Title: WSA-CS-008: A Phase III, Double- Blind, Randomized Study to Evaluate Safety and Efficacy of BAL8557 Versus a Caspofungin Followed by Voriconazole Regimen in the Treatment of Candidemia and Other Invasive Candida Infections

Principal Investigator: Jennifer Daly, M.D.

Sponsor: Astellas Pharma Global Developement, Inc. (APGD)

Purpose of Research
To compare safety and efficacy of treatment with isavuconazole (ISA) versus a caspofungin (CAS) → voriconazole (VRC) regimen in patients with candidemia or other invasive *Candida* infections.

Secondary Objectives:
- To compare the effects of treatment on:
- Time to first negative blood culture
- All-cause mortality at Day 14, End of Treatment (EOT) and all Follow-Up Visits

Isavuconazole (BAL4815) is a broad spectrum triazole. It inhibits sterol 14 α-demethylase, a microsomal P450 enzyme (P45014DM) essential for ergosterol biosynthesis in fungi. It's water soluble prodrug, isavuconazonium sulphate (BAL8557), was specifically developed to facilitate IV administration without the need for nephrotoxic excipients such as cyclodextrin and with an almost complete bioavailability after oral administration.

The initial 10 days of study medication will be administered parenterally. The patient must be hospitalized during the first 48 hours (loading regimen). The remainder of the IV treatment must be prepared by the hospital pharmacy and administered by a qualified healthcare professional. Adherence to the schedule of obtaining daily blood cultures must be maintained even in the outpatient setting. From Day 11 onwards, patients may be switched from IV to oral therapy at the discretion of the investigator. Neutropenic (ANC < 0.5 x 109/L [<500/mm3]) patients must remain on intravenous therapy and not switch to oral therapy while neutropenic. Reasons for not switching to oral therapy should be documented from Day 11 onwards, e.g. unable to swallow, gastric suction, concerns about adequate dosing, neutropenia not resolved.

Patients switched to oral therapy cannot be switched back to intravenous therapy.

Inclusion Criteria:
- Patients and/or legally authorized representative(s), if applicable, who have been fully informed and have given voluntary written informed consent

  OR

  patients unable to write and/or read but who fully understand the oral information given by the Investigator (or nominated representative) who have given oral informed consent witnessed in writing by an independent person. HIPAA authorization for US sites or equivalent privacy language as per national regulations must be obtained.
- Ability and willingness to comply with the protocol.
- Male and female patients aged ≥ 18 years at the time of signing informed consent.
- Female patients must be non-lactating and at no risk of pregnancy for one of the following reasons:
  - Postmenopausal (amenorrhea for at least 1 year)
  - Post-hysterectomy and/or post-bilateral ovariectomy
  - If of childbearing potential, having negative serum or urine human chorionic gonadotropin (hCG) pregnancy test at screening and is using a highly effective method of birth control throughout the study. Reliable sexual abstinence throughout the course of the study is acceptable as a highly effective method of birth control.
- Patients with candidemia or with an invasive *Candida* infection who have a positive blood or tissue culture obtained within 96 hours prior to randomization, accompanied by related clinical signs and symptoms or histological or cytological changes. Final culture results may still be pending at randomization if histology/cytology reveals yeast.

- Presence of fever (on one occasion > 38°C oral, or equivalent) or hypothermia (on one occasion <36°C oral, or equivalent) or hypotension (SBP < 100 mmHg or a decrease in SBP of at least 30 mmHg) or appropriate local signs within 96 hours prior to randomization.

Exclusion Criteria:

- Women who are pregnant or breastfeeding.
- Known history of allergy, hypersensitivity, or any serious reaction to any of the azole or echinocandin class of antifungal or to any component of the study medication.
- Patients for whom CAS or VRC is contra-indicated.
- Patients at high risk for QT/QTc prolongation e.g.
    a. Baseline prolongation of QTcF >/= 500 msec;
    b. Risk factors for Torsade de Pointes (e.g. uncompensated heart failure, abnormal potassium or magnesium levels that cannot be corrected, any unstable cardiac condition during the last 30 days, or a family history of long QT syndrome);
    c. The use of concomitant medications that prolong the QT/QTc interval.
- Patients with evidence of hepatic or renal dysfunction with any of the following abnormalities at the time of randomization (may be re-checked using local laboratory):
    - Total bilirubin ≥ 3 x upper limit of normal (ULN) or
    - Alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 5 x ULN or
    - Patients with known cirrhosis or chronic liver failure
    - Calculated creatinine clearance (Clcr) < 10 mL/minute or
    - Currently on dialysis or likely to require dialysis during administration of study medication.
- Concomitant use of sirolimus, efavirenz, ritonavir, astemizole, cisapride, rifampicin/rifampin, rifabutin, ergot alkaloids, long acting barbiturates, carbamazepine, pimozide, quinidine, neostigmine, ketoconazole, valproic acid, St. John's Wort, or terfenadine in the 5 days prior to first administration of study medication.
- Patients with a sole diagnosis of mucocutaneous candidiasis, i.e. oropharyngeal, esophageal or genital candidiasis; or candidal lower urinary tract infection or *Candida* isolated solely from respiratory tract specimens.
- Patients with candidemia who failed a previous antifungal therapy for the same infection.
- Patients with any invasive fungal infection other than C*andida* spp, e.g., cryptococcosis, mold infection or endemic fungal infection.
- Microbiological (e.g. bacterial infections) findings or other potential conditions that are temporally related and suggest an alternative etiology of the clinical features in the absence of culture/histology/cytology evidence of systemic *Candida* infection.
    - NB: For patients with intra-abdominal infection or intra-abdominal abscess, documentation of another pathogen (e.g. bacteria) would exclude the patient from enrollment.
- Patients who have received systemic antifungal therapy for more than 48 hours within 96 hours prior to the first administration of study medication.
- Severe prolonged immunosuppression (e.g. chronic granulomatous disease, severe combined immunodeficiency, advanced human immunodeficiency virus infection with CD4 count < 200 or acquired immunodeficiency syndrome-defining condition, severe graft versus host disease [grade III-IV associated with e.g., failure of initial treatment, increased liver enzymes or hypoalbuminaemia]), or any other concomitant medical condition that may impede the accurate assessment of efficacy of study drug treatment.
- Any known or suspected condition of the patient that may jeopardize adherence to the protocol requirements such as patients with fungal endocarditis, fungal osteomyelitis, fungal meningitis, or with life expectancy of < 30 days.
- Patients with a concomitant medical condition that, in the opinion of the investigator, may be an unacceptable additional risk to the patient should he/she participate in the study.
- Patients previously enrolled in a phase III study with isavuconazole.
- Treatment with any investigational drug in any clinical trial within 30 days prior to the first administration of study medication except for open label trials.
- Patients with a body weight < 40kg.