatus*, *A. terreus*, *A. flavus*, *A. nidulans*	Immunosuppressed, older patients
***Candida* species**	*C. glabrata*, *C. kefyr*	UTI, intra-abdominal infections, MDR infections
Other yeast species	*Cryptococcus neoformans*	HIV, Africa, South East Asia
	Trichosporon asahii	Immunocompromised

Assayed in inactivated human serum-containing media
MIC, minimal inhibitory concentration

VL-2397 Novel Mechanism of Action

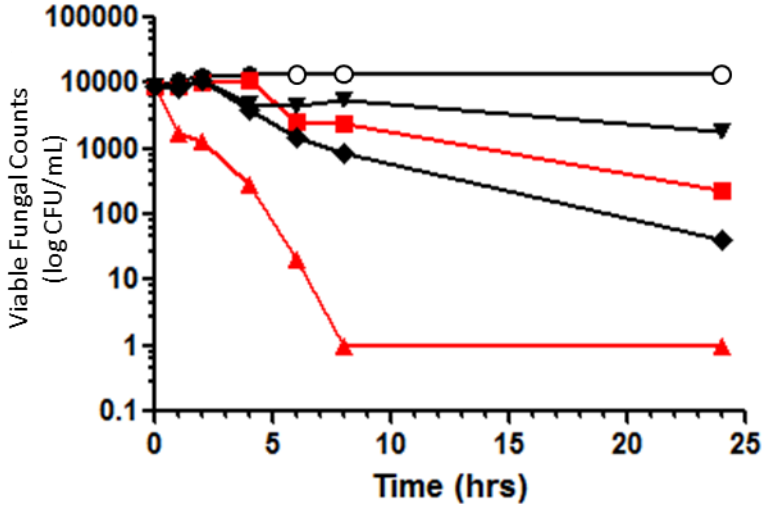


- **VL-2397 represents a potentially new class of antifungal agents**
- **Active transport into *A. fumigatus* occurs via Sit1**
  - Mammalian cells lack Sit1 transporter
- **Activity results from effect on an intracellular target**

Rapid Activity Against *Aspergillus*

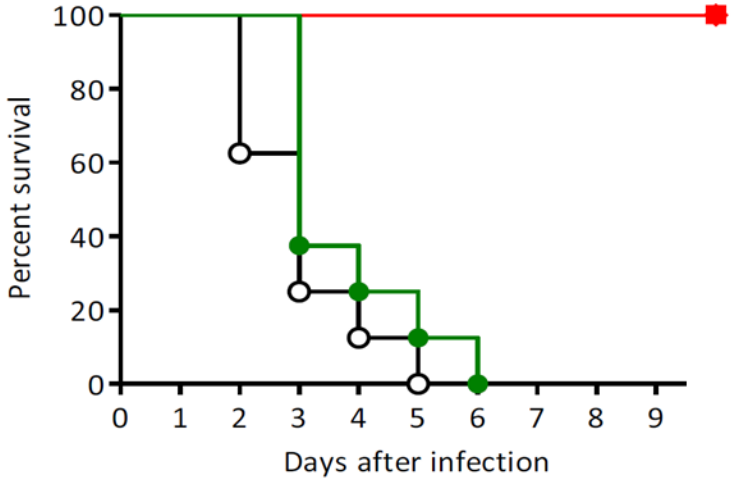
Including Drug-Resistant Isolates

Rapid Onset of Antifungal Activity



MIC: minimal inhibitory concentration
VRCZ: Voriconazole

Activity vs. Azole-Resistant *Aspergillus*



N = 10 mice /group
PSCZ: Posaconazole

Phase 1 Summary

- **Seven single-ascending dose cohorts, three 7-day multiple-ascending dose cohorts, one 28-day cohort**
  - Total enrollment 96 healthy subjects-ages 18 to 55
- **VL-2397 appeared to be safe and well-tolerated**
  - Safety review committee did not identify any overall concerns with the safety profile
- **Predictable PK**
  - Minimal inter-subject variability
  - No apparent accumulation of VL-2397 was observed
- **Data support advancement to Phase 2 in IA patients**

Planning for Phase 2 in IA

- **Potential expedited development pathway**
  - Intensive interaction with FDA under QIDP designation
  - VL-2397 will be eligible for Limited Use Indication approval assuming a successful outcome of a single Phase 2 trial
    - The trial must be carried out in accordance with a protocol and statistical analysis plan consistent with the Agency's advice
    - Final determination whether the drug is approvable will be made by FDA after review of all relevant data
- **Collaboration with the Mycoses Study Group Education and Research Consortium (MSGERC)**
  - Trial design and protocol input
- **Planned initiation in 4Q 2017**

Phase 2 Overview

- **Global, multicenter, randomized, open-label study**
- **N=200 adults with AML, ALL or allo HCT recipients**
- **2:1 randomization VL-2397 to active comparator**
  - Comparator: Physician's choice of voriconazole, isavuconazole or liposomal amphotericin B
- **6 weeks of antifungal treatment**
  - 4 weeks of VL-2397 followed by 2 weeks of comparator
- **Primary endpoint: All-cause mortality at 4 weeks**
  - Key secondary endpoint: ACM at 6 weeks
- **Noninferiority design**

VL-2397 Summary

- **First-in-class antifungal with novel MOA**
- **Extensive nonclinical data support rapid antifungal effect against azole-sensitive and resistant strains**
- **Favorable safety and PK profiles in Phase 1 trial support advancement to Phase 2 trial in IA patients**
- **Phase 2 trial in IA planned for initiation in 4Q 2017**
  - Potential for Limited Use Indication approval
  - Collaboration with MSGERC

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