CLINICAL STUDY PROTOCOL

An Open-Label Study to Evaluate the Efficacy and Safety of APX001 in Patients with Candidemia and/or Invasive Candidiasis Caused by *Candida auris*

Investigational Product: APX001

Protocol Number: APX001-203

Sponsor:

Amplyx Pharmaceuticals, Inc.

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Version Number: 4.0

Date: 08 April 2020

Confidentiality Statement

SIGNATURE PAGE

STUDY TITLE: An Open-Label Study to Evaluate the Efficacy and Safety of APX001 in Patients with Candidemia and/or Invasive Candidiasis Caused by *Candida auris*

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
PPD	08 April 2020

PPD MD
PPD
Amplyx Pharmaceuticals, Inc.

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Amplyx Pharmaceuticals, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Amplyx Pharmaceuticals, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Amplyx Pharmaceuticals, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: An Open-Label Study to Evaluate the Efficacy and Safety of APX001 in Patients with Candidemia and/or Invasive Candidiasis Caused by *Candida auris*

PROTOCOL NUMBER: APX001-203

INVESTIGATIONAL PRODUCT: APX001

PHASE: 2

INDICATION: Treatment of patients with candidemia and/or invasive candidiasis caused by *Candida auris*

OBJECTIVES:

The primary objective of this study is to evaluate the efficacy and safety of APX001 for the treatment of adult patients aged 18 years and above, with candidemia and/or invasive candidiasis caused by *Candida auris*, who have limited antifungal treatment options.

The secondary objectives of this study are to:

- Evaluate the time to first negative blood culture
- Evaluate the percentage of patients with successful Mycological Outcomes at End of Study Drug Treatment (EOST), and 2 and 4 weeks after EOST
- Evaluate the percentage of patients with Treatment Success 2 and 4 weeks after EOST
- Evaluate all-cause mortality at Study Day 30
- Evaluate safety parameters, including number of patients with treatment-emergent adverse events (TEAEs)
- Evaluate pharmacokinetic (PK) parameters of APX001

BACKGROUND:

Disseminated infections associated with *Candida* species (spp.) are a significant cause of morbidity and mortality. *Candida auris* is an emerging fungal pathogen which has caused invasive infections and hospital outbreaks on several continents. Since *C. auris* was first described in Japan in 2009, additional cases have been reported in South Korea, India, Kuwait, Kenya, South Africa and more recently in Colombia, Venezuela, Panama, Pakistan, the United Kingdom and the United States[1-14]. A whole genome sequencing study documented recent, near-simultaneous and independent emergence of *C. auris* clones on three different continents (Africa, Asia and South America), rather than spread of a single "clone" across the globe[15].

Invasive *C. auris* infections are associated with high mortality and are difficult to identify using traditional yeast identification methods[16]. The fungus persists on patients' skin and in the healthcare environment, allowing for transmission to occur between patients in healthcare facilities, and may be difficult to eliminate from the hospital environment[16].

C. auris is often multi-drug resistant. The majority of tested *C. auris* isolates are resistant to fluconazole, an important first-line antifungal agent[1-6, 15]. Furthermore, more than 40% of tested *C. auris* isolates from a recent global study were resistant to two or more major classes of antifungals[16].

APX001, a first-in-class small molecule drug candidate, is the water soluble phosphate prodrug of APX001A. APX001 is rapidly metabolized by circulating phosphatases *in vivo* to APX001A. APX001A has a novel mechanism of action targeting the conserved fungal enzyme glycosylphosphatidylinositol (GPI)-anchored wall transfer protein 1 (GWT1), which is required for the expression of GPI-anchored proteins on the fungal cell wall. Inhibition of GWT1 by APX001A compromises cell wall integrity, inhibits biofilm formation, blocks filamentation, enhances immunogenicity of unmasked β-glucan, and produces severe fungal growth defects. The closest mammalian ortholog of GWT1 is PIG-W, which has no demonstrable inhibition by APX001A.

APX001A has broad *in vitro* activity against major fungal pathogens, including *Candida*, *Cryptococcus*, *Aspergillus*, *Scedosporium*, *Fusarium*, and members of the Mucorales order[17-21]. The susceptibility of *Candida auris* to APX001A has been tested in over 100 diverse isolates including strains resistant to fluconazole, the echinocandins, and/or amphotericin B[22]. In these tests, APX001A is the most mycologically active agent against *C. auris* with markedly lower MIC values than the other antifungals tested. The MIC_{50} and MIC_{90} for APX001A were 0.002 mg/L and 0.008 mg/L, respectively. In addition, APX001A was active against all four *C. auris* clades[22].

APX001 was evaluated in a disseminated *C. auris* infection model in immunocompromised mice[23]. Anidulafungin, an echinocandin, was chosen as a comparator for this model. The mice were sacrificed at 48 hours post-inoculation for determination of the lung, kidney, and brain fungal burdens after intraperitoneal dosing of APX001 (78 mg/kg BID, 78 mg/kg TID, 104 mg/kg BID) and anidulafungin (10 mg/kg BID) versus the vehicle control. Treatment with APX001 resulted in significantly better survival than anidulafungin. Both APX001 and anidulafungin demonstrated significant and equivalent decreases in kidney and lung colony forming units (CFU) at 48 hours; however, only APX001 demonstrated a reduction in brain fungal burden.

In three completed Phase 1 clinical studies of APX001, the safety, tolerability, and PK of single ascending doses and multiple ascending doses administered intravenously (IV) and orally (PO) to healthy volunteers were studied. A total of 178 healthy volunteers were enrolled in the placebo-controlled Phase 1 studies of APX001. All APX001 doses studied in Phase 1 were considered well tolerated. No serious adverse events (SAEs) were reported, and most of the treatment-emergent adverse events (TEAEs) were mild, transitory, and required no intervention. No dose-limiting toxicities (DLTs) were observed and no TEAEs or safety laboratory test results met any of the *a priori* rules that prevented dose escalation to the next protocol-specified cohort. The maximum tolerated dose was not determined/reached in these Phase 1 studies. Pharmacokinetic parameters for maximum serum concentration and AUC in both single and

multiple APX001 IV and PO doses were linear and dose proportional. In both *in vitro* studies of APX001 and in a cohort embedded within the PO dose Phase 1 study, APX001 demonstrated a favorable drug-drug interaction profile. APX001A was shown to be a weak inducer of cytochrome P450 (CYP) 2B6; a moderate inducer of CYP1A2, CYP2C19, and CYP3A4; and a weak inhibitor of CYP2C9 and CYP2D6. The relative bioavailability of the PO formulation was >90% in healthy subjects. There was no evidence of an effect on the bioavailability of APX001 in the presence of food (high fat and high calorie). Most importantly, the target AUCs anticipated for efficacy against both yeast and molds have been achieved with both IV and PO dose formulations tested in Phase 1.

In summary, APX001 is a promising new antifungal agent with a novel mechanism of action having broad spectrum activity against *Candida* spp., including *Candida auris*. Because APX001 is a first-in-class drug candidate with a novel mechanism of action, no cross-resistance with other classes of antifungal drugs has been observed or is expected.

POPULATION:

This study will enroll male and female patients aged 18 years and above with an established diagnosis of candidemia and/or invasive candidiasis caused by *Candida auris* from a sample taken <120 hours (for patients with candidemia) or <168 hours (for patients with invasive candidiasis without candidemia) of inclusion in the study. Patients will have limited or no treatment options due to resistance, contraindication, intolerance or lack of clinical response to standard of care antifungal therapy, as advocated by the relevant regional/country treatment guidelines (e.g. South Africa: The Federation of Infectious Diseases Societies of Southern Africa (FIDSSA), 2019 in press; CDC: Recommendations for treatment of *Candida auris* infections). *Candida auris* must be confirmed in culture from blood or other tissue, aspirate or fluid sampled from a normally sterile site, and all eligibility criteria must be met prior to qualification for the study and subsequent dosing.

Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

1. Male or female aged 18 years and above
2. Limited or no treatment options due to resistance, contraindication, intolerance or lack of clinical response to standard of care antifungal therapy, as advocated by the relevant regional/country treatment guidelines
3. Established mycological and clinical diagnosis of candidemia and/or invasive candidiasis from a sample taken <120 hours (for candidemia) or <168 hours (for invasive candidiasis without candidemia) before study qualification:

    a. Candidemia criteria

        i. ≥1 blood culture positive for yeast/*Candida* spp. identified as *C. auris*;

        plus:

ii. Clinical signs attributable to candidemia within the 120 hours prior to qualification for the study, to include at least one of the following: (a) fever (>38ºC), or (b) hypothermia (<36ºC), or (c) hypotension (SBP <90mmHg or decrease of >30mmHg);

b. Invasive candidiasis criteria

i. ≥1 specimen (e.g., tissue, aspirate/fluid) sampled aseptically from a normally sterile site culture positive for yeast/*Candida* spp. identified as *C. auris*;

plus:

ii. Clinical signs attributable to invasive candidiasis within the 168 hours prior to qualification for the study, to include at least one of the following: (a) fever (>38ºC), or (b) hypothermia (<36ºC), or (c) hypotension (SBP <90mmHg or decrease of >30mmHg), or (d) signs associated with organ/site infected with *Candida* (e.g. eye, intra-abdominal).

4. Patients with single *C. auris* infection, or mixed *Candida auris* plus other *Candida* spp. (other than *C. krusei*) infection, are eligible for the study.
5. Able to have pre-existing intravascular catheters removed and replaced (if necessary).
6. Females of childbearing potential with male partners, and males with female partner(s) of childbearing potential, must agree to use 2 forms of highly effective contraception, 1 of which must be a barrier method, throughout the duration of the study and for 90 days following the last study drug administration. Acceptable barrier forms of contraception are condom and diaphragm. Acceptable non-barrier forms of contraception for this study are oral contraceptives (e.g. oral birth control pill, depot, patch, or injectable), abstinence, intrauterine device, and/or spermicide.

   Post-menopausal is defined as amenorrhea for >12 months without an alternative medical cause or documented surgical sterilization (e.g. bilateral salpingectomy, bilateral oophorectomy, or hysterectomy).

   True abstinence, when in line with the preferred and usual lifestyle of the patient, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug treatment. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception)
7. Females of childbearing potential must have a negative urine pregnancy test within 96 hours prior to Baseline (i.e. pre-dose on Study Day 1)
8. Willing to participate in the study, willing to give written informed consent, and willing to comply with the study restrictions; where permitted by local regulations, written informed consent from a legal authorized representative (LAR) will be obtained for patients who are unable to give consent.
9. Male patients must agree to abstain from sperm donation and use condoms with spermicide during sexual intercourse between Screening and at least 90 days after administration of the last dose of study drug. Male patients must ensure non-pregnant female partner(s) of

childbearing potential comply with the contraception requirements in Inclusion Criterion 6 (above).

Exclusion Criteria

Patients who meet any of the following criteria will not be eligible for the study:

1. Blood culture, or any other culture, positive for *C. krusei*
2. Life expectancy of <7 days in the opinion of the Investigator
3. Severe or moderate hepatic impairment (Child-Pugh Score >6 points) at any time during 2 weeks prior to dosing**.** The Child-Pugh score of >6 is applicable to patients with hepatic dysfunction and cirrhosis only.
4. Baseline neurological conditions such as abnormal movements or convulsive disorders
5. Human immunodeficiency virus-infected patients who are receiving antiretroviral therapy that are moderate to strong inducers of CYP3A4, or who have detectable viremia, or who have had an active opportunistic infection within 6 months prior to Screening
6. Alanine aminotransferase or aspartate aminotransferase ≥5 × upper limit of normal (ULN)
7. Total bilirubin >3 × ULN, unless isolated hyperbilirubinemia or due to documented Gilbert's disease.
8. Female patient is pregnant or lactating
9. Inappropriate fungal infection source control (e.g. persistent indwelling catheters or intravascular devices)
10. Investigational drug administered within 30 days prior to dosing or five half-lives whichever is longer
11. Concomitant use of medication that is a strong inducer of CYP enzymes (e.g. rifampin, carbamazepine, phenytoin, rifabutin, efavirenz, nevirapine, phenobarbital, modafinil, nafcillin, St. John's Wort, and enzalutamide)
12. Any other condition or laboratory abnormality that, in the opinion of the Investigator, would put the patient at unacceptable risk for participation in the study or may interfere with the assessments included in the study
13. Diagnosis of deep-seated *Candida*-related infections causing hardware associated septic arthritis, osteomyelitis, endocarditis, myocarditis, hepatosplenic candidiasis, or a central nervous system infection or site of infection that would require antifungal therapy to exceed the maximal duration of study drug treatment (i.e. 6 weeks [42 days]).

Dosing Criteria

Patients must meet the following criteria to begin dosing:

Confirmed diagnosis of candidemia and/or invasive candidiasis caused by *C. auris* (in a single or mixed *Candida* spp. infection) within <120 hours (for candidemia) or <168 hours (for invasive candidiasis without candidemia) of the indicative positive blood culture or indicative positive culture from a specimen sampled from a normally sterile site, plus confirmation that all other eligibility criteria are met, qualify the patient for dosing with APX001. The initiation of the first dose of APX001 must occur within 12 hours of qualification for the study.

STUDY DESIGN AND DURATION:

This is a multicenter, open-label, non-comparative, single-arm study to evaluate the efficacy and safety of APX001 for the treatment of candidemia and/or invasive candidiasis caused by *C. auris* in patients aged 18 years and over with limited antifungal treatment options. The Study Drug Treatment Period will be up to a maximum of 42 days (inclusive of the loading dose [Study Day 1]). There will be a Follow-up Period of 4 weeks (+4 days) after EOST. The total duration of participation in the study is up to approximately 10.5 weeks (inclusive of the Screening Period [≤168 hours prior to Baseline]). Patients must have had *C. auris* confirmed in culture <120 hours (for candidemia) or <168 hours (for invasive candidiasis without candidemia) prior to qualification and dosing in the study.

Screening and Baseline procedures will be performed within no more than 120 hours (for candidemia) or 168 hours (for invasive candidiasis without candidemia) from the time that the SOC blood and/or tissue sample or aspirate/fluid positive for *C. auris* was collected, and any outstanding baseline procedures completed before the first dose of study medication.

All patients (or the patient's LAR) will sign an ICF before any protocol specified procedures that are not indicated by SOC may be conducted. Inclusion/exclusion criteria assessments, medical history, demographics, and Acute Physiology and Chronic Health Evaluation II score will be collected before dosing. When an LAR is used for the initial consent, the patient will be consented during the study as soon as he/she is able to do so.

On Study Day 1 (or over the first 24 hours if dosing starts in the evening), a 1000 mg APX001 loading dose will be administered over 3 hours by IV infusion twice daily (BID). On Study Days 2 and 3, a 600 mg APX001 maintenance dose will be administered over 3 hours by IV infusion once daily (QD). On Study Day 4 and onward, the APX001 maintenance dose will be administered as either 600 mg APX001 IV infusion QD over 3 hours or 800 mg PO QD. Patients who have completed a minimum of 3 days of IV APX001, are clinically stable as determined by the Investigator, and are able to swallow tablets, may switch from IV to PO dosing on Study Day 4 and onward. Study drug will be administered for 14 days after clearance of *Candida* organisms from the bloodstream (two consecutive negative blood cultures), and in accordance with clinical judgment as applicable for other infected sites, up a maximum of 42 days.

Patients will be monitored by daily blood culture from signing informed consent, through dosing, during Study Drug Treatment until 2 consecutive blood cultures are negative for *Candida* spp., at EOST, and at 2 and 4 weeks after EOST, or Early Termination. For patients diagnosed with invasive candidiasis, relevant cultures, histopathology, and imaging tests to assess the site(s), extent, progress, and outcome of the *Candida* infection will be conducted as clinically indicated. All results should be recorded in the electronic Case Report Form. The management of intravascular catheters, intravascular devices, and, if applicable, any drains will be recorded, including any associated microbiology results.

Patients will be monitored for safety throughout the duration of the study. Safety assessments will include vital signs, clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis), physical examinations, neurological assessments (twice weekly on treatment), prior and concomitant medication reporting, and adverse event reporting. A 12-lead electrocardiogram (ECG) will be performed at Baseline (pre-dose), EOST, and 4 weeks after EOST, or Early Termination. A dilated fundoscopic examination will be performed at least once during the baseline period, which exclusively for this assessment may be up to Day 3 of the study. Follow-up fundoscopic examinations are required at EOST, and 4 weeks after EOST, or Early Termination for those patients who had positive findings up to Day 3 (or more if clinically indicated). A urine pregnancy test (for females of childbearing potential only) will be performed at Screening and Baseline (pre-dose), every 30 days during treatment if required by local regulations, at EOST, and 2 and 4 weeks after EOST, or Early Termination.

In the event of an inadequate response/failure on APX001 study treatment, the study drug may be discontinued and alternative antifungal treatment instituted.

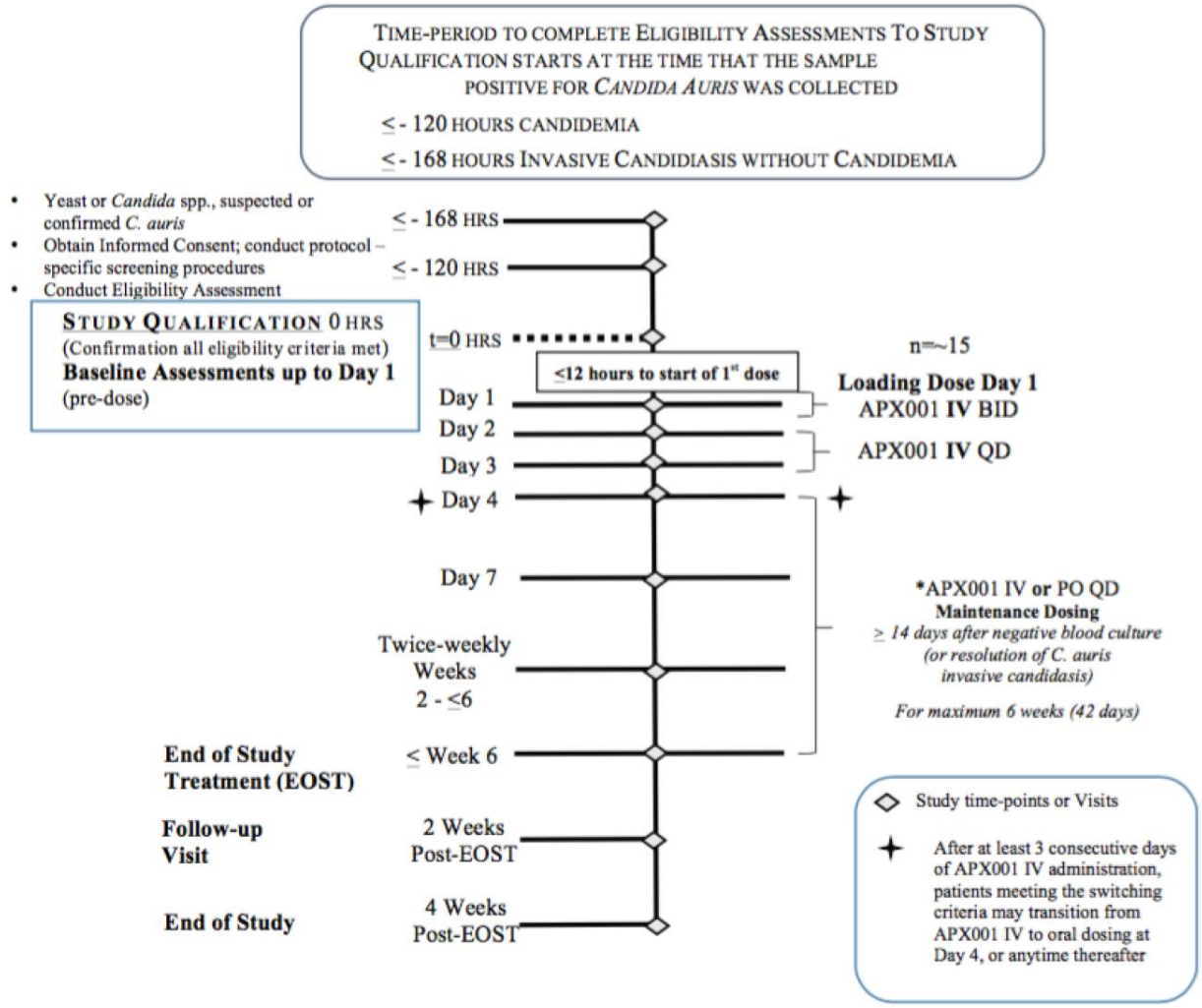
Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, and at EOST, 2 weeks after EOST, or Early Termination. Plasma samples for PK will be collected at the same time as samples are collected for the study's clinical laboratory assessments. Serum samples for (1,3)-β-D-glucan levels will be collected at Baseline (pre-dose) and EOST, or Early Termination (if applicable).

Optionally, if body fluids are sampled as part of routine patient management (e.g. bronchoalveolar lavage, lumbar puncture, paracentesis, vitreous fluid collection, abscess drainage) within approximately 2 hours of blood sampling for PK, these samples may be stored for future analysis of APX001 and APX001A levels.

The evaluation of treatment outcome will be assessed at EOST, and 2 and 4 weeks after EOST, or Early Termination.

The end of study will occur after the last visit of the last patient on the study.

A schematic representing the study's design is included on the following page.



***APX001 IV or PO QD**
Maintenance Dosing
For patients with invasive candidiasis, maintenance dosing will continue until at least one negative tissue culture or aspirate/fluid
For patients with a deep-seated site of infection from which a tissue culture is not obtainable, maintenance dosing should continue until after the resolution of the attributable clinical signs of infection recorded at Baseline, and, as applicable, radiological improvement associated with the site of infection
maximum 6 weeks (42 days)

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

On Study Day 1 (or over the first 24 hours if dosing starts in the evening), a 1000 mg APX001 loading dose will be administered over 3 hours by IV infusion BID.

On Study Days 2 and 3, a 600 mg APX001 maintenance dose will be administered over 3 hours by IV infusion QD.

The infusion volume for both the 1000 mg and the 600 mg APX001 doses will be 250 mL.

On Study Day 4 and onward, an APX001 maintenance dose will be administered as either:

- 600 mg APX001 IV infusion QD over 3 hours, or
- 800 mg PO QD

CRITERIA FOR SWITCHING FROM INTRAVENOUS TO ORAL DOSE:

Patients who have completed a minimum of 3 days of APX001 IV administration may be eligible for PO switch on Study Day 4 and onward. Patients must meet all of the following criteria to switch from IV to PO dosing of APX001:

- Is clinically stable, as determined by the Investigator
- Is able to swallow tablets

RATIONALE FOR DOSE AND SCHEDULE SELECTION:

Dose

In pharmacokinetic/pharmacodynamic (PK-PD) studies, immunocompromised mice were infected with one of three spp. of *Candida* (*C. albicans*, *C. glabrata*, or *C. auris*) and groups of animals were dosed with APX001 at different dose fractionations. The AUC/MIC ratio was determined to be the PK-PD variable that best correlated with antifungal efficacy as assessed by fungal burden (CFUs) in the kidney. The probability of target attainment (PTA) was calculated separately for each *Candida* spp. tested. The PTA calculation used the APX001A free drug AUC level at the stasis endpoint divided by the MIC required to inhibit the growth of 90% of organisms (MIC_{90}) of each of the *Candida* spp. tested.

The AUC level was estimated from a population PK model derived primarily from the Phase 1 PK data. The stasis endpoint was defined as the quantity of *Candida* spp. in CFUs just prior to APX001 administration compared to CFUs at the endpoint of assessment (i.e. 24 hours for *C. albicans*; 96 hours for *C. glabrata* and *C. auris*). The MIC data for the *Candida* strains tested were obtained from recent surveillance data.

Using the AUC at the stasis endpoint, along with the MIC_{90} from the surveillance data and the predicted exposure at the dose regimen to be used in this study, the PTA for the 3 *Candida* spp. tested was shown to be approximately 100%. Further, sensitivity analyses were conducted to evaluate the PTA under different scenarios including increased variability of PK parameters and higher *Candida* spp. MIC_{90} values. For both scenarios the PTA remained >90%.

In two Phase 1 studies in healthy volunteers, APX001 IV and PO formulations were safe and well tolerated. The majority of TEAEs were mild, transitory, and resolved without intervention. No DLTs were observed. Specifically, in the first-in-human Phase 1 clinical study, a loading dose regimen of APX001 1000 mg IV 2-hour infusion BID on Day 1, followed by a maintenance dose of APX001 600 mg IV 1-hour infusion QD on Days 2 through 7, was safe and well tolerated. In an additional Phase 1 study of APX001, a dose regimen consisting of a loading dose of APX001 1000 mg IV 3-hour infusion BID on Day 1, followed by a maintenance dose of APX001 600 mg IV 3-hour infusion QD on Days 2 through 7, and then APX001 800 mg orally QD on Days 8 through 42 was also safe and well tolerated.

Schedule

To ensure the safety and tolerability of APX001 dosing for 42 days, this study will use an APX001 dose and infusion duration already studied in Phase 1 for 42 days of therapy inclusive of IV and PO investigational drug therapy. The loading dose regimen of APX001 1000 mg IV BID over a 3-hour infusion followed by APX001 600 mg IV QD over a 3-hour infusion has been designed to optimize patient safety and tolerability during the study. At Study Day 4 and onward, provided the protocol-defined criteria for a PO switch are met, the patient may be switched to oral APX001 800 mg QD. Study drug will be administered for 14 days after clearance of *Candida* organisms from the bloodstream, and in accordance with clinical judgment as applicable for other infected sites, up to a maximum of 42 total days combined IV and PO APX001 therapy.

EFFICACY ENDPOINTS:

The primary efficacy parameter is percentage of patients with Treatment Success at EOST as determined by the Data Review Committee (DRC).

The secondary efficacy parameters include the following:

- Time to first negative blood culture
- Percentage of patients with successful Mycological Outcomes at EOST, and at 2 and 4 weeks after EOST
- Percentage of patients with Treatment Success at EOST as determined by the investigator
- Percentage of patients with Treatment Success 2 and 4 weeks after EOST, as determined by the investigator and the DRC
- All-cause mortality at Study Day 30
- Number of patients with TEAEs

The exploratory efficacy parameters include the following:

- Change in serum (1,3)-β-D-glucan levels from Baseline (pre-dose) to EOST

EFFICACY ASSESSMENTS:

At End of Study Drug Treatment (EOST):

Treatment Success is defined as meeting all of the following criteria:

- Two consecutive blood cultures negative for *Candida* spp., and/or for patients with a deep-seated site of infection, at least one negative tissue culture or aspirate/fluid culture
    - For patients with a deep-seated site of infection involving visceral organs from which a tissue culture is not obtainable, resolution of the attributable clinical signs of infection recorded at Baseline, and, as applicable, radiological improvement associated with the site of infection is required
- Alive at EOST
- No concomitant use of any other systemic antifungal therapies through EOST

  Note: administration of another systemic antifungal immediately following EOST for suspected or documented *Candida* infection at any site does not constitute a treatment success at EOST

Treatment Failure is defined as any case that does not meet the criteria for Treatment Success.

Successful Mycological Outcomes:

- Eradication is defined as a negative blood (and/or other infection site) culture(s) for *Candida* spp. in the absence of concomitant antifungal therapy through EOST
- Presumed Eradication (applicable to invasive candidiasis) is defined as clinical resolution of invasive *Candida* spp. infection where tissue samples are unavailable (supported by evidence of resolution/improvement in the diagnostic parameters used at Baseline)

Both of the above definitions are in the absence of concomitant or additional systemic antifungal therapy.

At Follow-up (2 Weeks and 4 Weeks After End of Study Drug Treatment [EOST]):

- Treatment Success (sustained) is defined as having met the criteria for Treatment Success at EOST with no change during the follow-up period
- Relapse is defined as re-occurrence of *Candida* in blood culture, or from other infection sites during the Follow-up Period, or diagnostic parameters indicative of recurrence or late spread of the *Candida* infection
- Other:
    - Death
    - Unavailable for follow-up, or unevaluable at follow up for other reasons

  Additional DRC assessment categories are provided in the DRC Charter

Mycological Recurrence is defined as mycologically confirmed infection based on blood culture (or other specimen(s) cultured from a normally sterile site), with the same Baseline *Candida* spp. during the 4 weeks after EOST.

SAFETY VARIABLES:

Safety parameters include the following:

- Evaluation of adverse events at Screening, Baseline, during Study Drug Treatment, at EOST, and 2 and 4 weeks after EOST, or Early Termination

  Infusion site reactions should be graded according to the current version of the Common Terminology Criteria for Adverse Events
- Vital signs (temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight) collected at Screening, Baseline (pre-dose), daily on Study Days 1 through 4 and twice weekly thereafter during Study Drug Treatment for outpatients (daily while inpatient), at EOST, and 2 and 4 weeks after EOST, or Early Termination. Height will be collected (from the patient's medical record) at Baseline
- Clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis) will occur at Screening, Baseline (pre-dose), twice weekly during Study Drug Treatment, at EOST, and 2 and 4 weeks after EOST, or Early Termination. If clinically indicated and at the discretion of the Investigator, or if a suspected adverse event is identified, clinical laboratory assessments may be conducted at any time during the study and compared to Baseline.
- Physical examination, including a neurological assessment at Baseline (pre-dose), during Study Drug Treatment (neurological assessments twice weekly), at EOST, and 2 and 4 weeks after EOST, or Early Termination
- ECGs at Baseline (pre-dose), EOST, and 4 weeks after EOST, or Early Termination

WITHDRAWAL CRITERIA:

Study drug dosing may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
- Occurrence of significant drug-induced liver injury (DILI) [Appendix D]
- Any SAE, clinically significant adverse event, severe laboratory, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient
- Pregnancy
- Requirement of prohibited concomitant medication
- Patient failure to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or a regulatory authority

Patients who discontinue study drug due to withdrawal of consent, death, or loss to follow-up will discontinue study participation. Patients who fail on study treatment and start alternative antifungals will be assessed for safety 4 weeks after stopping study medication. Patients who discontinue study drug for other reasons will enter the follow-up phase of the study.

The study may be discontinued for any of the following reason: five or more subjects in study (cumulative) experience a same grade 2 (or higher) related AE (laboratory or systemic) which is coded in the same high-level group term per MedDRA coding, throughout the duration of study; a recommendation from the DSMB based on other safety signals; lack of Investigational Product availability; inability to enroll the study; or decision by a regulatory authority or the sponsor.

INDEPENDENT DATA REVIEW COMMITTEE:

To ensure standardization of interpretation regarding the validity of study patients, the medical management, and response to treatment in this open-label study, a panel of recognized experts in the field of fungal infectious diseases will constitute a DRC. The DRC serves to provide independent oversight to confirm eligibility for efficacy analysis, to confirm the diagnosis of *C. auris* candidemia and/or invasive candidiasis at study entry, and to adjudicate efficacy outcome. The DRC assessments for each patient will be recorded in the database and used in the primary efficacy analysis of the study. The DRC members will not be Principal Investigators in the study. Guidelines for the DRC are described in the DRC Charter.

DATA AND SAFETY MONITORING BOARD:

A Data and Safety Monitoring Board (DSMB) comprised of members with pertinent expertise will review the accumulating data from the study periodically as set forth in the DSMB Charter, or more frequently at the request of the DSMB. The DSMB will advise the Sponsor on the continuing safety of the study patients and those yet to be recruited to the study, as well as the continuing validity and scientific merit of the study. At any time, the independent DSMB may temporarily suspend enrollment until any significant safety concerns are resolved or terminate the study to ensure patient safety, if in the opinion of the DSMB, further dosing would pose an inappropriate safety risk. Guidelines for what constitutes inappropriate safety risks are described in the DSMB Charter.

ANALYSIS POPULATIONS:

Intent-to-Treat Population/Safety Population

The Intent-to-Treat Population/Safety Population will include all patients who have received at least 1 dose of APX001.

Modified Intent-to-Treat Population

The Modified Intent-to-Treat (MITT) Population will include all patients who satisfy the following criteria:

- Received at least 1 dose of study drug

- Have a confirmed diagnosis of candidemia and/or invasive candidiasis caused by *C. auris* within 120 hours (for candidemia) or 168 hours (for invasive candidiasis without candidemia) of study qualification

Per-Protocol Population

The Per-Protocol Population will include all patients in the MITT Population who satisfy the following criteria:

- Meet the protocol's key inclusion and exclusion criteria
- Receive at least 80% of the intended doses
- Have no major protocol violations

Pharmacokinetic (PK) Population

The PK Population will include all patients who receive any amount of study drug and have evaluable PK data.

STATISTICAL ANALYSES:

Efficacy Analyses

The primary population for efficacy analysis will be the MITT Population.

The efficacy endpoints will be summarized descriptively. The percentage of patients with Treatment Success at EOST (as assessed by the DRC) will be summarized. The same summary will be repeated for the Per-Protocol Population.

For the secondary efficacy endpoints, the percentage of patients with Treatment Success 2 and 4 weeks after EOST will be summarized. Similarly, the proportion of patients with successful Mycological Outcomes at EOST, and 2 and 4 weeks after EOST will be summarized. A descriptive summary of overall survival at Study Day 30 and time to first negative blood culture will also be provided.

Safety Analyses

All safety analyses will be performed on the Safety Population. Safety data will be subject to clinical review and summarized by appropriate descriptive statistics. A DSMB will be assigned to monitor safety on an ongoing basis throughout the study.

Pharmacokinetic Analysis

Pharmacokinetic analysis of plasma concentration data will be performed using validated software in order to derive the population mean (and variance) values of specific PK parameters.

Plasma concentrations will be summarized descriptively by treatment group and time point of collection. Summary statistics in the tabulation will include n, mean, standard deviation, CV% median, minimum, and maximum. Pharmacokinetic parameters will be estimated using population PK analysis methods, which will be described in a separate data analysis plan. Results of the PK analysis will be reported separately.

SAMPLE SIZE DETERMINATION:

A sample size of approximately 15 patients with documented *C. auris* infection will be recruited in this open-label study. No formal statistical assessment for sample size determination has been performed. This sample size is considered adequate to provide the necessary data to evaluate the efficacy and safety of APX001 in patients with documented candidemia and/or invasive candidiasis caused by *C. auris*.

SITES: Approximately 4-6 sites selected from the Republic of South Africa and Panama

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
APACHE	Acute Physiology and Chronic Health Evaluation
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve from time 0 to infinity
BID	Twice daily
CFR	Code of Federal Regulations
CFU	Colony-forming units
C_{max}	Maximum serum concentration
CRA	Clinical research associate
CRP	C-reactive protein
CTA	Clinical trial authorization
CTCAE	Common Terminology Criteria for Adverse Events
CVC	Central venous catheter
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DRC	Data Review Committee
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOST	End of Study Drug Treatment
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GPI	Glycosylphosphatidylinositol
GWT1	GPI-anchored wall transfer protein 1
HCV	Hepatitis C virus
IB	Investigator's Brochure
ICF	Informed Consent Form

Abbreviation	Definition
ICH	International Council for Harmonisation
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
IFD	Invasive fungal disease
IRB	Institutional Review Board
IV	Intravenous(ly)
LAR	Legal authorized representative
MDRD	Modification of Diet in Renal Disease
MIC	Minimal inhibitory concentration
MIC_{90}	Minimal inhibitory concentration required to inhibit the growth of 90% of organisms tested
MITT	Modified Intent-to-Treat
MTD	Maximum tolerated dose
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Oral(ly)
PTA	Probability of target attainment
QD	Once daily
SAE	Serious adverse event
SOC	Standard of care
spp.	Species
T2MR	T2 magnetic resonance
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

1 INTRODUCTION AND BACKGROUND INFORMATION

Disseminated infections associated with *Candida* species (spp.) are a significant cause of morbidity and mortality. *Candida auris* is an emerging fungal pathogen which has caused invasive infections and hospital outbreaks on several continents. Since *C. auris* was first described in Japan in 2009, additional cases have been reported in South Korea, India, Kuwait, Kenya, South Africa and more recently in Colombia, Venezuela, Panama, Pakistan, the United Kingdom and the United States[1-14]. A whole genome sequencing study documented recent, near-simultaneous and independent emergence of *C. auris* clones on three different continents (Africa, Asia and South America), rather than spread of a single "clone" across the globe[15].

Invasive *C. auris* infections are associated with high mortality and are difficult to identify using traditional yeast identification methods[16].The fungus persists on patients' skin and in the healthcare environment, allowing for transmission to occur between patients in healthcare facilities, and may be difficult to eliminate from the hospital environment[16].

C. auris is often multi-drug resistant. The majority of tested *C. auris* isolates are resistant to fluconazole, an important first-line antifungal agent[1-6, 15]. Furthermore, more than 40% of tested *C. auris* isolates from a recent global study were resistant to two or more major classes of antifungals[16].

APX001, a first-in-class small molecule drug candidate, is the water soluble phosphate prodrug of APX001A. APX001 is rapidly metabolized by circulating phosphatases *in vivo* to APX001A. APX001A has a novel mechanism of action targeting the conserved fungal enzyme glycosylphosphatidylinositol (GPI)-anchored wall transfer protein 1 (GWT1), which is required for the expression of GPI-anchored proteins on the fungal cell wall. Inhibition of GWT1 by APX001A compromises cell wall integrity, inhibits biofilm formation, blocks filamentation, enhances immunogenicity of unmasked β-glucan, and produces severe fungal growth defects. The closest mammalian ortholog of GWT1 is PIG-W, which has no demonstrable inhibition by APX001A.

APX001A has broad *in vitro* activity against major fungal pathogens, including *Candida*, *Cryptococcus*, *Aspergillus*, *Scedosporium*, *Fusarium*, and members of the Mucorales order[17-21]. The susceptibility of *Candida auris* to APX001A has been tested in over 100 diverse isolates including strains resistant to fluconazole, the echinocandins, and/or amphotericin B[22]. In these tests, APX001A is the most mycologically active agent against *C. auris* with markedly lower MIC values than the other antifungals tested. The MIC_{50} and MIC_{90} for APX001A were 0.002 mg/L and 0.008 mg/L, respectively. In addition, APX001A was active against all four *C. auris* clades[22].

APX001 was evaluated in a disseminated *C. auris* infection model in immunocompromised mice[23]. Anidulafungin, an echinocandin, was chosen as a comparator for this model. The mice were sacrificed at 48 hours post-inoculation for determination of the lung, kidney, and brain fungal burdens after intraperitoneal dosing of APX001 (78 mg/kg BID, 78 mg/kg TID, 104 mg/kg BID) and anidulafungin (10 mg/kg BID) versus the vehicle control. Treatment with APX001 resulted in significantly better survival than anidulafungin. Both APX001 and anidulafungin demonstrated

significant and equivalent decreases in kidney and lung colony forming units (CFU) at 48 hours; however, only APX001 demonstrated a reduction in brain fungal burden.

In three completed Phase 1 clinical studies of APX001, the safety, tolerability, and PK of single ascending doses and multiple ascending doses administered intravenously (IV) and orally (PO) to healthy volunteers were studied. A total of 178 healthy volunteers were enrolled in the placebo-controlled Phase 1 studies of APX001. All APX001 doses studied in Phase 1 were considered well tolerated. No serious adverse events (SAEs) were reported, and most of the treatment-emergent adverse events (TEAEs) were mild, transitory, and required no intervention. No dose-limiting toxicities (DLTs) were observed and no TEAEs or safety laboratory test results met any of the *a priori* rules that prevented dose escalation to the next protocol-specified cohort. The maximum tolerated dose was not determined/reached in these Phase 1 studies. Pharmacokinetic parameters for maximum serum concentration and AUC in both single and multiple APX001 IV and PO doses were linear and dose proportional. In both *in vitro* studies of APX001 and in a cohort embedded within the PO dose Phase 1 study, APX001 demonstrated a favorable drug-drug interaction profile. APX001A was shown to be a weak inducer of cytochrome P450 (CYP) 2B6; a moderate inducer of CYP1A2, CYP2C19, and CYP3A4; and a weak inhibitor of CYP2C9 and CYP2D6. The relative bioavailability of the PO formulation was >90% in healthy subjects. There was no evidence of an effect on the bioavailability of APX001 in the presence of food (high fat and high calorie). Most importantly, the target AUCs anticipated for efficacy against both yeast and molds have been achieved with both IV and PO dose formulations tested in Phase 1.

In summary, APX001 is a promising new antifungal agent with a novel mechanism of action having broad spectrum activity against *Candida* spp., including *Candida auris*. Because APX001 is a first-in-class drug candidate with a novel mechanism of action, no cross-resistance with other classes of antifungal drugs has been observed or is expected.

1.1 Rationale

The need for improved treatment of infections caused by the emerging and increasingly prevalent pathogen *Candida auris* is high, particularly given its resistance to fluconazole, and reduced susceptibility to other triazoles. A number of isolates have demonstrated raised MICs to multiple classes of antifungal agents, raising the possibility of pandrug resistance. Outbreaks of *C. auris* infection have been associated with treatment failure and in some cases with death. APX001 has potent activity against *C. auris* isolates *in vitro* and *in vivo*, which in combination with its demonstrated favourable tissue penetration, pharmacokinetic and pharmacodynamic properties supports its preliminary clinical investigation for the treatment of *C. auris* infection.

1.2 Risk/Benefit

Subjects participating in this study will receive a drug in clinical development without regulatory approval for treatment of fungal diseases. Administration of APX001 in a concentration of 1000 mg IV BID will be administered on Day 1, 600 mg IV QD will be administered on Days 2 through 3, and then subsequently 600 mg IV or 800 mg PO QD will be administered throughout the Study Drug Treatment Period. This treatment may have advantages over standard of care (SOC) therapy against certain resistant fungal diseases, where SOC treatment might show no or limited therapeutic effectiveness, furthermore APX001 has a differentiated safety profile, is available as IV and oral formulation and may have fewer drug-drug interactions than SOC. Since the efficacy of APX001 has not yet been proven in patients, no additional protection of APX001 in this concentration can be assured. Potential adverse events associated with APX001 were headache, dizziness, fatigue, nausea and vomiting. For more information on APX001 safety profile please refer to the Investigator's Brochure. Subjects participating in this clinical study will receive more intense health monitoring as detailed in the schedule of procedures.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy and safety of APX001 for the treatment of adult patients aged 18 years and above, with candidemia and/or invasive candidiasis caused by *Candida auris*, who have limited antifungal treatment options.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the time to first negative blood culture
- Evaluate the percentage of patients with successful Mycological Outcomes at End of Study Drug Treatment (EOST), and at 2 and 4 weeks after EOST
- Evaluate the percentage of patients with Treatment Success 2 and 4 weeks after EOST
- Evaluate all-cause mortality at Study Day 30
- Evaluate safety parameters, including number of patients with treatment-emergent adverse events (TEAEs)
- Evaluate pharmacokinetic (PK) parameters of APX001

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a multicenter, open-label, non-comparative, single-arm study to evaluate the efficacy and safety of APX001 for the treatment of candidemia and/or invasive candidiasis caused by *C. auris* in patients aged 18 years and over who have limited antifungal treatment options. The Study Drug Treatment Period will be up to a maximum of 42 days (inclusive of the loading dose [Study Day 1]). There will be a Follow-up Period of 4 weeks (+4 days) after EOST. The total duration of participation in the study is up to approximately 10.5 weeks (inclusive of the Screening Period [≤168 hours prior to Baseline]). Patients must have had *C. auris* confirmed in culture <120 hours (for candidemia) or <168 hours (for invasive candidiasis without candidemia) prior to qualification and dosing in the study.

Screening and Baseline procedures will be performed within no more than 120 hours (for candidemia) or 168 hours (for invasive candidiasis without candidemia) from the time that the SOC blood and/or tissue sample or aspirate/fluid positive for *C. auris* was collected, and any outstanding baseline procedures completed before the first dose of study medication.

All patients (or the patient's LAR) will sign an ICF before any protocol specified procedures that are not indicated by SOC may be conducted. Inclusion/exclusion criteria assessments, medical history, demographics, and Acute Physiology and Chronic Health Evaluation II score will be collected before dosing. When an LAR is used for the initial consent, the patient will be consented during the study as soon as he/she is able to do so.

On Study Day 1 (or over the first 24 hours if dosing starts in the evening), a 1000 mg APX001 loading dose will be administered over 3 hours by IV infusion twice daily (BID). On Study Days 2 and 3, a 600 mg APX001 maintenance dose will be administered over 3 hours by IV infusion once daily (QD). On Study Day 4 and onward, the APX001 maintenance dose will be administered as either 600 mg APX001 IV infusion QD over 3 hours or 800 mg PO QD. Patients who have completed a minimum of 3 days of IV APX001, are clinically stable as determined by the Investigator, and are able to swallow tablets, may switch from IV to PO dosing on Study Day 4 and onward. Study drug will be administered for 14 days after clearance of *Candida* organisms from the bloodstream, and in accordance with clinical judgment as applicable for other infected sites, up to a maximum of 42 days.

Patients will be monitored by daily blood culture from signing informed consent, through dosing, during Study Drug Treatment until 2 consecutive blood cultures are negative for *Candida* spp., at EOST, and at 2 and 4 weeks after EOST, or Early Termination. For patients diagnosed with invasive candidiasis, relevant cultures, histopathology, and imaging tests to assess the site(s), extent, progress, and outcome of the *Candida* infection will be conducted as clinically indicated. All results should be recorded in the electronic Case Report Form. The management of intravascular catheters, intravascular devices, and, if applicable, any drains will be recorded, including any associated microbiology results.

Patients will be monitored for safety throughout the duration of the study. Safety assessments will include vital signs, clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis), physical examinations, neurological assessments (twice weekly on study treatment), prior and concomitant medication reporting, and adverse event reporting. A 12-lead electrocardiogram (ECG) will be performed at Baseline (pre-dose), EOST, and 4 weeks after EOST, or Early Termination. A dilated fundoscopic examination will be performed at least once during the baseline period, which exclusively for this assessment may be up to Day 3 of the study. Follow-up fundoscopic examinations are required at EOST, and 4 weeks after EOST, or Early Termination for those patients who had positive findings up to Day 3 (or more if clinically indicated). A urine pregnancy test (for females of childbearing potential only) will be performed at Screening and Baseline (pre-dose), every 30 days during treatment if required by local regulations, at EOST, and 2 and 4 weeks after EOST, or Early Termination.

In the event of an inadequate response/failure on APX001 study treatment, the study drug may be discontinued and alternative antifungal treatment instituted.

Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, and at EOST, 2 weeks after EOST, or Early Termination. Plasma samples for PK will be collected at the same time as samples are collected for the study's clinical laboratory assessments. Serum samples for (1,3)-β-D-glucan levels will be collected at Baseline (pre-dose) and EOST, or Early Termination (if applicable).

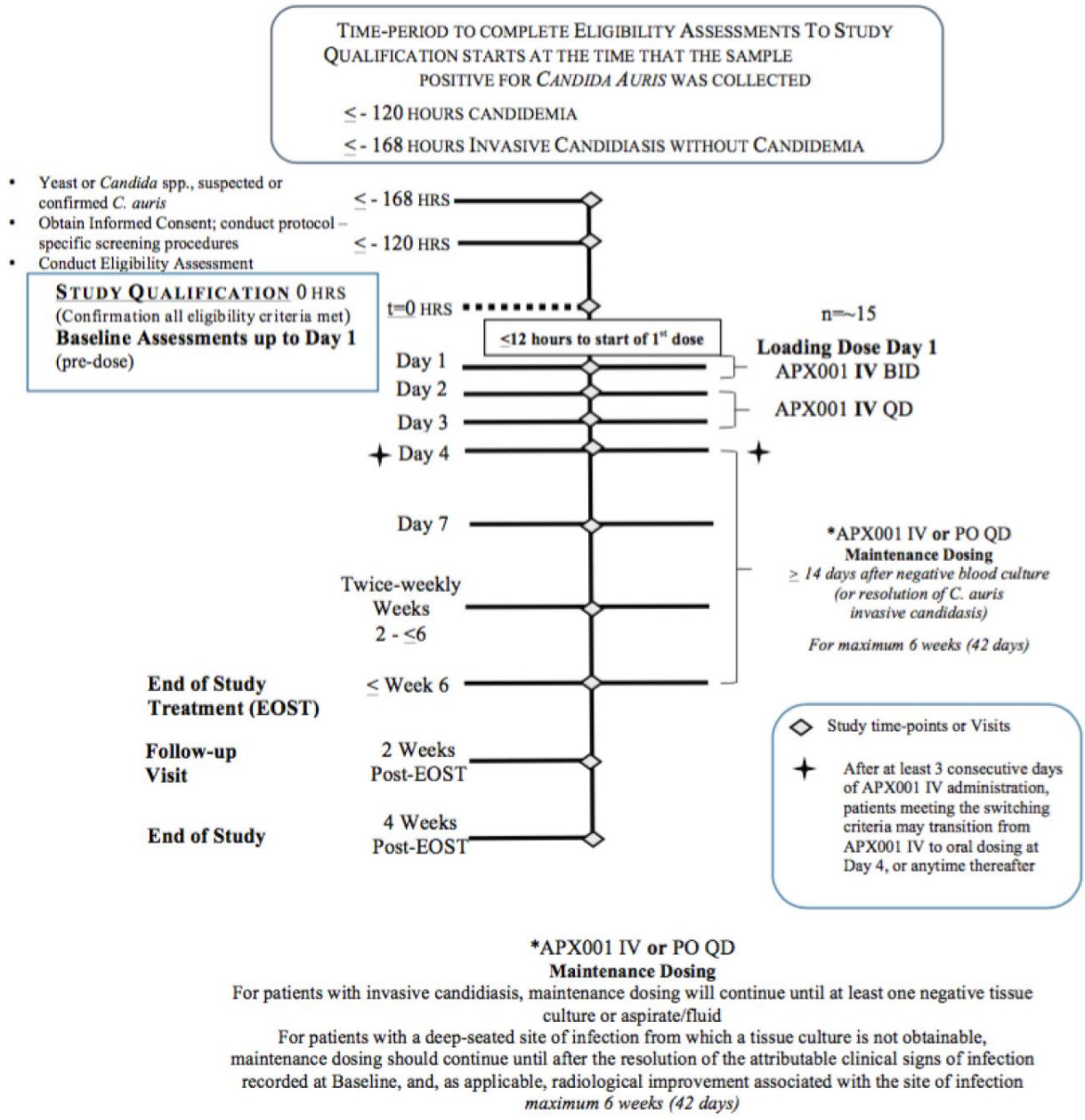
Optionally, if body fluids are sampled as part of routine patient management (e.g. bronchoalveolar lavage, lumbar puncture, paracentesis, vitreous fluid collection, abscess drainage) within approximately 2 hours of blood sampling for PK, these samples may be stored for future analysis of APX001 and APX001A levels.

The evaluation of treatment outcome will be assessed at EOST, and 2 and 4 weeks after EOST, or Early Termination.

The end of study will occur after the last visit of the last patient on the study.

A schematic representing the study's design follows.

Figure 1. APX001-203 Study Schematic



*APX001 IV **or** PO QD
Maintenance Dosing
For patients with invasive candidiasis, maintenance dosing will continue until at least one negative tissue culture or aspirate/fluid
For patients with a deep-seated site of infection from which a tissue culture is not obtainable, maintenance dosing should continue until after the resolution of the attributable clinical signs of infection recorded at Baseline, and, as applicable, radiological improvement associated with the site of infection
maximum 6 weeks (42 days)

3.2 Study Indication(s)

APX001 is indicated in this study for the treatment of patients with candidemia and/or invasive candidiasis caused by *Candida auris*.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

This study will enroll male and female patients aged 18 years and above with an established diagnosis of candidemia and/or invasive candidiasis caused by *Candida auris* from a sample taken <120 hours (for patients with candidemia) or <168 hours (for patients with invasive candidiasis without candidemia) of enrollment in the study. Patients with a blood culture, or specimen sampled from a normally sterile site, positive for yeast suspected to be *Candida auris* who also have limited antifungal treatment options may sign the Informed Consent Form (ICF) and undergo Screening procedures for the study. However, *Candida* spp. must be confirmed in culture from blood or other tissue, aspirate or fluid sampled from a normally sterile site, and all eligibility criteria must be met prior to qualification for the study and subsequent dosing.

4.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

1. Male or female aged 18 years and above
2. Limited or no treatment options due to resistance, contraindication, intolerance or lack of clinical response to standard of care antifungal therapy, as advocated by the relevant regional/country treatment guidelines
3. Established mycological and clinical diagnosis of candidemia and/or invasive candidiasis from a sample taken <120 hours (for candidemia) or <168 hours (for invasive candidiasis without candidemia) before study qualification:

    a. Candidemia criteria

    i. ≥1 blood culture positive for yeast/*Candida* spp. identified as *C. auris*;

    plus:

    ii. Clinical signs attributable to candidemia within the 120 hours prior to qualification for the study, to include at least one of the following: (a) fever (>38ºC), or (b) hypothermia (<36ºC), or (c) hypotension (SBP <90mmHg or decrease of >30mmHg);

    b. Invasive candidiasis criteria

    i. ≥1 specimen (e.g., tissue, aspirate/fluid) sampled aseptically from a normally sterile site culture positive for yeast/*Candida* spp. identified as *C. auris*;

    plus:

ii. Clinical signs attributable to invasive candidiasis within the 168 hours prior to qualification for the study, to include at least one of the following: (a) fever (>38ºC), or (b) hypothermia (<36ºC), or (c) hypotension (SBP <90mmHg or decrease of >30mmHg), or (d) signs associated with organ/site infected with *Candida* (e.g. eye, intra-abdominal).

4. Patients with single *C. auris* infection, or mixed *Candida auris* plus other *Candida* spp. (other than *C. krusei*) infection, are eligible for the study.
5. Able to have pre-existing intravascular catheters removed and replaced (if necessary)
6. Females of childbearing potential with male partners, and males with female partner(s) of childbearing potential, must agree to use 2 forms of highly effective contraception, 1 of which must be a barrier method, throughout the duration of the study and for 90 days following the last study drug administration. Acceptable barrier forms of contraception are condom and diaphragm. Acceptable non-barrier forms of contraception for this study are oral contraceptives (e.g. oral birth control pill, depot, patch, or injectable), abstinence, intrauterine device, and/or spermicide.

   Post-menopausal is defined as amenorrhea for >12 months without an alternative medical cause or documented surgical sterilization (e.g. bilateral salpingectomy, bilateral oophorectomy, or hysterectomy).

   True abstinence, when in line with the preferred and usual lifestyle of the patient, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug treatment. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception)
7. Females of childbearing potential must have a negative urine pregnancy test within 96 hours prior to Baseline (i.e. pre-dose on Study Day 1)
8. Willing to participate in the study, willing to give written informed consent, and willing to comply with the study restrictions; where permitted by local regulations, written informed consent from a legal authorized representative (LAR) will be obtained for patients who are unable to give consent.
9. Male patients must agree to abstain from sperm donation and use condoms with spermicide during sexual intercourse between Screening and at least 90 days after administration of the last dose of study drug. Male patients must ensure non-pregnant female partner(s) of childbearing potential comply with the contraception requirements in Inclusion Criterion 6 (above).

4.2 Exclusion Criteria

Participants who meet any of the following criteria will not be eligible for the study:

1. Blood culture, or any other culture, positive for *C. krusei*
2. Life expectancy of <7 days in the opinion of the Investigator
3. Severe or moderate hepatic impairment (Child-Pugh Score >6 points) at any time during 2 weeks prior to dosing. The Child-Pugh score of >6 is applicable to patients with hepatic dysfunction and cirrhosis only.
4. Baseline neurological conditions such as abnormal movements or convulsive disorders
5. Human immunodeficiency virus-infected patients who are receiving antiretroviral therapy that are moderate to strong inducers of CYP3A4, or who have detectable viremia, or who have had an active opportunistic infection within 6 months prior to Screening
6. Alanine aminotransferase or aspartate aminotransferase ≥5 × upper limit of normal (ULN)
7. Total bilirubin >3 × ULN, unless isolated hyperbilirubinemia or due to documented Gilbert's disease.
8. Female patient is pregnant or lactating
9. Inappropriate fungal infection source control (e.g. persistent indwelling catheters or intravascular devices)
10. Investigational drug administered within 30 days prior to dosing or five half-lives whichever is longer
11. Concomitant use of medication that is a strong inducer of CYP enzymes (e.g. rifampin, carbamazepine, phenytoin, rifabutin, efavirenz, nevirapine, phenobarbital, modafinil, nafcillin, St. John's Wort, and enzalutamide)
12. Any other condition or laboratory abnormality that, in the opinion of the Investigator, would put the patient at unacceptable risk for participation in the study or may interfere with the assessments included in the study
13. Diagnosis of deep-seated *Candida*-related infections causing hardware associated septic arthritis, osteomyelitis, endocarditis, myocarditis, hepatosplenic candidiasis, or a central nervous system infection or site of infection that would require antifungal therapy to exceed the maximal duration of study drug treatment (i.e. 6 weeks [42 days])

4.3 Dosing Criteria

Participants must meet the following criteria to begin dosing:

Confirmed diagnosis of candidemia and/or invasive candidiasis caused by *C. auris* (in a single or mixed *Candida* spp. infection) within <120 hours (for candidemia) or within <168 hours (for invasive candidiasis without candidemia) of the indicative positive blood culture or the indicative positive culture from a specimen sampled from a normally sterile site, plus confirmation that all other eligibility criteria are met, qualify the patient for dosing with APX001. The initiation of the first dose of APX001 must occur within 12 hours of qualification for the study.

4.4 Withdrawal Criteria

Study drug dosing may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
- Occurrence of significant drug-induced liver injury (DILI) [Appendix D]
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient
- Pregnancy
- Requirement of prohibited concomitant medication
- Patient failure to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or the regulatory authority
- Patients who discontinue study drug due to withdrawal of consent, death, or loss to follow-up will discontinue study participation. Patients who fail on study treatment and start alternative antifungals will be assessed for safety 4 weeks after stopping study medication. Patients who discontinue study drug for other reasons will enter the follow-up phase of the study.

If a patient withdraws prematurely from the study due to any of the above criteria or for any other reason, study staff should make every effort to contact the Sponsor prior to discontinuation, if possible, and to complete the full panel of assessments scheduled for the Early Termination Visit. The reason for patient withdrawal must be documented in the eCRF.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

Withdrawn patients will not be replaced.

The study may be discontinued for any of the following reasons: five or more subjects in study (cumulative) experience a same Grade 2 (or higher) related AE (laboratory or systemic) which is coded in the same high-level group term per MedDRA coding, throughout the duration of study; a recommendation from the DSMB based on other safety signals; lack of Investigational Product availability; inability to enroll the study; or decision by a regulatory authority or the sponsor.

5 STUDY TREATMENTS

5.1 Treatment Groups

All patients will be administered a 1000 mg APX001 loading dose BID on Study Day 1 (or over the first 24 hours if dosing starts in the evening) followed by a 600 mg APX001 maintenance dose QD on Study Day 2 and Study Day 3. From Study Day 4 onwards, the APX001 maintenance dose will be administered as either 600 mg APX001 IV infusion QD or may be switched to 800 mg PO QD when/if the criteria for oral dosing are met (Section 5.5.3).

5.2 Rationale for Dosing

In pharmacokinetic/pharmacodynamic (PK-PD) studies, immunocompromised mice were infected with one of three spp. of *Candida* (*C. albicans*, *C. glabrata*, or *C. auris*) and groups of animals were dosed with APX001 at different dose fractionations. The AUC/MIC ratio was determined to be the PK-PD variable that best correlated with antifungal efficacy as assessed by fungal burden (CFUs) in the kidney. The probability of target attainment (PTA) was calculated separately for each *Candida* spp. tested. The PTA calculation used the APX001A free drug AUC level at the stasis endpoint divided by the MIC required to inhibit the growth of 90% of organisms (MIC_{90}) of each of the *Candida* spp. tested.

The AUC level was estimated from a population PK model derived primarily from the Phase 1 PK data. The stasis endpoint was defined as the quantity of *Candida* spp. in CFUs just prior to APX001 administration compared to CFUs at the endpoint of assessment (i.e. 24 hours for *C. albicans*; 96 hours for *C. glabrata* and *C. auris*). The MIC data for the *Candida* strains tested were obtained from recent surveillance data.

Using the AUC at the stasis endpoint, along with the MIC_{90} from the surveillance data and the predicted exposure at the dose regimen to be used in this study, the PTA for the 3 *Candida* spp. tested was shown to be approximately 100%. Further, sensitivity analyses were conducted to evaluate the PTA under different scenarios including increased variability of PK parameters and higher *Candida* spp. MIC_{90} values. For both scenarios the PTA remained >90%.

In two Phase 1 studies in healthy volunteers, APX001 IV and PO formulations were safe and well tolerated. The majority of TEAEs were mild, transitory, and resolved without intervention. No DLTs were observed. Specifically, in the first-in-human Phase 1 clinical study, a loading dose regimen of APX001 1000 mg IV 2-hour infusion BID on Day 1, followed by a maintenance dose of APX001 600 mg IV 1-hour infusion QD on Days 2 through 7, was safe and well tolerated. In an additional Phase 1 study of APX001, a dose regimen consisting of a loading dose of APX001 1000 mg IV 3-hour infusion BID on Day 1, followed by a maintenance dose of APX001 600 mg IV 3-hour infusion QD on Days 2 through 7, and then APX001 800 mg orally QD on Days 8 through 42 was also safe and well tolerated.

Schedule

To ensure the safety and tolerability of APX001 dosing for 42 days, this study will use an APX001 dose and infusion duration already studied in Phase 1 for 42 days of therapy inclusive of IV and PO investigational drug therapy. The loading dose regimen of APX001 1000 mg IV BID over a 3-hour infusion followed by APX001 600 mg IV QD over a 3-hour infusion has been designed to optimize patient safety and tolerability during the study. At Study Day 4 and onward, provided the protocol-defined criteria for a PO switch are met, the patient may be switched to oral APX001 800 mg QD. Study drug will be administered for 14 days after clearance of *Candida* organisms from the bloodstream, and in accordance with clinical judgment as applicable for other infected sites, up to a maximum of 42 total days combined IV and PO APX001 therapy.

5.3 Randomization and Blinding

This is a non-randomized, open-label study.

5.4 Breaking the Blind

This is an open-label study.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

APX001 Injection is formulated at a concentration of 20 mg/mL. [redacted]

APX001 tablets are formulated at a strength of 200 mg white-coated tablets. [redacted]

Although the size of the vial used for APX001 Injection and/or the APX001 tablet strength may be potentially modified (as re-supplies are manufactured), the APX001 doses to be administered will not change. Any changes will be detailed in the Pharmacy Manual.

All APX001 supplies will be labeled according to the requirements of local law and legislation, as well as current Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines.

5.5.2 Study Drug Preparation and Dispensing

Study drug will be delivered to the study site by an authorized delegate of the Sponsor. Site staff who have been delegated the task of drug dispensing by the Investigator will dispense the appropriate treatment.

Additional details regarding study drug preparation and dispensing will be provided in the Pharmacy Manual.

5.5.3 Study Drug Administration

On Study Day 1 (or over the first 24 hours if started in the evening), a 1000 mg APX001 loading dose will be administered over 3 hours by IV infusion BID.

The infusion volume for both the 1000 mg and the 600 mg APX001 doses will be 250 mL.

On Study Day 4 and onward, an APX001 maintenance dose will be administered as either:

- 600 mg APX001 IV infusion QD over 3 hours, or
- 800 mg APX001 PO QD

Subjects who have completed a minimum of 3 days of IV APX001, are clinically stable as determined by the Investigator, and able to swallow tablets may switch from IV to PO dosing on Study Day 4 and onward. Study drug will be administered for a minimum of 14 days after clearance of *Candida* spp. Duration of APX001 treatment for other deep-seated sites of infection will be according to investigator judgment and treatment guidelines, but may not exceed up to a maximum of 6 weeks total (42 days, inclusive of the loading dose [Study Day 1]).

Tablets are to be administered at the same time each day, whole, and taken by mouth with water within 30 minutes of being removed from the refrigerator. No splitting or crushing of tablets is allowed.

5.5.4 Treatment Compliance

Study drug will be administered at the study site. Compliance with treatment dosing will be monitored and recorded by site personnel. If patients are discharged home with study treatment, compliance will be documented in a dosing diary.

5.5.5 Storage and Accountability

APX001 Injection will be stored at -20°C and tablets will be stored at 2 to 8°C in a secured location (locked) with access restricted to authorized personnel only. Detailed storage and handling instructions will be described in the study-specific Pharmacy Manual. Storage temperature will be monitored and recorded. Further details for storage and accountability of study drug will be provided in the Pharmacy Manual.

Upon receipt of study drug, the Investigator or designee will conduct a complete inventory of all study drug and ensure no damage occurred during shipment.

The Investigator will maintain adequate records documenting the receipt, use, loss, or other disposition of study drug. Drug accountability logs will identify the study drug code number and account for the disposition on a participant-by-participant basis, including specific dates and quantities. The drug accountability logs will be signed by the individual who dispenses the study drug and copies will be provided to the Sponsor.

All used and unused supplies will be appropriately inventoried and verified by the clinical research associate (CRA).

Any unused study drug will be returned to the Sponsor or destroyed on site per local standard operating procedure after monitoring has occurred.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

5.6.1.1 APX001A as a Victim Substrate for Cytochrome P450 Drug-drug Interactions

APX001A is metabolized by multiple CYP enzymes. Patients who are receiving or will receive strong inducers of multiple CYP enzymes (e.g., rifampin, carbamazepine, phenytoin, rifabutin) are excluded from participating in the study. Concomitant use of multiple medications that are strong inhibitors of different CYP pathways may increase levels of APX001A, which in consequence may potentially affect the safety risk of APX001 administration. Caution should be advised when co-administering medications that are strong inhibitors of CYP enzymes.

5.6.1.2 APX001A as a Perpetrator of Cytochrome P450 Drug-drug Interactions

APX001A was shown to be a weak inducer of CYP2B6; a moderate inducer of CYP1A2, CYP2C19, and CYP3A4; and a weak inhibitor of CYP2C9 and CYP2D6. The potential clinical significance of any APX001A DDI will depend on the extent of induction or inhibition and therapeutic margin of the specific victim substrate or substrates.

Co-administration of drugs that are metabolized by the CYP enzymes in this study should be approached with caution and the need for increased frequency of drug monitoring (where applicable) should be considered, especially for CYP substrates that have a narrow therapeutic window.

Refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for an exhaustive list of CYP enzyme inducers and inhibitors.

5.6.2 Prohibited Medications and/or Procedures

Once on study, patients may not receive concomitant systemic anti-fungal therapy for the treatment of candidemia and/or invasive candidiasis.

Subjects cannot have received any investigational drug within 30 days (or five half-lives whichever is longer) prior to dosing.

5.6.3 Documentation of Prior and Concomitant Medication Use

All prior medications received by the participant within 14 days prior to study drug administration and any concomitant medications used throughout the duration of the study will be recorded in the source documents and on the appropriate eCRF. The medication name, route of administration, dose, frequency, indication, and duration of treatment (start and stop dates) will be recorded.

6 STUDY PROCEDURES

6.1 Informed Consent

Written informed consent will be obtained from all participants prior to any study-specific procedures being performed. *C. auris* must be confirmed in culture prior to patient qualification for the study and dosing with study medication. Only those patients who have transient loss of capacity (e.g. mechanical ventilation, sedation) can have an LAR sign consent on their behalf. These patients will be allowed to make their own informed medical decisions and undergo the consent process if and when they are able to do so. Patients with permanent loss of capacity are not eligible for study participation.

6.2 Eligibility

The following cultures drawn or sampled as SOC, prior to informed consent, will determine study eligibility:

- Blood culture positive for *Candida* spp. confirmed to be *C. auris*
- Tissue, aspirate or fluid sampled from a normally sterile site, culture positive for *Candida* spp. confirmed to be *C. auris*

Limited antifungal treatment options are also a requirement for study eligibility. Limited treatment options may be due to one or more of the following factors:

- Resistance of *C. auris* to antifungal drug(s) in question
- Patient unable to tolerate antifungal treatment
- Antifungal contraindicated for given patient
- Inadequate response to antifungal treatment, including refractory and relapsing *C. auris* infection

Screening may start on confirmation of *Candida auris* candidemia or invasive candidiasis in a patient with limited antifungal treatment options.

6.3 Screening

Screening procedures must occur within a 120-hour window (for patients with candidemia) or 168-hour window (for patients with invasive candidiasis without candidemia) prior to qualification for the study.

The following procedures will be performed at Screening:

- Obtain informed consent
- Review inclusion/exclusion criteria
- Record medical history
- Record demography information
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight
- Intravascular catheter management and log of the line changes, to include any catheter tip culture results
- Perform clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis)
- Perform urine pregnancy test (for females of childbearing potential only)
- Collect blood cultures (daily)
- Collect other cultures and histopathology from other sites, as clinically indicated
- Perform imaging tests as clinically indicated to assess the site(s) and extent of invasive candidiasis infection at study baseline
- Record prior/concomitant medications
- Record adverse events

6.4 Treatment Period (up to 6 Weeks)

6.4.1 Baseline (Day -1 or Day 1, Pre-Dose)

Baseline procedures are to be completed predose and within 12 hours of the first dose of study drug (Day 1). The following procedures will be performed at Baseline (Day 1 Pre-dose):

- Confirm inclusion/exclusion criteria
- Perform APACHE II score calculation (Appendix C)
- Collect blood culture for *Candida* spp.
- Collect other cultures and histopathology from other sites, as clinically indicated

- Perform imaging investigations as clinically indicated to define the site(s) and extent of invasive candidiasis infection
- Intravascular catheter management and log of the line changes; any indwelling intravascular catheters should be removed and catheter tips cultured within 24 hours of starting APX001 dosing; entrance site tissue should also be cultured if it appears infected
- Implementation of other fungal infection control measures, as clinically indicated
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight; height will be collected (from the patient's medical record) at Baseline only
- Perform clinical laboratory assessments (serum chemistry, hematology, coagulation and urinalysis)
- Perform 12-lead ECG
- Perform urine pregnancy test (for females of childbearing potential only)
- Perform complete physical examination including an assessment of general appearance, skin, eyes, heart, chest, abdomen, and the body site that corresponds to the entry site of candidemia (e.g., central venous catheter entry site) and/or the site of invasive candidiasis, if applicable, and a neurological examination (cranial nerve, sensory and motor examination, reflex and gait testing, coordination assessment)
- Perform dilated fundoscopic examination. This exam should be performed at least once during the baseline period, which exclusively for this assessment may be up to Day 3 of the study.
- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety]). Plasma samples for PK will be collected at the same time as samples are collected for the study's clinical laboratory assessments.
- Collect serum sample for analysis of(1,3)-β-D-glucan
- Record concomitant medications
- Record adverse events

6.4.2 Study Drug Treatment (≤6 Weeks)

Day 1 dose

Prior to the initiation of the first APX001 dose, a diagnosis of candidemia and/or invasive candidiasis caused by *C. auris* (in a single or mixed *Candida* spp. infection) must be confirmed within 120 hours (for candidemia) or 168 hours (for invasive candidiasis without candidemia) of formal qualification for the study. The initiation of the first dose of APX001 must occur within 12 hours of qualification for the study.

- Study drug to be administered as a 3-hour IV loading dose BID on Day 1 (or over the first 24 hours if started in the evening).

Day 2 onwards (maximum to Day 42)

- On Study Days 2 to 3, study drug to be administered over 3 hours by IV QD; on Day 4 and onward, oral administration of the study drug may be considered if the patient meets the IV to oral switch criteria
- Study drug to be administered for a minimum of 14 days after clearance of *Candida* organisms from the bloodstream or other infected sites,
- Maximum duration of study drug treatment is up to 6 weeks total (42 days, inclusive of the loading dose [Study Day 1])

The following procedures will be performed during the period of Study Drug Treatment:

- For patients with candidemia (with or without invasive candidiasis) **daily** blood cultures are to be performed on Days 1 through 4 (minimum), continuing until 2 negative blood culture results are reported from 2 consecutive samples. (Considered negative at least 48 hours after collection).
- For patients with invasive candidiasis, with or without candidemia, appropriate material from the infected site(s) is to be sampled for culture or histopathology to monitor the progress of infection, as clinically indicated until mycological and/or clinical resolution.

- Imaging tests are to be performed as clinically indicated to monitor the site(s), extent and progress of invasive candidiasis infection
- Intravascular catheter management log; all changes are to be recorded until EOST while inpatient, and as clinically indicated thereafter or for outpatients
- Daily vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight while an inpatient. Measurements are to be continued twice weekly while on treatment as an outpatient.

During Study Drug Treatment, twice weekly visits are required with a minimum window of 2 days and a maximum window of 4 days. Subjects who are outpatients will be asked to record daily dosing on a diary and bring the diary and study drug bottles with them to every clinic visit.

- Perform clinical laboratory assessments (serum chemistry, hematology, coagulation and urinalysis) twice weekly
- Perform urine pregnancy test (for females of childbearing potential only); every 30 days if required by local regulations
- Perform neurological examinations twice weekly
- Perform focused, symptom-based physical examination, as clinically indicated, once weekly

- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety]) twice weekly. Plasma samples for PK will be collected at the same time as samples are collected for the study's clinical laboratory assessments.
    - Optional: If body fluids are sampled as part of routine patient management (e.g., bronchoalveolar lavage, lumbar puncture, paracentesis, vitreous fluid collection, abscess drainage, etc.), within approximately 2 hours of blood sampling for PK, these samples may be stored for future analysis of APX001 levels
- Record concomitant medications
- Assess adverse events

6.4.3 End of Study Drug Treatment (≤6 Weeks)

The EOST for patients completing the study is at least 14 days from the date of clearance of candidemia, as documented by the first of the two consecutive negative blood cultures up to a maximum of 6 weeks total (42 days, inclusive of the loading dose [Study Day 1]). For patients with a deep-seated site of infection amenable to sampling, EOST is after at least one negative tissue culture or aspirate/fluid, up to a maximum of 6 weeks total (42 days, inclusive of the loading dose [Study Day 1]).

- For patients with a deep-seated site of infection involving visceral organs from which a tissue culture is not obtainable, EOST is after the resolution of the attributable clinical signs of infection recorded at Baseline, and, as applicable, radiological improvement associated with the site of infection, up to a maximum of 6 weeks total.

The following procedures will be performed at EOST:

- Collect blood cultures for *Candida* spp.
- Collect other cultures and histopathology from other sites, as clinically indicated
- Perform imaging tests as clinically indicated to monitor the site(s) and extent of invasive candidiasis infection
- Perform dilated fundoscopic examination (only required in those patients who had baseline positive fundoscopic findings [up to Day 3], or as clinically indicated)
- Intravascular catheter management log
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight
- Perform clinical laboratory assessments (serum chemistry, hematology, coagulation and urinalysis)
- Perform 12-lead ECG
- Perform urine pregnancy test (for females of childbearing potential only)
- Perform neurological examination

- Perform focused, symptom-based physical examination as clinically indicated
- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety]). Plasma samples for PK will be collected at the same time as samples are collected for the study's clinical laboratory assessments.
- Collect serum sample for analysis of(1,3)-β-D-glucan
- Evaluate treatment outcome
- Record concomitant medications
- Assess adverse events

6.5 Follow-up (2 Weeks and 4 Weeks After End of Study Drug Treatment)

6.5.1 Follow-up 2 Weeks After End of Study Drug Treatment

The following procedures will be performed at the follow-up visit 2 weeks after EOST:

- Collect blood cultures for *Candida* spp.
- Collect other cultures and histopathology from other sites, as clinically indicated
- Perform imaging tests as clinically indicated to monitor the site(s) and extent of invasive candidiasis infection
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight
- Intravascular catheter management log, as clinically indicated
- Perform clinical laboratory assessments (serum chemistry, hematology, coagulation and urinalysis)
- Perform urine pregnancy test (for females of childbearing potential only)
- Perform neurological examination
- Perform focused, symptom-based physical examination, as clinically indicated
- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety]). Plasma samples for PK will be collected at the same time as samples are collected for the study's clinical laboratory assessments.
- Evaluate treatment outcome
- Record concomitant medications
- Assess adverse events

6.5.2 Follow-up 4 Weeks After End of Study Drug Treatment

The following procedures will be performed at the follow-up visit 4 weeks after EOST:

- Collect blood culture for *Candida* spp.
- Collect other cultures and histopathology from other sites, as clinically indicated
- Perform imaging tests as clinically indicated to monitor the site(s) and extent of invasive candidiasis infection
- Perform dilated fundoscopic examination (only required in those patients who had baseline positive fundoscopic findings [up to Day 3] or as clinically indicated)
- Intravascular catheter management log, as clinically indicated
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight
- Perform clinical laboratory assessments (serum chemistry, hematology, and urinalysis)
- Perform 12-lead ECG
- Perform urine pregnancy test (for females of childbearing potential only)
- Perform neurological examination
- Perform focused, symptom-based physical examination, as clinically indicated
- Evaluate treatment outcome
- Record concomitant medications
- Assess adverse events

6.5.3 Early Termination Visit and Withdrawal Procedures

For patients who are withdrawn from the study prior to completion, all EOST procedures will be performed at an Early Termination visit. These procedures include the following:

- Collect blood culture for *Candida* spp.
- Collect other cultures and histopathology from other sites, as clinically indicated
- Perform imaging tests as clinically indicated to monitor the site(s) and extent of invasive candidiasis infection
- Perform dilated fundoscopic examination (only required in those patients who had baseline positive fundoscopic findings [up to Day 3], or as clinically indicated)
- Intravascular catheter management log, as clinically indicated
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight

- Perform clinical laboratory assessments (serum chemistry, hematology, coagulation and urinalysis)
- Perform 12-lead ECG
- Perform urine pregnancy test (for females of childbearing potential only)
- Perform neurological examination
- Perform focused, symptom-based physical examination, as clinically indicated
- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety])
- Collect serum sample for analysis of(1,3)-β-D-glucan
- Evaluate treatment outcome
- Record concomitant medications
- Assess adverse events

7 EFFICACY ASSESSMENTS

7.1 Primary Efficacy Endpoint

The primary efficacy parameter is percentage of patients with Treatment Success at EOST as determined by the Data Review Committee (DRC).

7.2 Secondary Efficacy Endpoints

The secondary efficacy parameters include the following:

- Time to first negative blood culture
- Percentage of patients with successful Mycological Outcomes at EOST, and at 2 and 4 weeks after EOST
- Percentage of patients with Treatment Success at EOST as determined by the investigator
- Percentage of patients with Treatment Success 2 and 4 weeks after EOST, as determined by the investigator and by the DRC
- All-cause mortality at Study Day 30
- Number of patients with TEAEs

7.3 Exploratory Efficacy Endpoint

The exploratory efficacy parameters include the following:

- Change in serum (1,3)-β-D-glucan levels from Baseline (pre-dose) to EOST

7.4 Definitions for Efficacy Assessments

7.4.1 At End of Study Drug Treatment

Treatment Success is defined as meeting all of the following criteria:

- Two consecutive blood cultures negative for *Candida* spp. and/or for patients with a deep-seated site of infection, at least one negative tissue culture or aspirate/fluid
    - for patients with a deep-seated site of infection involving visceral organs from which a tissue culture is not obtainable, resolution of the attributable clinical signs of infection recorded at Baseline, and, as applicable, radiological improvement associated with the site of infection is required
- Alive at EOST
- No concomitant use of any other systemic antifungal therapies through EOST

  Note: administration of another systemic antifungal immediately following EOST for suspected or documented *Candida* infection at any site does not constitute a treatment success at EOST

Treatment Failure is defined as any case that does not meet the criteria for Treatment Success.

Successful Mycological Outcome:

- Eradication is defined as a negative blood (and/or other infection site) culture(s) for *Candida* spp. in the absence of concomitant antifungal therapy through EOST
- Presumed Eradication (applicable to invasive candidiasis) is defined as clinical resolution of invasive *Candida* spp. infection where tissue samples are unavailable (supported by evidence of resolution/improvement in the diagnostic parameters used at Baseline)

Both of the above definitions are in the absence of concomitant or additional systemic antifungal therapy.

7.4.2 At Follow-Up (2 Weeks and 4 Weeks After End of Study Drug Treatment [EOST])

- Treatment Success (sustained) is defined as having met the criteria for Treatment Success at EOST with no change during the follow-up period
- Relapse is defined as re-occurrence of *Candida* in blood culture, or from other infection sites, during the Follow-up Period, or diagnostic parameters indicative of recurrence or late spread of the *Candida* infection
- Other:
    - Death
    - Unavailable for follow-up, or unevaluable at follow up for other reasons

  Additional DRC assessment categories are provided in the DRC Charter

Mycological Recurrence is defined as mycologically confirmed infection based on blood culture (or other specimen(s) cultured from a normally sterile site), with the same Baseline *Candida* spp. during the 4 weeks after EOST.

7.5 Microbiological Assessments

7.5.1 Blood Cultures

For patients with candidemia, *Candida auris* confirmed in blood culture is required for qualification into the study, which must occur within 120 hours of the collection of the indicative positive blood sample. The study site's local microbiology laboratory will analyze blood and other cultures for *Candida* spp. Isolates of all *Candida* spp from SOC eligibility cultures must be submitted to the mycology reference laboratory for confirmation of identification and susceptibility testing.

For all patients (candidemia or invasive candidiasis), once consent is obtained, the first blood collection should comprise two consecutive sets (1 aerobic and 1 anaerobic blood culture bottle in each set) of blood cultures from 2 separate IV sites (1 from a central venous catheter (CVC) and 1 peripheral, or 2 peripherals if CVC is not applicable); a minimum of 1 set (1 aerobic and 1 anaerobic blood culture bottle in each set) of blood cultures is required thereafter.

Blood cultures for *Candida* spp. will be performed during the Screening period (daily), at Baseline (pre-dose), during Study Drug Treatment, at EOST, and 2 and 4 weeks after EOST, or Early Termination. During the Study Drug Treatment Period, blood cultures are required daily on Study Days 1 through 4; thereafter, blood cultures during study drug treatment may be stopped after negative results on 2 consecutive blood culture tests are obtained.

The study site's local microbiology laboratory will analyze all blood cultures for *Candida* spp. The local microbiology lab will send all *Candida* isolates from blood cultures to the mycology reference laboratory for confirmation of identification and susceptibility testing.

In the event that the study site uses a rapid diagnostic test for the diagnosis of candidemia, subsequent confirmatory blood cultures are required, and resulting isolates should be submitted to the mycology reference laboratory for confirmation of identification and susceptibility testing. Results from rapid diagnostic tests performed must be captured in the eCRF.

7.5.2 Cultures from Other Sites of Infection

For patients with invasive candidiasis, a tissue culture or aspirate/fluid sample confirmed positive for *Candida auris* that has been collected aseptically from a normally sterile site is required for inclusion in the study. Study qualification will occur within 168 hours of a confirmed positive tissue culture or aspirate/fluid collection. Isolates of all *Candida* spp. from SOC eligibility cultures and baseline and follow-up cultures must be submitted to the mycology reference laboratory for confirmation of identification and susceptibility testing. Tissue culture or aspirate/fluid samples

for *Candida* spp. will be collected at Baseline (pre-dose), and where amenable to sampling during Study Drug Treatment, at EOST, and 2 and 4 weeks after EOST, or Early Termination. Collection of culture or aspirate/fluid samples may be stopped after at least one negative tissue culture or aspirate/fluid sample.

The study site's local microbiology laboratory will analyze all tissue cultures or aspirate/fluid samples for *Candida* spp. The local microbiology lab will send all *Candida* isolates from tissue cultures or aspirate/fluid cultures to the mycology reference laboratory for confirmation of identification and susceptibility testing.

7.5.3 Intravascular Catheter Management and Log

If possible, all intravascular catheters should be removed and the catheter tips cultured by the local microbiology laboratory within 24 hours of APX001 dosing. The entrance site should also be cultured by the local microbiology laboratory if it appears infected. The local microbiology lab will send all *Candida* isolates from intravascular catheter or entrance site cultures to the mycology reference laboratory for confirmation of identification and susceptibility testing. Intravascular catheter management should be managed at the site level as per local SOC.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until study participation is complete. Subjects should be instructed to report any adverse event that they experience to the Investigator. Beginning with Day 1 of study drug, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at Screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at Baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event. A laboratory finding that is abnormal but not clinically significant (e.g., does not warrant intervention) is not considered an adverse event.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a study drug related to any dose should be considered an adverse drug reaction. "Responses" to a study drug means that a causal relationship between a study drug and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Drug-induced liver injury is defined in Appendix D, and requires study drug withdrawal.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For APX001, the reference safety information is included in the Investigator's Brochure (IB) currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event and will also categorize each adverse event as to its potential relationship to study drug using the categories of "yes" or "no."

Assessment of Severity:

The severity of all adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. These criteria can be found at http://ctep.cancer.gov/reporting/ctc.html. For those adverse events not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with patient's daily activities

- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with patient's usual activities, but still acceptable
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the patient's daily activities, unacceptable
- Life-threatening (CTCAE Grade 4): Life threatening or disabling adverse event
- Death (CTCAE Grade 5): Death-related adverse event

Causality Assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
  - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event
- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have
- Concomitant drug-
  - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question
- Known response pattern for this class of study drug-
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect

- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and PK of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
  - An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death
- Requires hospitalization or prolongation of existing hospitalizations
  - Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to [redacted] fety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

To report the SAE, the Investigator must complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] personnel will be notified electronically and will retrieve the form. If the event meets seriousness criteria and it is not possible to access the EDC system, the Investigator should send an e-mail to [redacted] fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

[redacted]

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to [redacted] via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Expedited Reporting

The Sponsor will comply with all country-specific regulations relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA, applicable competent authorities concerned, and to the Central Ethics Committee as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

8.5 Stopping Rules

8.5.1 Study Stopping Rule

At any time, the independent DSMB may temporarily suspend enrollment until any significant safety concerns are resolved or terminate the study to ensure patient safety, if in the opinion of the DSMB, further dosing would pose an inappropriate safety risk. Guidelines for what constitutes inappropriate safety risks are described in the DSMB Charter.

Additionally, the study may be discontinued for any of the following reasons: five or more subjects in study (cumulative) experience a same Grade 2 (or higher) related AE (laboratory or systemic) which is coded in the same high-level group term per MedDRA coding, throughout the duration of study; lack of investigational product availability; inability to enroll the study; or decision by a regulatory authority or the sponsor.

8.5.2 Subject Stopping Rule

Study treatment for an individual patient may be discontinued for any adverse event, SAE, laboratory abnormality, or intercurrent illness which, in the opinion of the Investigator, indicates that continued dosing in the study is not in the best interest of the patient.

8.6 Pregnancy Reporting

A urine pregnancy test will be performed at Screening and Baseline (pre-dose), every 30 days during treatment if required by local regulations, EOST, and 2 and 4 weeks after EOST, or Early Termination for all female patients of childbearing potential. If the patient or partner of a patient participating in the study becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to [redacted]y within 24 hours of being notified. [redacted] will then forward the Exposure In Utero Form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and Early Termination study procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify [redacted]. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy within 24 hours. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.7 Clinical Laboratory Evaluations

Screening laboratory assessments to determine eligibility will be performed at the local laboratory and may have been collected as SOC within the previous 24 hours. Laboratory assessments collected after Screening will be sent to the central laboratory for analysis.

Clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis) will occur at Baseline (pre-dose), twice weekly during Study Drug Treatment, at EOST, and at 2 and 4 weeks after EOST, or Early Termination. If clinically indicated and at the discretion of the Investigator, or if a suspected adverse event is identified, clinical laboratory assessments may be conducted at any time during the study and compared to Baseline. See Appendix B for a complete list of clinical laboratory analytes.

8.8 Vital Signs

Vital signs will include temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight and will be collected at Screening, Baseline (pre-dose), daily on Study Days 1 through 4 and twice weekly thereafter during Study Drug Treatment for outpatients (daily while inpatient), EOST, and 2 and 4 weeks after EOST, or Early Termination. Height will be collected (from the patient's medical record) at Baseline only.

8.9 APACHE II Score

The APACHE II score (Appendix C) will be determined at Baseline (pre-dose).

8.10 Electrocardiograms

A 12-lead ECG will be obtained at Baseline (pre-dose), EOST, and 4 weeks after EOST, or Early Termination.

8.11 Physical Examinations

A complete physical examination will be conducted at Baseline (pre-dose). Complete physical examination will include an assessment of general appearance, skin, eyes, heart, chest, abdomen, the body site that corresponds to the entry site of candidemia (e.g., central venous catheter entry site), if applicable, and a neurological examination. Components of the neurological examination include cranial nerve, sensory and motor examination, reflex and gait testing, and coordination assessment.

A neurological examination will be performed twice weekly during study drug treatment. A focused, symptom-based physical examination will be performed once weekly during study treatment. Neurological and focused, symptom-based examinations will also be performed at EOST, and 2 and 4 weeks after EOST, or Early Termination.

8.12 Pharmacokinetics

Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, EOST, and 2 weeks after EOST, or Early Termination.

Optionally, if body fluids are sampled as part of routine patient management (e.g., bronchoalveolar lavage, lumbar puncture, paracentesis, vitreous fluid collection, abscess drainage, etc.), within approximately 2 hours of blood sampling for PK, these samples may be stored for future analysis of APX001 levels.

8.13 Dilated Fundoscopic Examination

A dilated fundoscopic examination will be performed at Baseline + 3 days. Thereafter, a dilated fundoscopic examination is only required in those patients who had positive fundoscopic findings at Baseline + 3 days, or as clinically indicated.

8.14 Imaging Tests

Imaging should be performed to assess the site(s) and extent of invasive candidiasis infection as clinically indicated.

9 STATISTICS

9.1 Analysis Populations

Intent-to-Treat Population/Safety Population

The Intent-to-Treat Population/Safety Population will include all patients who have received at least 1 dose of APX001.

Modified Intent-to-Treat Population

The Modified Intent-to-Treat (MITT) Population will include all patients who satisfy the following criteria:

- Received at least 1 dose of study drug
- Have a confirmed diagnosis of candidemia and/or invasive candidiasis caused by *C. auris* within 120 hours (for candidemia) or 168 hours (for invasive candidiasis without candidemia) of study qualification

Per-Protocol Population

The Per-Protocol Population will include all patients in the MITT Population who satisfy the following criteria:

- Meet the protocol's key inclusion and exclusion criteria
- Receive at least 80% of the intended doses
- Have no major protocol violations

Pharmacokinetic (PK) Population

- The PK Population will include all patients who receive any amount of study drug and have evaluable PK data.

9.2 Statistical Methods

Summary statistics will be presented. For continuous variables, the number of observations (n), mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, the frequency and percentage in each category will be displayed.

9.2.1 Analysis of Efficacy

9.2.1.1 Primary Efficacy Analysis

The primary population for efficacy analysis will be the MITT Population.

The efficacy endpoints will be summarized descriptively. The percentage of patients with Treatment Success at EOST will be summarized. The same summary will be repeated for the Per-Protocol Population.

9.2.1.2 Secondary Efficacy Analysis

The percentage of patients with Treatment Success at 2 and 4 weeks after EOST will be summarized. Similarly, the proportion of patients with Mycological Outcomes eradication or presumed eradication at EOST, and recurrence or relapse 2 and 4 weeks after EOST will be summarized. A descriptive summary of overall survival at Study Day 30 and time to first negative culture will also be provided.

9.2.1.3 Analysis of Safety

All safety analyses will be performed on the Safety Population. Safety data will be subject to clinical review and summarized by appropriate descriptive statistics. A DSMB will be assigned to monitor safety on an ongoing basis throughout the study.

Analyses will be based on adverse events, vital signs, clinical laboratory assessments, and ECGs. Safety analyses will be descriptive and will be presented in tabular format with the appropriate summary statistics.

A TEAE is defined as an adverse event started on or after the administration of study drug. The number and percentage of patients with TEAEs will be tabulated by system organ class, preferred term, and by severity and relationship to treatment. Serious adverse events and adverse events leading to discontinuation from study drug will be summarized. Listings will also be provided for SAEs and adverse events leading to discontinuation of study drug.

Descriptive statistics will be provided for clinical laboratory data for both actual values and changes from baseline over time.

Descriptive statistics will be provided for vital sign data presented as both actual values and changes from baseline over time.

Abnormal physical examination findings will be listed.

Descriptive statistics will be provided for ECG interval data and presented as both actual values and changes from baseline.

9.2.1.4 Pharmacokinetic Analysis

Pharmacokinetic analysis of plasma concentration data will be performed using validated software. Pharmacokinetic analysis of plasma concentration data will be performed using validated software in order to derive the population mean (and variance) values of specific PK parameters.

Plasma concentrations will be summarized descriptively by treatment group and time point of collection. Summary statistics in the tabulation will include n, mean, standard deviation, CV%, median, minimum, and maximum. Pharmacokinetic parameters will be estimated using population PK analysis methods, which will be described in a separate data analysis plan. Results of the PK analysis will be reported separately.

9.2.2 Interim Analysis

No interim analysis is planned for the study.

9.2.3 Independent Data Review Committee (DRC)

To ensure standardization of interpretation regarding the validity of study patients, the medical management, and response to treatment in this open-label study, a panel of recognized experts in the field of fungal infectious diseases will constitute a DRC. The DRC serves to provide independent oversight to confirm eligibility for efficacy analysis, to confirm the diagnosis of candidemia and/or invasive candidiasis at study entry, and to adjudicate efficacy outcome. The DRC assessments for each patient will be recorded in the database and used in the primary efficacy analysis of the study. The DRC members will not be Principal Investigators in the study. Guidelines for the DRC are described in the DRC Charter.

9.2.4 Data and Safety Monitoring Board (DSMB)

A DSMB comprised of members with pertinent expertise will review the accumulating data from the study periodically as set forth in the DSMB Charter, or more frequently at the request of the DSMB. The DSMB will advise the Sponsor on the continuing safety of the study patients and those yet to be recruited to the study, as well as the continuing validity and scientific merit of the study. The DSMB may recommend to the Sponsor that dosing in the study be suspended if, in the opinion of the DSMB, further dosing in the study would pose an inappropriate safety risk. Guidelines for what constitutes inappropriate safety risks are described in the DSMB Charter.

9.2.5 Sample Size Determination

A sample size of approximately 15 patients will be recruited in this open-label study. No formal statistical assessment for sample size determination has been performed. This sample size is considered adequate to provide the necessary data to evaluate the efficacy and safety of APX001.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the most recent versions of the following thesauri will be used:

- Medical Dictionary for Regulatory Activities for medical history and adverse events
- World Health Organization Drug Dictionary for prior and concomitant medications

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) require that approval be obtained from an IRB/IEC prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB/IEC.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The patient (or the patient's LAR) will sign and date the ICF, and the original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Patient Card

On qualification for the study, the patient will receive a patient card. The patient card will state that the patient is participating in a clinical research study, type of treatment administered, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as

specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (i.e., initiation of study centers) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

12.2 Address List

12.2.1 Sponsor

Amplyx Pharmaceuticals, Inc.

[redacted]

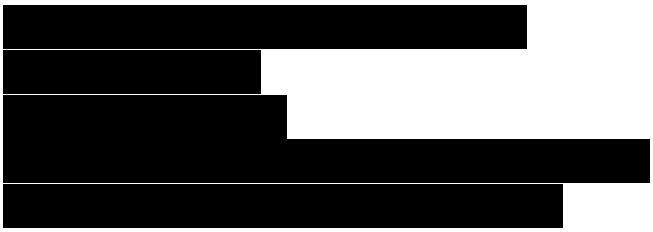
12.2.2 Contract Research Organization

[redacted]

12.2.3 Drug Safety

[redacted]

12.2.4 Biological Specimens



12.2.5 Mycology Reference Laboratory

12.2.6 Pharmacokinetic Laboratory

13 REFERENCES

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APPENDIX A: SCHEDULE OF PROCEDURES

Procedure	Eligibility	Screening (≤120 or ≤168 Hours of Baseline)[a]	Treatment Period[b]			Follow-up		Early Termination
			Baseline (Day 1 Pre-Dose)	Study Drug Treatment (≤42 Days)	End of Study Drug Treatment (EOST)[c]	Follow-up 2 Weeks After EOST +2 Days	Follow-up 4 Weeks After EOST +4 Days	
Informed consent		X[d]						
Inclusion/exclusion criteria		X	X					
Medical history		X						
Demographics		X						
APACHE II score			X					
Vital signs/temperature[e]		X	X	X	X	X	X	X
Intravascular catheter/device management log (including any drains, if applicable)[f]		X[g]	X[g]	X	X	X[h]	X[h]	X
Dilated fundoscopic examination			X*		X[i]		X[i]	X[i]
Clinical safety laboratory tests[j]		X	X	X	X	X	X	X
12-lead electrocardiogram			X		X		X	X
Urine pregnancy test (for females of childbearing potential only)		X	X	X[k]	X	X	X	X
Physical examination[l]			X	X	X	X	X	X
Blood sample for *Candida auris* spp. culture [m,o]	X[p]	X[m,p]	X[m,n,o]	X[n,o]	X[n,o]	X[n,o]	X[n,o]	X[n,o]
Blood sample for rapid diagnostic test[p]	X							

APPENDIX A: SCHEDULE OF PROCEDURES (CONT'D)

Procedure	Eligibility	Screening (≤120 or ≤168 Hours of Baseline)[a]	Treatment Period[b]			Follow-up		Early Termination
			Baseline (Day 1 Pre-Dose)	Study Drug Treatment (≤42 Days)	End of Study Drug Treatment (EOST)[c]	Follow-up 2 Weeks After EOST +2 Days	Follow-up 4 Weeks After EOST +4 Days	
Other cultures and histopathology[h,r]	X[u]	X[u]	X	X	X	X	X	X
Imaging tests[h,r]	X[u]	X[u]	X	X	X	X	X	X
Pharmacokinetic sample[q]			X	X	X	X		X
Serum sample[s]			X		X			X
Evaluation of treatment outcome					X	X	X	X
Study drug administration[t]				X				
Prior/concomitant medications		X	X	X	X	X	X	X
Adverse event evaluation		X	X	X	X	X	X	X

a. To be completed within 120 hours (for candidemia) or 168 hours (for invasive candidiasis without candidemia) from blood or tissue/fluid/aspirate sampling time for culture positive for *Candida* spp.
b. For outpatients during Study Drug Treatment, twice weekly visits are required with a maximum window of ±2 days. Patients will be asked to record daily dosing on a diary and to bring the diary and study drug bottles with them to every clinic visit.
c. End of Study Drug Treatment (EOST) occurs after completion of APX001 dosing.
d. To be obtained prior to the initiation of any protocol-specific procedure outside of SOC.
e. Vital signs will include temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight. Vital signs will be collected at Screening, Baseline (pre-dose), daily on Study Days 1 to 4, and twice weekly thereafter for outpatients (daily while inpatient) during Study Drug Treatment, EOST, and 2 and 4 weeks after EOST, or Early Termination. Height will be collected (from the patient's medical record) at Baseline.
f. Intravascular catheters logged until EOST while inpatient, and as clinically indicated thereafter or for outpatients.
g. If possible, all indwelling intravascular catheters should be removed and the catheter tips cultured prior to starting APX001 dosing. The entrance site should also be cultured if it appears infected. Any removed catheter tip should be sent for culture.
h. As clinically indicated.
i. (* Baseline dilated fundoscopy may be performed up to Day 3 of study) Only required in those patients who had positive fundoscopic findings up to Day 3 or as clinically indicated.

Footnotes from appendix above (cont'd)

j. Screening laboratory assessments to determine eligibility will be performed at the local laboratory and may have been collected as SOC within the previous 24 hours. Laboratory assessments collected after Screening will be sent to the central laboratory for analysis. Clinical safety laboratory assessments (serum chemistry [including testing for C-reactive protein], hematology, coagulation, and urinalysis) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, at EOST, and 2 and 4 weeks after EOST, or Early Termination. If clinically indicated and at the discretion of the Investigator, or if a suspected adverse event is identified, clinical laboratory assessments may be conducted at any time during the study and compared to Baseline.
k. Urine pregnancy test (for females of childbearing potential only) every 30 days if required by local regulations.
l. A complete physical examination will be conducted at Baseline (pre-dose). Complete physical examination will include an assessment of general appearance, skin, eyes, heart, chest, abdomen, the body site that corresponds to the entry site of candidemia (e.g. central venous catheter entry site) and/or site of invasive candidiasis, if applicable, and a neurological examination. Components of the neurological examination include cranial nerve, sensory and motor examination, reflex and gait testing, and coordination assessment. A neurological examination will be performed twice weekly during study drug treatment. A focused, symptom-based physical examination will be performed once weekly during study drug treatment, EOST, and 2 and 4 weeks after EOST, or Early Termination.
m. Blood cultures (daily) during 120-hour (5-day) screening period: after consent obtained the first blood collection to comprise two sets taken at one time, within 120 hours before the initiation of APX001 study treatment; 1 set thereafter.
n. All *Candida* spp. isolates must be submitted to the mycology reference laboratory for confirmation of identification and susceptibility testing.
o. During Study Drug Treatment, daily blood cultures on Study Days 1 through 4 (minimum), continuing daily until 2 negative blood culture results on 2 consecutive tests reported.
p. Optional rapid diagnostic test, if available, for *Candida* diagnosis; test (e.g. T2MR or PCR); subsequent confirmatory blood cultures must also be performed.
q. Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, EOST, 2 weeks after EOST, or Early Termination. Plasma samples for PK will be collected at the same time as samples are collected for the study's clinical laboratory assessments. Optional: If body fluids are sampled as part of routine patient management (e.g. bronchoalveolar lavage, lumbar puncture, paracentesis, vitreous fluid collection, abscess drainage), within approximately 2 hours of blood sampling for PK, these samples may be stored for future analysis of APX001 and APX001A levels.
r. Other cultures, histopathology, and imaging tests to assess the site(s) and extent of invasive candidiasis infection, if applicable. If performed, these will be analyzed at the local study site.
s. Serum samples for (1,3)-β-D-glucan levels will be collected at Baseline (pre-dose) and EOST, or Early Termination (if applicable).
t. Study drug will be administered as an IV loading dose over 3 hours BID on Study Day 1 (or over the first 24 hours if started in the evening); on Study Days 2 and 3 study drug will be administered over 3 hours by IV QD; on Study Day 4 and onward, PO administration of the study drug may be considered if the patient meets the IV to PO switch criteria. Study drug will be administered for up to 42 days (inclusive of the loading dose [Study Day 1])
u. (i) Tissue cultures or aspirate/fluid aseptically sampled from normally sterile sites confirmed for *C. auris*, (ii) imaging diagnostic for invasive candidiasis, may be obtained up to 168 hours prior to qualification for the study.

APACHE = Acute Physiology and Chronic Health Evaluation; BID = twice daily; eCRF = electronic Case Report Form; EOST = End of Study Drug Treatment; IV = intravenous(ly); PK = pharmacokinetic; PO = oral(ly); QD = once daily; SOC = standard of care; spp. = species; T2MR = T2 magnetic resonance.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Bilirubin (total, direct, and indirect)	Blood urea nitrogen
C-Reactive Protein	Chloride
Calcium	Creatinine
Creatine kinase	Gamma-glutamyl transferase
Estimated glomerular filtration rate	Inorganic phosphorus
Glucose	Lipase
Lactate dehydrogenase	Sodium
Potassium	Uric acid
Total protein	Uric acid

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

Prothrombin time	International normalized ratio

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Microscopy is performed only as needed based on positive dipstick test results.

Other Tests

Urine pregnancy test (females of childbearing potential only)

APPENDIX C: APACHE II SCORE FORM

		High Abnormal Range					Low Abnormal Range			
	Physiologic Variable	+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature rectal (°C)	≥41	39-40.9		38.5-38.9	36.0-38.4	34-35.9	32-33.9	30-31.9	≤29.9
2	Mean arterial pressure = (2 x diastolic + systolic)/3	≥160	130-159	110-129		70-109		50-69		≤49
3	Heart rate (ventricular response)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
4	Respiratory rate (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
5	Oxygenation A-aDO_2 or PaO_2 (mmHg) a)FiO_2≥0.5 record A-aDO_2	≥500	350-499	200-349		<200				
	b)FiO_2<0.5:record only PaO_2					>70	61-70		55-60	<55
6	Arterial pH If no ABGs record serum HCO_3 below	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
7	Serum sodium	≥180	160-179	155-159	150-154	130-139		120-129	111-119	≤110
8	Serum potassium	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
9	Serum creatinine (mg/dL) Double point for acute renal failure	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
10	Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
11	White blood count	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
12	Glasgow Coma Scale (see next page) (Score = 15 minus actual GCS)	15 minus the GCS =								
A	Total Acute Physiology Score (APS)	Sum of the 12 individual variable points =								
*	Serum HCO_3 (venous-mmol/L) Not preferred, use if no ABGs	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

APPENDIX C: APACHE II SCORE FORM (CONT'D)

<table>
<tr>
<th colspan="2">Glasgow Coma Scale
(Circle appropriate response)</th>
<th><u>B</u> Age Points</th>
<th><u>C</u> Chronic Health Points</th>
<th>Apache II Score (sum of A+B+C)</th>
</tr>
<tr>
<td>Eyes open
4 - spontaneously
3 - to verbal
2 - to painful stimuli
1 - no response

Motor response
6 - to verbal command
5 - localizes to pain
4 - withdraws to pain
3 - decorticate
2 - decerebrate
1 - no response</td>
<td>Verbal - <u>nonintubated</u>
5 - oriented and conversant
4 - disoriented and talks
3 - inappropriate words
2 - incomprehensible sounds
1 - no response

Verbal - <u>intubated</u>
5 - seems able to talk
3 - questionable ability to talk
1 - generally unresponsive</td>
<td>Age Points
≤44 0
45-54 2
55-64 3
65-74 5
≥75 6

Age points =</td>
<td>If any of the 5 CHE categories below is answered with yes, give +5 points for non-operative or emergency postoperative patients or +2 points for elective postoperative patients.

Liver - Cirrhosis with PHT or encephalopathy
Cardiovascular - Class IV angina or at rest or with minimal self-care activities
Pulmonary - Chronic hypoxemia or hypercapnia or polycythaemia of PHT >40 mmHg
Kidney - Chronic peritoneal or haemodialysis
Immune - Immune compromised host
Chronic Health Points =</td>
<td>A APS points (from prior page)
+ B Age points
+ C Chronic Health points
_____
= Total APACHE II</td>
</tr>
</table>

$A\text{-}aDO_2$ = alveolar-arterial oxygen difference; ABG = arterial blood gases; APACHE = Acute Physiology and Chronic Health Evaluation; APS = acute physiology score; CHE = chronic health evaluation; FiO_2 = fraction of inspired oxygen; GCS = Glasgow coma scale; HCO_3 = bicarbonate; IV = intravenous; PaO_2 = arterial partial pressure of oxygen; PHT = pulmonary hypertension.

Source: Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10);818–29

APPENDIX D: DRUG-INDUCED LIVER INJURY CRITERIA

For patients with normal liver transaminases and bilirubin at baseline:

If patients with normal baseline liver indices develop new elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or alkaline phosphatase (ALP) >3x upper limit of normal (ULN) or total bilirubin (TBL) >2xULN values during the study, repeat testing should be performed within 48 to 72 hours. Investigators should also ask the patient if he/she has symptoms.

If there are persistent elevations (ALT or AST >3x ULN or TBL >2x ULN) upon repeat testing, then close observation (as described below) should be implemented and discontinuation of drug should be considered.

Drug should be discontinued, and the patient followed until resolution of symptoms or signs in the following situations:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks.
- ALT or AST >3x ULN and (TBL >2x ULN or INR >1.5)
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

For patients with elevations in baseline transaminases or bilirubin:

If patients with abnormal baseline liver indices develop elevations of AST or ALT >2 x baseline or TBL >2 x baseline values during the study, repeat testing should be performed within 48 to 72 hours. Investigators should also ask to the patient if he/she has symptoms.

If there are persistent elevations (ALT or AST >2x baseline or TBL >2x baseline values) upon repeat testing, then close observation (as described below) should be implemented and discontinuation of drug should be considered.

Drug should be discontinued, and the patient followed until resolution of symptoms or signs in the following situations:

- If baseline measurements were <2x ULN, discontinue if ALT or AST increases to >5x baseline measurements.
- If baseline average measurements >2x ULN, discontinue if ALT or AST increases to >3x baseline measurements.
- Discontinue if ALT or AST increase >2x baseline measurements AND the increase is accompanied by a concomitant increase in TBL to >2x baseline measurements or the INR concomitantly increases by >0.2.
- For any patients who present with a constellation of syndromes indicative of liver disease as per the Investigator's overall assessment (ie, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]).

Close observation for suspected drug-induced liver injury includes the following:

- Repeating liver enzyme (ALT, AST, and ALP) and TBL tests 2 or 3 times weekly. The frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (eg, INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.