INVESTIGATIONAL PRODUCT: VL-2397 FOR INJECTION

PROTOCOL VL2397-201

A PHASE 2 STUDY OF VL-2397 COMPARED TO STANDARD FIRST-LINE TREATMENT FOR INVASIVE ASPERGILLOSIS IN ADULTS WITH ACUTE MYELOGENOUS LEUKEMIA, ACUTE LYMPHOCYTIC LEUKEMIA, OR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS

Indication Studied:	Invasive aspergillosis
Trial Design:	Prospective, randomized, open-label, comparator-controlled, Phase 2 trial
Sponsor:	Vical Incorporated 10390 Pacific Center Court San Diego, California 92121-4340, USA
Developmental Phase:	Phase 2
First Subject Enrolled:	03 October 2018
Last Subject Completed:	14 January 2019
Date of Report:	28 March 2019
Sponsor's Responsible Medical Officer:	[redacted] Senior Vice President, Clinical Development
Sponsor's Signatory:	[redacted] Senior Vice President, Research Vical Incorporated Tel: +1-858-646-1134; Fax: +1-858-646-1151

This trial was conducted in compliance with Good Clinical Practice.

TRIAL SYNOPSIS

Name of Sponsor/Company: Vical Incorporated 10390 Pacific Center Court San Diego, California 92121	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
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Name of Active Ingredient(s): VL-2397; Cyclo{-Asn-Leu-d-Phe-[(N^5-acetyl-N^5-hydroxy-Orn)-(N^5-acetyl-N^5-hydroxy-Orn)-(N^5-acetyl-N^5-hydroxy-Orn)]-}・Al(III)	**Page:**	

Title of Study:

A Phase 2 Study of VL-2397 Compared to Standard First-Line Treatment for Invasive Aspergillosis in Adults with Acute Myelogenous Leukemia, Acute Lymphocytic Leukemia, or Allogeneic Hematopoietic Cell Transplant Recipients

Investigators: A total of 29 investigators were activated for enrollment.

Site Number	Investigator
01-01	Pranatharthi Haran Chandrasekar, MD
01-03	John W. Baddley, MD
01-04	John Fred Reinhardt, MD
01-06	Jose Vazquez, MD
01-07	George R Thompson III, MD
01-08	Luis Ostrosky, MD
01-09	Randy Taplitz, MD
01-10	Jo-Anne Young, MD
01-13	Michael Boeckh, MD
01-14	Zouyan Lu, MD
01-17	Andrej Spec, MD
02-01	Shariq Haider, MD
02-02	Shahid Husain, MD
02-03	Donald Vinh, MD
03-03	Marie von Lilienfeld-Toal, MD
03-04	Meinolf Karthaus, MD
03-06	Johanna Maria Kessel, MD
04-01	Johan André Maertens, MD
04-02	Dominik Luc Selleslag, MD
04-03	Mickaël Aoun, MD
04-04	Anke Verlinden, MD
04-05	Anne Sonet, MD
05-01	Raoul Herbrecht, MD
05-03	Anne Thiebaut, MD
05-04	Sophie Ducastelle-Leprêtre, MD
06-01	Sung-Hang Kim, MD
06-02	Sung-Soo Yoon, MD
06-03	Sung-Hoon Jung, MD
06-04	Kyong Ran Peck, MD

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Study Centers: A total of 29 clinical sites were activated for enrollment on the trial: 11 in the United States, 5 in Belgium, 4 in South Korea, 3 in Canada, 3 in France, and 3 in Germany.

Site Number	Study Center
01-01	Karmanos Cancer Institute; Detroit, MI 48201, USA
01-03	University Hospital; Birmingham, AL 35233, USA
01-04	Christiana Care Health Services; Newark, DE 19713, USA
01-06	Augusta University; Augusta, GA 30912, USA
01-07	UC Davis Medical Center; Sacramento, CA 95817, USA
01-08	The University of Texas Health Science Center; Houston, TX 77030, USA
01-09	UC San Diego Moores Cancer Center; La Jolla, CA 92093, USA
01-10	The University of Minnesota Medical Center, Fairview; Minneapolis, MN 55455, USA
01-13	Fred Hutchinson Cancer Research Center; Seattle, WA 98109, USA
01-14	Froedtert Memorial Lutheran Hospital; Milwaukee, WI 53226, USA
01-17	Washington University School of Medicine; St. Louis, MO 63110, USA
02-01	Hamilton Health Sciences – Juravinski Site; Hamilton, Ontario L8V 1C3, Canada
02-02	University Health Network – Toronto General Hospital; Toronto, Ontario M5G 2N2, Canada
02-03	Chronic Viral Illness Service McGill University Health Centre (MUHC)/Royal Victoria Hospital; Montreal, Quebec H4A 3J1, Canada
03-03	Universitätsklinikum Jena, Klinik für Innere Medizin II; Jena 07740, Deutschland
03-04	Städtisches Klinikum München GmbH ; München 81737, Deutschland
03-06	Johann Wolfgang Goethe-Universität; Medizinische Klinik II; Frankfurt-am-Main 60950, Germany
04-01	University Hospitals Leuven; Leuven 3000, Belgium
04-02	General Hospital Saint-Jan, Department of Hematology; Brugge 8000, Belgium
04-03	Jules Bordet Institute; Brussels 1000, Belgium
04-04	University Hospital Antwerp (UZA); Edegem B-2650, Belgium
04-05	UCL Mont-Godinne University Hospitals, Belgium
05-01	Centre Hospitalier Universitaire de Strasbourg – Hôpital de Hautepierre; Strasbourg cedex 67098, France
05-03	Centre Hospitalier Universitaire - Hôpital Albert Michallon; Grenoble Cedex 09, 38043, France
05-04	Centre Hospitalier Lyon Sud; Pierre Bénite, 69495, France
06-01	Asan Medical Center; Seoul 05505 Korea
06-02	Seoul National University Hospital; Seoul 03080, Korea
06-03	Chonnam National University Hwasun Hospital; Jeollanam-do 58128, Korea
06-04	Samsung Medical Center; Seoul 06351, Korea

Publication (Reference):

None

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Studied Period (years): **(date of first enrollment)** 03-Oct-2018 **(date of last completed)** 14-Jan-2019	**Phase of Development:** 2

Objectives: The objective of this study was to compare the safety and efficacy of VL-2397 for Injection to Standard First-Line Treatment (voriconazole, isavuconazole, or liposomal amphotericin B) for invasive pulmonary or sinopulmonary aspergillosis in immunocompromised adults with a diagnosis of *possible*, *probable*, or *proven* invasive aspergillosis (IA) according to the 2008 European Organization for Research and Treatment of Cancer and the US National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definitions.

Methodology: Immunocompromised adults (≥ 18 years of age) with a diagnosis of *possible*, *probable*, or *proven* IA according to the 2008 EORTC/MSG definitions were to be enrolled. Participants were to be stratified in the randomization scheme for covariates associated with the primary outcome of ACM. The stratification groups were:

1) allogeneic hematopoietic cell transplant (allo-HCT) or other; and

2) prior systemic mold-active antifungal prophylaxis or none.

Participants were to be randomized in a 2:1 ratio to receive either VL-2397 or standard first-line treatment for IA (voriconazole, isavuconazole, or if needed, liposomal amphotericin B). Participants randomized to the VL-2397 arm were to receive 28 days (4 weeks) of VL-2397 followed by 14 days (2 weeks) of standard treatment to complete 6 weeks of total treatment. Participants randomized to the Comparator arm were to receive 6 weeks of standard treatment.

Participants were to be followed for pharmacokinetics during the first day of dosing, and safety, tolerability, and efficacy during the 6-week dosing period.

After initiation of the trial under protocol amendment 02, the protocol was amended twice. No participants were enrolled under either of the amendments.

Amendment 03 included modifications to the exclusion criteria to exclude patients unlikely to recover their neutrophils during the study or those who have untreatable or uncontrollable systemic bacterial or viral infections, and to allow patients with prior episodes of IA as long as the infections were adequately treated. Amendment 03 also included addition of the category "Early Discontinuation of Initial Study Drug" to capture the reason for discontinuation and the patient's status and added a global response assessment for such patients.

Amendment 04 broadened the number of underlying conditions of patients who might have been enrolled in the study with a diagnosis of possible, probable, or proven IA, to consist of allo-HCT or auto-HCT recipients; solid organ transplant recipients; and patients with acute leukemia (AML, ALL), chronic leukemia (CML, CLL), aplastic anemia, myelodysplastic syndrome, or multiple myeloma. Exclusion criteria were modified to allow patients with relapsed leukemia who had a potential to respond to chemotherapy; however patients with refractory or relapsed leukemia who were unlikely to respond to reinduction chemotherapy were to be excluded. Patients with graft versus host disease (GvHD) who might be responsive to additional immunosuppressive treatment were to be allowed into the study, whereas, patients with refractory chronic GvHD were excluded from the study. Patients who had a recent episode of IA that responded to treatment were to be allowed; however those who were unresponsive to treatment were not eligible.

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Number of Participants (Planned and Analyzed): For business reasons and due to slow enrollment, the trial was terminated early (19-Feb-2019).

Planned: Approximately 200
Randomized: 4
Treated: 4
Analyzed for Safety: 4
Analyzed for Efficacy: 0

Diagnosis and Main Criteria for Inclusion:

1. Male or female (non-pregnant) participants, ≥ age 18 years at the time of consent
2. Acute leukemia (AML or ALL) patient or allo-HCT recipient, hospitalized, with a new diagnosis of possible, probable, or proven pulmonary IA or sinopulmonary IA as defined by the 2008 EORTC/MSG criteria

Test Product, Dose and Mode of Administration, Batch Number:

VL-2397 for Injection containing 600 mg VL-2397 per dose administered by intravenous (IV) infusion

VL-2397 for Injection batch number FG-15-0325

Test Product Duration of Treatment:

Monotherapy with VL-2397 for Injection dosed daily for 28 days followed by 14 days of Standard Treatment

Reference Therapy, Dose and Mode of Administration, Batch Number:

Voriconazole loading dose of 6 mg/kg IV Q12H for two doses (if loading dose has not already been given) followed by 4 mg/kg IV Q12H; the dose and route of administration may be switched to 200mg PO Q12H at the discretion of the Investigator; therapeutic drug monitoring was to be used to optimize dosing.

Voriconazole 200 mg IV batch numbers Z527707, Z499510; 200-mg tablets batch number 00011495; 500-mg tablets batch numbers 00012357, 0009270.

Liposomal amphotericin B 3-5 mg/kg IV daily could have been substituted for voriconazole or isavuconazole only in certain clinical situations: 1) breakthrough IA that developed while receiving mold-active antifungal prophylaxis, 2) suspected or documented infection caused by azole-resistant *Aspergillus* species, or 3) intolerance to voriconazole and intolerance to isavuconazole.

Liposomal amphotericin B batch numbers 015330, 012534.
(Isavuconazole was not used during the trial.)

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Reference Therapy Duration of Treatment:

42 days of monotherapy; choice of therapy determined by the Investigator

Criteria for Evaluation:

Efficacy:

Primary Endpoint: All-cause mortality (ACM) at 4 weeks in the Intention-to-Treat (ITT) population (survival at Day 28)

Key Secondary Endpoint:

ACM at 6 weeks in the ITT population (survival at Day 42)

Other Secondary Endpoints:

- ACM at 4 weeks in the modified ITT (mITT) population
- ACM at 4 weeks in the per protocol population
- Median time to death in the ITT population
- Clinical response at 4 weeks (Day 28), assessed by the Investigator, based on clinical symptoms and physical findings attributed to IA in the mITT population
- Radiological response at 4 weeks (Day 28), assessed by the Investigator, based on computed tomography (CT) scans of the chest performed at baseline and on Days 14 and 28 including change in number and size of lung nodules, if present, in the mITT population
- Mycological response at 4 weeks (Day 28), assessed by the Investigator, based on results of fungal cultures and serum galactomannan (GM) testing conducted at a local laboratory, in the mITT population
- Global response at 4 weeks (Day 28), adjudicated by a Data Review Committee, which was to incorporate the individual clinical, radiological, and mycological responses. The clinical response was to be assessed by the Investigator. The radiological response was to be assessed by the central radiologist. The mycological response was to incorporate results of fungal cultures and BAL and serum GM testing from the local laboratory (if available) and results of serial serum GM testing performed at a central laboratory.

Safety:

Safety and tolerability of VL-2397 for Injection as assessed by physical examination, vital signs, adverse events, and clinical laboratory testing during the study period.

Statistical Methods:

VL2397-201 was a non-inferiority study where the Primary Endpoint was ACM at 4 weeks in the ITT population, and had the associated null and alternative hypothesis test:

H_0: T–C$\geq\Delta$ (T is inferior to C) and H_1: T–C$<\Delta$ (T is inferior to C by less than Δ)

where T=VL-2397
C= Comparator
Δ=non-inferiority margin (NI Margin)

The hypothesis was to be tested with a 2.5% one-sided alpha by comparing the upper bound of the confidence interval for T–C with the NI margin. If the upper bound is less than the NI margin, non-inferiority of T relative to C would have been declared.

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The Primary Endpoint was ACM at 4 weeks analyzed in the ITT population. The key secondary endpoint is ACM at 6 weeks analyzed in the ITT population. The non-inferiority hypothesis was to be tested for both endpoints by comparing two proportions with unequal sample sizes in the ITT population. Comparison parameters of the proportion difference and risk difference were to be calculated, with each associated confidence interval and presented. An unadjusted analysis was to be conducted first, followed by an adjusted analysis for the randomization stratification.

Due to the low number of participants enrolled in the trial, no statistical analyses were conducted.

SUMMARY – CONCLUSIONS

Study Population: The total number of participants planned for inclusion in the VL2397-201 trial was approximately 200. The total number of participants that were enrolled was 4. All 4 participants completed the trial; no participants discontinued.

Gender, Race, and Age:

Of the 4 participants on the trial, 2 were female and 2 were male. All were white. Their ages ranged from 18 to 68 years of age, with a mean value of 52 years of age.

EFFICACY RESULTS:

Due to the low number of participants enrolled in the trial, no efficacy evaluations were conducted.

SAFETY RESULTS:

No serious adverse events were reported in any of the 4 subjects. Two participants were randomized to VL-2397 for Injection. Adverse events (AEs) reported (1 incidence each) were grade 1 acid reflux, PICC line site erythema, contact dermatitis, worsening elevated alanine transaminase, worsening elevated aspartate transaminase, worsening elevated gamma-glutamyl transferase, worsening elevated alkaline phosphatase, and diarrhea; and grade 2 shoulder pain, weight loss, and itching rash. All AEs were determined by the investigators to be unrelated.

In the standard treatment group, AEs reported were 1 incidence each of grade 1 arrhythmia, increased creatinine, rhinitis, and tooth fracture; grade 2 nausea, diabetes mellitus (steroid-induced), pain after bone marrow punction, rash, epistaxis, abdominal discomfort, worsening cough, dysgeusia, weight gain, respiratory syncytial virus, and periodontitis. Two instances of grade 2 headache were noted. One subject experienced two events of grade 3 febrile neutropenia and one event of grade 3 decreased neutropenia. All AEs were determined by the investigator to be unrelated.