CLINICAL STUDY PROTOCOL

An Open-Label Study to Evaluate the Efficacy and Safety of APX001 in Non-Neutropenic Patients with Candidemia, with or without Invasive Candidiasis, Inclusive of Patients with Suspected Resistance to Standard of Care Antifungal Treatment

Investigational Product: APX001
Protocol Number: APX001-201
EudraCT Number: 2017-003571-56

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Amendment Number: 2.0
Protocol Version Number: 3.0
Date: 03 June 2019

SYNOPSIS

TITLE: An Open-Label Study to Evaluate the Efficacy and Safety of APX001 in Non-Neutropenic Patients with Candidemia, with or without Invasive Candidiasis, Inclusive of Patients with Suspected Resistance to Standard of Care Antifungal Treatment

PROTOCOL NUMBER: APX001-201

INVESTIGATIONAL PRODUCT: APX001

PHASE: 2

INDICATION: Treatment of non-neutropenic patients with candidemia – inclusive of those patients with suspected or confirmed antifungal-resistant candidemia

OBJECTIVES:

The primary objective of this study is to evaluate the efficacy and safety of APX001 for the treatment of adult non-neutropenic patients ≥18 years of age with candidemia that may include patients with suspected or confirmed resistance to standard of care (SOC) antifungal treatment.

The secondary objectives of this study are to:

- Evaluate the time to first negative blood culture
- Evaluate the percentage of patients with Mycological Outcomes at End of Study Drug Treatment (EOST), End of Antifungal Treatment (EOT), and 2 and 4 weeks after EOT
- Evaluate the percentage of patients with Treatment Success at EOT, and 2 and 4 weeks after EOT
- Evaluate overall survival 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. Candidemia is a common cause of healthcare-associated blood stream infections with approximately 50% of isolates identified as non-*Candida albicans* for which the Infectious Diseases Society of America (IDSA) revised clinical practice guidance in 2016. Recently, the Centers for Disease Control and Prevention released a clinical alert for the ongoing transmission of *C. auris* in healthcare facilities with most isolates identified in blood. Antifungal susceptibility testing revealed resistance to one or more classes of antifungals, including echinocandins, which have been first line empiric therapy for candidemia pending definitive speciation.

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 with broad spectrum activity versus major fungal pathogens including *Candida* spp. and *Aspergillus* spp., including isolates with resistance to azoles, echinocandins, and polyenes. APX001A targets 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 demonstrated broad in vitro antifungal activity against *Candida* spp., including activity against azole-resistant and echinocandin-resistant strains. APX001A has demonstrated synergy with echinocandins (*Aspergillus*) and azoles (*Candida*). In invasive fungal disease animal models, including those for *Aspergillus* spp. and *Candida* spp. that are resistant to azoles, APX001A has demonstrated high survival rates and reduced colony counts of fungi in the lungs of infected mice. The PK-pharmacodynamic (PD) driver for efficacy of APX001A was associated with area under the concentration-time curve (AUC)/minimal inhibitory concentration (MIC).

In 2 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 166 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 non-SAEs 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 either of the 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 the in vitro studies 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 activity against azole- and echinocandin-resistant *Candida* spp. 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 ≥18 years of age with a new diagnosis of candidemia (positive blood test for *Candida* spp.). Patients with a positive blood culture taken as SOC with yeast suspected to be *Candida* spp. or from a positive rapid diagnostic method may sign the Informed Consent Form (ICF) and undergo Screening procedures, but must have confirmed *Candida* spp. from blood culture and meet the eligibility criteria to be dosed.

Inclusion Criteria

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

1. Male or female ≥18 years of age
2. New diagnosis of candidemia based on a blood sample drawn within 96 hours of dosing with:
   a. Positive blood culture for *Candida* spp., including those *Candida* spp. with suspected (in the opinion of the Investigator) or documented resistance to at least 1 SOC systemic antifungal agent

      OR

   b. Positive result from a Sponsor-approved rapid diagnostic blood test for *Candida* spp. infection (a rapid diagnostic test may be used to begin eligibility assessments; however, a subsequent confirmatory blood culture is required prior to dosing of APX001)
3. Able to have pre-existing intravascular catheters removed and replaced (if necessary)
4. 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 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)
5. 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)
6. 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

Exclusion Criteria

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

1. Neutropenia defined as absolute neutrophil count <500 cells/µL
2. Diagnosis of deep-seated *Candida*-related infections causing intraperitoneal Candidiasis, septic arthritis, osteomyelitis, endocarditis, myocarditis, meningitis, or central nervous system infection or site of infection that would require antifungal treatment to exceed maximal duration of study drug (14 days)
3. Hepatosplenic Candidiasis
4. Blood culture, or any other culture, positive for *C. krusei*
5. Received >2 days (>48 hours) equivalent of prior systemic antifungal treatment at approved doses to treat the current episode of candidemia (e.g., 2 consecutive doses of an echinocandin)

   Note: ≤5 days (≤120 hours) equivalent of prior antifungal treatment is permitted for patients with candidemia caused by *Candida* spp. with documented resistance to the specific prior antifungal administered
6. Life expectancy of <72 hours in the opinion of the Investigator
7. Severe hepatic impairment (Child-Pugh Score >9 points) at any time during 2 weeks prior to dosing
8. Patients receiving hemodialysis
9. Known human immunodeficiency virus, active hepatitis B virus, or hepatitis C virus (HCV) infections (defined as hepatitis B surface antigen or HCV ribonucleic acid positivity)
10. Alanine aminotransferase or aspartate aminotransferase ≥5 × upper limit of normal (ULN)
11. Total bilirubin >3 × ULN, unless isolated hyperbilirubinemia or due to documented Gilbert's disease
12. Female patient is pregnant or lactating
13. Inappropriate fungal infection source control (e.g., persistent indwelling catheters or intravascular devices)
14. Investigational drug administered within 30 days prior to dosing
15. Prior participation in this or any previous study of APX001
16. 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)
17. 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

Dosing Criteria

Patients must meet the following criteria to begin dosing:

1. Confirmed diagnosis of candidemia
2. Received ≤2 days (≤48 hours) equivalent of prior systemic antifungal treatment at approved doses to treat the current episode of candidemia

   OR

   ≤5 days (≤120 hours) equivalent of prior treatment for candidemia caused by *Candida* spp. with documented resistance to the specific prior antifungal administered

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 first-line treatment for candidemia, including suspected or confirmed antifungal-resistant candidemia in non-neutropenic patients ≥18 years of age. Suspicion of antifungal-resistant candidemia is sufficient and subsequent documented resistance is not required for enrollment. The Study Drug Treatment Period will be up to a maximum of 14 days (inclusive of the loading dose [Study Day 1]). After completion of 14 days study drug therapy, if further antifungal treatment is indicated to complete treatment of candidemia in accordance with standard practice guidelines, fluconazole (unless susceptibility results warrant alternative antifungal therapy) may commence for up to a further 7 days. There will be a Follow-up Period of 4 weeks (+4 days) after EOT. The total duration of participation in the study is up to approximately 7.5 weeks (inclusive of the Screening Period [≤96 hours prior to Baseline]).

Patients with a yeast identified in a blood culture or a positive rapid diagnostic method are eligible to be consented and screened for the study. Patients must have at least 1 positive blood test for *Candida* spp. (or yeast suspected to be *Candida*) for a diagnosis of candidemia to be considered for enrollment into the study. Patients with a positive blood culture showing yeast suspected to be *Candida* must have identification of *Candida* spp. from positive blood culture confirmed prior to dosing. Screening and Baseline procedures and the start of APX001 study drug will be initiated within 96 hours from the time that the SOC blood sample for the *Candida* spp. positive culture or rapid diagnostic test was drawn.

Patients with >2 days (>48 hours) equivalent of prior systemic antifungal treatment at approved doses to treat the current episode of candidemia within 96 hours before first dose will be excluded. However, patients with *Candida* infections proven to be resistant to the specific antifungal administered may have received ≤5 days (≤120 hours) equivalent of that prior treatment (results of susceptibility testing are required prior to enrollment).

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.

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 twice daily (BID). On Study Days 2 and 3 of study drug, 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 700 mg PO QD. Patients who have completed a minimum of 3 days of IV APX001, are clinically stable as determined by the Investigator, able to swallow tablets, and have no further growth of the infecting organism 48 hours following the most recent blood culture, may switch from IV to PO dosing on Study Day 4 and onward. Study drug will be administered for a maximum of 14 days. At the Investigator's discretion, patients requiring a longer duration of antifungal therapy will be switched to fluconazole (unless susceptibility results warrant alternative antifungal therapy), to adhere to the IDSA clinical practice guidelines for the treatment of Candidiasis.

Candida spp. bloodstream infection will be monitored by daily blood culture during Study Drug Treatment until 2 consecutive blood cultures are negative, and at EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination. Simultaneously drawn blood samples will be collected for *Candida* testing by T2 magnetic resonance (T2MR) assay at Baseline, during Study Drug Treatment, and EOST, or Early Termination. Other cultures, histopathology, and imaging tests to assess the site(s) and extent of candidemia infection at other sites will be conducted as clinically indicated, and the 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 (including neurological assessment), prior and concomitant medication reporting, and adverse event reporting. A 12-lead electrocardiogram (ECG) will be performed at Baseline (pre-dose), EOST, EOT, and 4 weeks after EOT, or Early Termination. A dilated fundoscopic examination will be performed at Screening for all patients and at EOST, EOT, and 4 weeks after EOT, or Early Termination for those patients who had positive fundoscopic findings at Screening, or as 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, EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination.

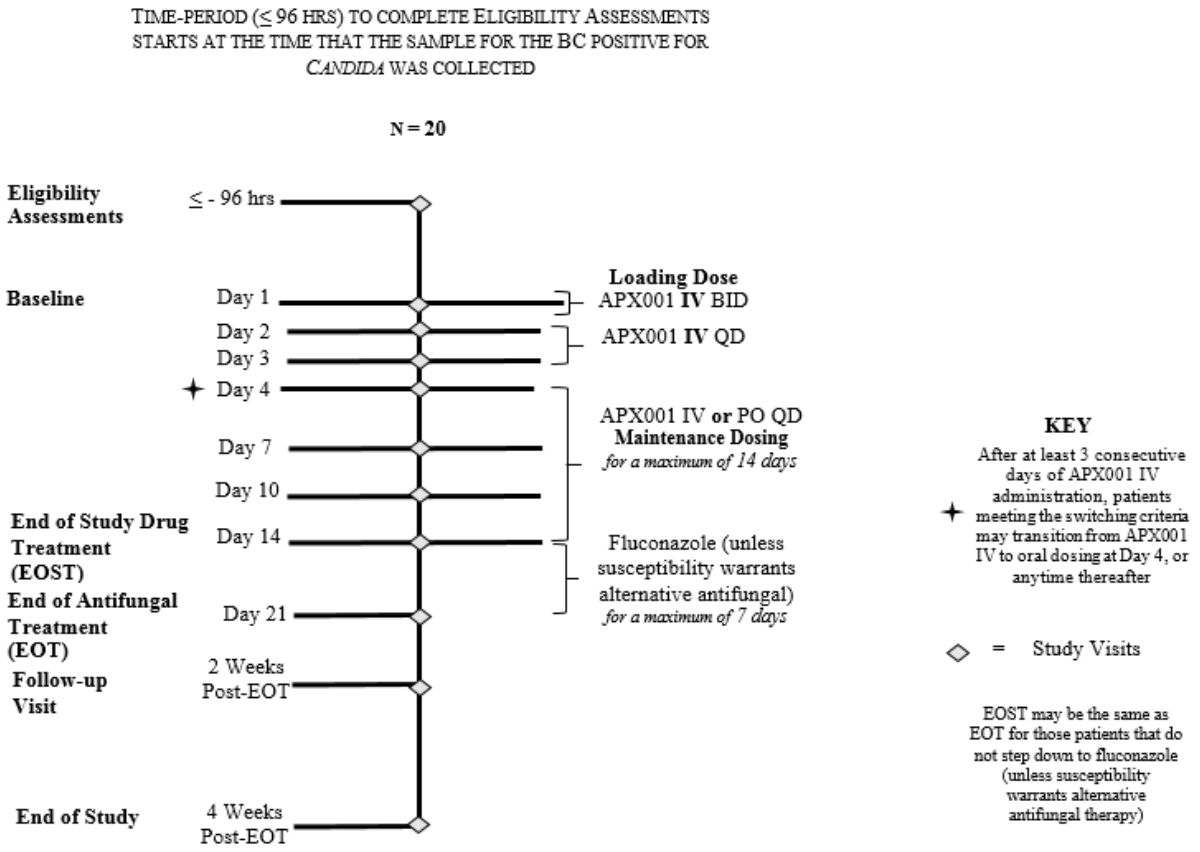
Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, EOST, EOT, 2 weeks after EOT, or Early Termination. Serum samples for (1,3)-β-D-glucan levels will be collected at Baseline (pre-dose) and EOST, or Early Termination (if applicable).

Optionally, if body fluids are sampled as part of routine patient management (e.g., bronchoalveolar lavage, lumbar puncture, paracentesis, vitreal 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, EOT, and 2 and 4 weeks after EOT, 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 below.



BC = blood culture; BID = twice daily; EOST = End of Study Drug Treatment; EOT = End of Antifungal Treatment; IV = intravenous(ly); PO = oral(ly); QD = once daily.

DOSAGE FORMS AND ROUTE OF 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.

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

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
- 700 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
- Is demonstrated to have no further growth of the infecting organism for 48 hours following the most recent blood culture

RATIONALE FOR DOSE AND SCHEDULE SELECTION:

Dose

In PK-PD studies, immunocompromised mice were infected with 1 of 3 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 (colony-forming units [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%. This is reassuring, as hospitalized patients with severe infections may exhibit a higher clearance of antifungal drugs and/or a patient may be infected with a *Candida* spp. with a particularly high MIC above the MIC_{90}.

In 2 Phase 1 studies in healthy volunteers, APX001 IV and PO formulations were safe and well tolerated. The majority of the 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 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. This IV dose regimen is identical to the IV dose regimen that will be used in this study. In the second Phase 1 clinical study, a dose of APX001 1000 mg administered PO QD on Days 1 through 14 was safe and well tolerated. This PO-dose regimen is higher than the 700 mg PO dose that will be used in this study.

Schedule

To ensure the safety and tolerability of APX001 dosing for 14 days, this study will use an APX001 dose and infusion duration already studied in Phase 1 for 14 days of therapy inclusive of IV and PO investigational drug therapy. The loading dose 1000 mg IV BID over a 3-hour infusion followed by 600 mg IV QD over a 3-hour infusion will optimize patient safety and tolerability on study. At Study Day 4, provided a patient meets the protocol-defined criteria for a PO switch, then the switch will occur to PO APX001 dose at 700 mg QD for no more than 14 days of combined IV and PO APX001 therapy.

Step-Down Therapy

The IDSA clinical practice guidelines for treatment of Candidiasis recommend that the total duration of therapy for candidemia is 14 days after documented clearance of *Candida* spp. from the bloodstream (i.e., first consecutive negative blood culture) and resolution of symptoms attributable to candidemia. Hence, the duration of antifungal treatment required to treat patients with candidemia in this study will be driven by the time to clearance of candidemia. In 3 randomized controlled trials in candidemia and invasive Candidiasis, the median time to bloodstream infection clearance after receiving appropriate antifungal therapy was 2 to 3 days. Therefore, patients enrolled in this study may need a few additional days of fluconazole therapy (unless susceptibility results warrant alternative antifungal therapy) for a total duration of antifungal treatment of approximately 16 to 17 days. Likewise, any patients who have deep-seated sites of infections diagnosed after enrollment, while they can continue to receive APX001 study drug treatment per protocol, will require additional days of fluconazole therapy.

If appropriate, additional antifungal drug therapy with fluconazole (unless susceptibility results warrant alternative antifungal therapy) can be administered beyond 14 days of APX001. The recommended dose of fluconazole is 800 mg QD on the first day followed by 400 mg QD, for a maximum of 7 days.

EFFICACY ENDPOINTS:

The primary efficacy parameter is 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 Mycological Outcomes at EOST, EOT, and 2 and 4 weeks after EOT
- Percentage of patients with Treatment Success at EOT, and 2 and 4 weeks after EOT as determined by the DRC
- Overall survival 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
- Correlation of blood culture and T2MR assay *Candida* spp. results from Baseline (pre-dose) through 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.
- Alive at EOST
- No concomitant use of any other systemic antifungal therapies through EOST

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

Mycological Outcome:

- Eradication is defined as a negative blood culture(s) for *Candida* spp. in the absence of concomitant antifungal therapy through EOST.

At End of Antifungal Treatment (EOT):

After completion of 14 days study drug therapy, if further antifungal treatment is indicated to complete treatment of candidemia in accordance with standard practice guidelines, fluconazole (unless susceptibility results warrant alternative antifungal therapy) may commence for up to a further 7 days. If applicable, an assessment of efficacy will also be made at the end of this antifungal treatment at EOT.

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

- Two consecutive blood cultures negative for *Candida* spp.
- Alive at EOT
- No additional systemic antifungal therapies (except for protocol-allowed step-down treatment [e.g., fluconazole]) through EOT

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

Mycological Outcome:

- Eradication is defined as a negative blood culture(s) for *Candida* spp. in the absence of additional antifungal therapy (except for protocol-allowed step-down treatment [e.g., fluconazole]) through EOT.

At Follow-up (2 Weeks and 4 Weeks After End of Antifungal Treatment):

- Recurrence (mycological) is defined as a mycologically confirmed infection based on blood culture with the same Baseline *Candida spp.* during the 4 weeks after EOT.

- Relapse (DRC Assessment) is defined as re-occurrence of *Candida* in blood culture during the Follow-up Period, or diagnostic parameters indicative of recurrence or late spread of the *Candida* infection.

SAFETY VARIABLES:

Safety parameters include the following:

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

  Infusion site reactions should be graded according to the Common Terminology Criteria for Adverse Events v4.03.

- Vital signs (temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight) collected at Screening, Baseline (pre-dose) daily on Study Days 2 through 4 and twice weekly thereafter during Study Drug Treatment, at EOST, EOT, and 2 and 4 weeks after EOT, 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, EOST, EOT, and 2 and 4 weeks after EOT 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, EOST, EOT, and 2 and 4 weeks after EOT or Early Termination.
- ECGs at Baseline (pre-dose), EOST, EOT, and 4 weeks after EOT, or Early Termination.

WITHDRAWAL CRITERIA:

Participation of a patient in this clinical study 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
- 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 a regulatory authority

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 candidemia 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 within 96 hours of the start of treatment with APX001

Per-Protocol Population

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

- Received at least 1 dose of study drug
- Have a confirmed diagnosis of candidemia within 96 hours of the start of treatment with APX001
- Did not exceed prior antifungal treatment (per eligibility)
- Meet the protocol's key inclusion and exclusion criteria
- Have no major protocol violations

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 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 at EOT, and 2 and 4 weeks after EOT will be summarized. Similarly, the percentage of patients with Mycological Outcomes at EOST, EOT, and 2 and 4 weeks after EOT 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 patient 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 20 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.

SITES: Approximately 20 sites in the United States and globally

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
CTA	Clinical trial authorization
CTCAE	Common Terminology Criteria for Adverse Events
CVC	Central venous catheter
CYP	Cytochrome P450
DDI	Drug-drug interaction
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
EOT	End of Antifungal Treatment
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GI	Gastrointestinal
GPI	Glycosylphosphatidylinositol
GWT1	GPI-anchored wall transfer protein 1
HCV	Hepatitis C virus
IB	Investigator's Brochure
ICF	Informed Consent Form
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

Abbreviation	Definition
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
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. Candidemia is a common cause of healthcare-associated blood stream infections with approximately 50% of isolates identified as non-*C. albicans* for which the Infectious Diseases Society of America (IDSA) revised clinical practice guidance in 2016.[1] Recently, the Centers for Disease Control and Prevention released a clinical alert for the ongoing transmission of *C. auris* in healthcare facilities with most isolates identified in blood. Antifungal susceptibility testing revealed resistance to one or more classes of antifungals, including echinocandins, which have been first line empiric therapy for candidemia pending definitive speciation.[1,2]

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 with broad spectrum activity versus major fungal pathogens including *Candida* spp. and *Aspergillus* spp., including isolates with resistance to azoles, echinocandins, and polyenes.[3,4,5] APX001A targets 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.[6,7] The closest mammalian ortholog of GWT1 is PIG-W, which has no demonstrable inhibition by APX001A.

APX001A has demonstrated broad in vitro antifungal activity against *Candida* spp., including activity against azole-resistant and echinocandin-resistant strains. APX001A has demonstrated synergy with echinocandins (*Aspergillus*)[8,9] and azoles (*Candida*). In invasive fungal disease (IFD) animal models, including those for *Aspergillus* spp. and *Candida* spp. that are resistant to azoles, APX001A has demonstrated high survival rates and reduced colony counts of fungi in the lungs of infected mice.[8,9] The pharmacokinetic (PK)-pharmacodynamic (PD) driver for efficacy of APX001A was associated with area under the concentration-time curve (AUC)/minimal inhibitory concentration (MIC).

In 2 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 166 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 non-SAEs were mild, transitory, and required no intervention. No dose-limiting toxicities (DLTs) were observed and no treatment-emergent adverse events (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 (MTD) was not determined/reached in either of the Phase 1 studies. Pharmacokinetic parameters for maximum serum concentration (C_{max}) and AUC in both single and multiple APX001 IV and PO doses were linear and dose proportional. In both the in vitro studies and in a cohort embedded within the PO dose Phase 1 study, APX001 demonstrated a favorable drug-drug interaction (DDI) 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 is >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 activity against azole- and echinocandin-resistant *Candida* spp. Because APX001 is 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 IFDs remains high, particularly with the growing number of immunocompromised patients, such as hematopoietic stem cell and solid organ transplant recipients, who are at particular risk for developing these infections and in whom treatment can be complex. Species of *Candida* and *Aspergillus* are well recognized as the 2 major causes of fungal diseases in these patients, although other emerging fungi, such as non-*C. albicans* (e.g., *C. glabrata* and *C. auris*), *Fusarium* spp., *Scedosporium* spp., and Mucorales fungi, are contributing to the need to find new and better strategies for managing these infections. Existing antifungal agents can be difficult to use, are often poorly tolerated, or have become increasingly ineffective due to the rise of drug resistant fungal strains.

1.2 Risk/Benefit

The safety, tolerability, and PK of single and multiple doses of APX001 administered by IV infusion and PO in healthy volunteers were studied in 2 Phase 1 studies, APX001-101 and APX001-102.

Study APX001-101 was a first-in-human (FIH) Phase 1, randomized, placebo-controlled study to investigate the safety, tolerability, and PK of single and multiple doses of APX001 administered by IV infusion in healthy subjects. A final Clinical Study Report has been issued for this study. No severe or SAEs have been reported and most of the adverse events were mild, transitory, and resolved with no intervention. There were no clinically relevant changes from baseline in laboratory safety tests. The AUC from time 0 to infinity (AUC_{inf}) and C_{max} were linear and dose proportional.

All doses of APX001 were safe and well tolerated, and the majority of TEAEs were mild, transitory, and resolved without intervention. Single IV doses of APX001 up to 350 mg over a 3-hour infusion and single IV doses of 1000 mg over 0.5-, 1-, 2-, and 3-hour infusions were well tolerated. Shorter infusion periods (i.e., 1000 mg over 0.5 to 2 hours) appeared to have similar toleration compared to 3-hour infusion periods. Multiple IV doses of APX001 up to 600 mg once daily (QD), for 14 consecutive days, were well tolerated by the majority of subjects; however, the total number of TEAEs related to gastrointestinal (GI) and nervous system disorders increased when the dose was increased from 300 mg to 600 mg. A loading dose of 1000 mg administered twice daily (BID) on Day 1 followed by a maintenance dose of 600 mg QD for 6 consecutive days was well tolerated.

Study APX001-102 was a Phase 1, randomized, placebo-controlled study to investigate the safety, tolerability, and PK of single and multiple PO doses of APX001 and to investigate the absolute bioavailability of APX001, the effect of food on APX001, and the DDI potential of APX001.

A final Clinical Study Report has been issued for this study. No severe or SAEs were reported and most of the adverse events were mild, transitory, and resolved with no intervention. There were no clinically relevant changes from baseline in laboratory safety tests. The AUC_{inf} and C_{max} were linear and dose proportional. There was no impact of food on the PK of APX001A exposures (single dose of 400 mg). In cohort 3 (1000 mg, QD for 14 days), there was an increase in the number of subjects reporting adverse events; however, the intensity of reported events did not increase with multiple doses.

All doses of APX001 were safe and well tolerated, and the majority of TEAEs were mild, transitory, and resolved without intervention. The single IV doses of 200 mg APX001 and single PO doses in the dose range of 100 mg to 500 mg were well tolerated. Multiple PO doses of 500 mg and 1000 mg of APX001 administered QD for 14 consecutive days were well tolerated by the majority of subjects; however, the number of moderate TEAEs, primarily those related to GI disorders, increased when the PO dose of APX001 increased from 500 mg to 1000 mg. Dosing under fed conditions improved tolerability by decreasing TEAEs related to GI (nausea, vomiting) and nervous system disorders (headache, fatigue).

There were no deaths or SAEs reported during the study nor were there any withdrawals due to adverse events. There were no clinically significant findings with respect to laboratory safety tests, vital signs, electrocardiogram (ECG), physical examination, or weight. No DLTs were observed. No TEAEs or laboratory safety tests met any of the criteria to prevent dose escalation. The MTD was not reached in this study.

Patients 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 700 mg PO 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. Since the efficacy of APX001 has not yet been proven in patients, no additional protection of APX001 in this concentration can be assured. Patients 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 non-neutropenic patients ≥18 years of age with candidemia that may include patients with suspected or confirmed resistance to SOC antifungal treatment.

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 Mycological Outcomes at the End of Study Drug Treatment (EOST), End of Antifungal Treatment (EOT), and 2 and 4 weeks after EOT
- Evaluate the percentage of patients with Treatment Success at EOT, and 2 and 4 weeks after EOT
- Evaluate overall survival at Study Day 30
- Evaluate safety parameters, including number of patients with TEAEs
- Evaluate PK parameters of APX001

3 STUDY DESCRIPTION

3.1 Summary of Study Design

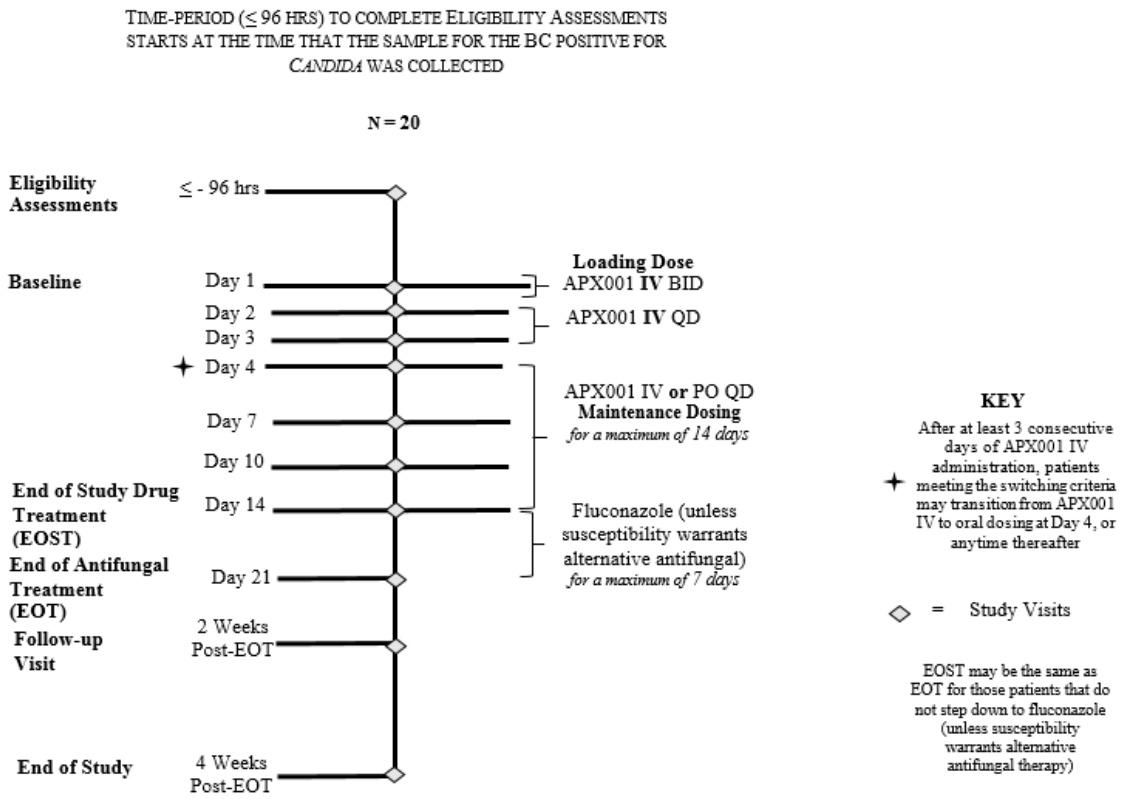
This is a multicenter, open-label, non-comparative, single-arm study to evaluate the efficacy and safety of APX001 for the first-line treatment for candidemia including suspected or confirmed antifungal-resistant candidemia in non-neutropenic patients ≥18 years of age. Suspicion of antifungal-resistant candidemia is sufficient and subsequent documented resistance is not required for enrollment. The Study Drug Treatment Period will be up to a maximum of 14 days (inclusive of the loading dose [Study Day 1]). After completion of 14 days study drug therapy, if further antifungal treatment is indicated to complete treatment of candidemia in accordance with standard practice guidelines, fluconazole (unless susceptibility results warrant alternative antifungal therapy) may commence for up to a further 7 days. There will be a Follow-up Period of 4 weeks (+4 days) after EOT. The total duration of participation in the study is up to approximately 7.5 weeks (inclusive of the Screening Period [≤96 hours prior to Baseline]).

This study will be conducted at approximately 20 sites in the United States and globally.

A complete schedule of procedures for the study is found in Appendix A.

Figure 1 presents a schematic for the study.

Figure 1. Study Schematic



BC = blood culture; BID = twice daily; EOST = End of Study Drug Treatment; EOT = End of Antifungal Treatment; IV = intravenous(ly); PO = oral(ly); QD = once daily.

Patients with a yeast identified in a blood culture or a positive rapid diagnostic method are eligible to be consented and screened for the study. Patients must have at least 1 positive blood test for *Candida* spp. (or yeast suspected to be *Candida*) for a diagnosis of candidemia to be considered for enrollment into the study. Patients with a positive blood culture showing yeast suspected to be *Candida* must have identification of *Candida* spp. from positive blood culture confirmed prior to dosing. Screening and Baseline procedures and the start of APX001 study drug will be initiated within 96 hours from the time that the SOC blood sample for the *Candida* spp. positive culture or rapid diagnostic test was drawn.

Patients with >2 days (>48 hours) equivalent of prior systemic antifungal treatment at approved doses to treat the current episode of candidemia within 96 hours before first dose will be excluded. However, patients with *Candida* infections proven to be resistant to the specific antifungal administered may have received ≤5 days (≤120 hours) equivalent of that prior treatment (results of susceptibility testing are required prior to enrollment).

All patients (or the patient's legal authorized representative [LAR]) will sign an Informed Consent Form (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 (APACHE) II score will be collected before dosing.

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. On Study Days 2 and 3 of study drug, a 600 mg APX001 maintenance dose will be administered over 3 hours by IV infusion 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 700 mg PO QD. Patients who have completed a minimum of 3 days of IV APX001, are clinically stable as determined by the Investigator, able to swallow tablets, and have no further growth of the infecting organism 48 hours following the most recent blood culture, may switch from IV to PO dosing on Study Day 4 and onward. Study drug will be administered for a maximum of 14 days. At the Investigator's discretion, patients requiring a longer duration of antifungal therapy will be switched to fluconazole (unless susceptibility results warrant alternative antifungal therapy), to adhere to the IDSA clinical practice guidelines for the treatment of Candidiasis.[1]

Candida spp. bloodstream infection will be monitored by daily blood culture during Study Drug Treatment until 2 consecutive blood cultures are negative, and at EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination. Simultaneously drawn blood samples will be collected for *Candida* testing by T2 magnetic resonance (T2MR) assay at Baseline, during Study Drug Treatment, and EOST, or Early Termination. Other cultures, histopathology, and imaging tests to assess the site(s) and extent of candidemia infection at other sites will be conducted as clinically indicated, and the results should be recorded in the electronic Case Report Form (eCRF). 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 (including neurological assessment), prior and concomitant medication reporting, and adverse event reporting. A 12-lead ECG will be performed at Baseline (pre-dose), EOST, EOT, and 4 weeks after EOT, or Early Termination. A dilated fundoscopic examination will be performed at Screening for all patients and EOST, EOT, and 4 weeks after

EOT, or Early Termination for those patients who had positive fundoscopic findings at Screening, or as 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, EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination.

Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, EOST, EOT, 2 weeks after EOT, or Early Termination. 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, vitreal 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, EOT, and 2 and 4 weeks after EOT, or Early Termination.

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

3.2 Study Indication(s)

APX001 is indicated for the treatment of non-neutropenic patients with candidemia, inclusive of those patients with suspected or confirmed antifungal-resistant candidemia.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

This study will enroll male and female patients ≥18 years of age with a new diagnosis of candidemia (positive blood test for *Candida* spp.). Patients with a positive blood culture taken as SOC with yeast suspected to be *Candida* spp. or from a positive rapid diagnostic method may sign the ICF and undergo Screening procedures, but must have confirmed *Candida* spp. from blood culture and meet the eligibility criteria to be dosed.

4.1 Inclusion Criteria

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

1. Male or female ≥18 years of age
2. New diagnosis of candidemia based on a blood sample drawn within 96 hours of dosing with:
   a. Positive blood culture for *Candida* spp., including those *Candida* spp. with suspected (in the opinion of the Investigator) or documented resistance to at least 1 SOC systemic antifungal agent

      OR

   b. Positive result from a Sponsor-approved rapid diagnostic blood test for *Candida* spp. infection (a rapid diagnostic test may be used to begin eligibility assessments; however, a subsequent confirmatory blood culture is required prior to dosing of APX001)
3. Able to have pre-existing intravascular catheters removed and replaced (if necessary)
4. 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 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)
5. 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)
6. 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 LAR will be obtained for patients who are unable to give consent

4.2 Exclusion Criteria

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

1. Neutropenia defined as absolute neutrophil count <500 cells/µL
2. Diagnosis of deep-seated *Candida*-related infections causing intraperitoneal Candidiasis, septic arthritis, osteomyelitis, endocarditis, myocarditis, meningitis, or central nervous system infection or site of infection that would require antifungal treatment to exceed maximal duration of study drug (14 days)
3. Hepatosplenic Candidiasis
4. Blood culture, or any other culture, positive for *C. krusei*
5. Received >2 days (>48 hours) equivalent of prior systemic antifungal treatment at approved doses to treat the current episode of candidemia (e.g., 2 consecutive doses of an echinocandin)

   Note: ≤5 days (≤120 hours) equivalent of prior antifungal treatment is permitted for patients with candidemia caused by *Candida* spp. with documented resistance to the specific prior antifungal administered
6. Life expectancy of <72 hours in the opinion of the Investigator
7. Severe hepatic impairment (Child-Pugh Score >9 points) at any time during 2 weeks prior to dosing
8. Patients receiving hemodialysis
9. Known human immunodeficiency virus, active hepatitis B virus, or hepatitis C virus (HCV) infections (defined as hepatitis B surface antigen or HCV ribonucleic acid positivity)
10. Alanine aminotransferase or aspartate aminotransferase ≥5 × upper limit of normal (ULN)
11. Total bilirubin >3 × ULN, unless isolated hyperbilirubinemia or due to documented Gilbert's disease
12. Female patient is pregnant or lactating
13. Inappropriate fungal infection source control (e.g., persistent indwelling catheters or intravascular devices)
14. Investigational drug administered within 30 days prior to dosing
15. Prior participation in this or any previous study of APX001
16. 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)
17. 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

4.3 Dosing Criteria

Patients must meet the following criteria to begin dosing:

1. Confirmed diagnosis of candidemia
2. Received ≤2 days (≤48 hours) equivalent of prior systemic antifungal treatment at approved doses to treat the current episode of candidemia

   OR

   ≤5 days (≤120 hours) equivalent of prior treatment for candidemia caused by *Candida* spp. with documented resistance to the specific prior antifungal administered

4.4 Withdrawal Criteria

Participation of a patient in this clinical study 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
- 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 a regulatory authority

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.

5 STUDY TREATMENTS

5.1 Treatment Groups

All patients will be administered a 1000 mg APX001 loading dose BID 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 over 3 hours QD or may be switched to 700 mg PO QD when/if the criteria for PO dosing are met (Section 5.5.3).

5.2 Rationale for Dosing

5.2.1 Dose

In PK-PD studies, immunocompromised mice were infected with 1 of 3 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 (colony-forming units [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.

In 2 Phase 1 studies in healthy volunteers, APX001 IV and PO formulations were safe and well tolerated. The majority of the TEAEs were mild, transitory, and resolved without intervention. No DLTs were observed. Specifically, in the FIH Phase 1 clinical study, a loading dose 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. This IV dose regimen is identical to the IV dose regimen that will be used in this study. In the second Phase 1 clinical study, a dose of APX001 1000 mg administered PO QD on Days 1 through 14 was safe and well tolerated. This PO-dose regimen is higher than the 700 mg PO dose that will be used in this study.

5.2.2 Schedule

To ensure the safety and tolerability of APX001 dosing for 14 days, this study will use an APX001 dose and infusion duration already studied in Phase 1 for 14 days of therapy inclusive of IV and PO investigational drug therapy. The loading dose 1000 mg IV BID over a 3-hour infusion followed by 600 mg IV QD over a 3-hour infusion will optimize patient safety and tolerability on study. At Study Day 4, provided a patient meets the protocol-defined criteria for a PO switch, then the switch will occur to PO APX001 dose at 700 mg QD for no more than 14 days of combined IV and PO APX001 therapy.

5.2.3 Step-Down Therapy

The IDSA clinical practice guidelines for treatment of Candidiasis recommend that the total duration of therapy for candidemia is 14 days after documented clearance of *Candida* spp. from the bloodstream (i.e., first consecutive negative blood culture) and resolution of symptoms attributable to candidemia. Hence, the duration of antifungal treatment required to treat patients

with candidemia in this study will be driven by the time to clearance of candidemia. In 3 randomized controlled trials in candidemia and invasive Candidiasis, the median time to bloodstream infection clearance after receiving appropriate antifungal therapy was 2 to 3 days. Therefore, patients enrolled in this study may need a few additional days of fluconazole therapy (unless susceptibility results warrant alternative antifungal therapy) for a total duration of antifungal treatment of approximately 16 to 17 days. Likewise, any patients who have deep-seated sites of infections diagnosed after enrollment, while they can continue to receive APX001 study drug treatment per protocol, will require additional days of fluconazole therapy.

If appropriate, additional antifungal drug therapy with fluconazole (unless susceptibility results warrant alternative antifungal therapy) can be administered beyond 14 days of APX001. The recommended dose of fluconazole is 800 mg QD on the first day followed by 400 mg QD, for a maximum of 7 days.

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. Preparation and dilution instructions will be provided in the Pharmacy Manual.

APX001 tablets are formulated at strengths of 100 mg and 200 mg white-coated tablets. The tablets are stored in high-density polyethylene bottles with a child-resistant container.

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.

On Study Days 2 and 3 of study drug, a 600 mg APX001 maintenance dose will be administered over 3 hours by IV infusion 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 700 mg PO QD. Patients who have completed a minimum of 3 days of IV APX001, are clinically stable as determined by the Investigator, able to swallow tablets, and have no further growth of the infecting organism 48 hours following the most recent blood culture, may switch from IV to PO dosing on Study Day 4 and onward. Study drug will be administered for a maximum of 14 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. No splitting or crushing of tablets is allowed.

If antifungal treatment is indicated for longer than 14 days, fluconazole may commence at the Investigator's discretion (unless susceptibility results warrant alternative antifungal therapy) for up to a further 7 days of therapy, to adhere to IDSA clinical practice guidelines for the treatment of Candidiasis.[1]

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 are located 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 patient-by-patient 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 and thus any single CYP enzyme that is inhibited or induced is unlikely to result in clinically significant changes in the levels of APX001A.

However, patients who are receiving or will receive strong inducers of multiple CYP enzymes (e.g., rifampin, carbamazepine, phenytoin, rifabutin, efavirenz, nevirapine, phenobarbital, modafinil, nafcillin, St. John's Wort, and enzalutamide) are excluded from participating in the study.

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.

Considering the magnitude of CYP inhibition/induction effects of APX001A, a review of drugs commonly used as part of the SOC for patients with candidemia indicates that clinically significant DDIs are unlikely to occur. Nonetheless, 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) considered, especially for CYP substrates that have a narrow therapeutic window.

5.6.2 Prohibited Medications and/or Procedures

Eligible patients are prohibited from receiving >2 days (>48 hours) equivalent of antifungal treatment in the 96 hours prior to starting study treatment. The exception to this rule applies only to patients whose candidemia is caused by *Candida* spp. with laboratory-confirmed resistance to the specific antifungal administered, for whom ≤5 days (≤120 hours) equivalent of prior antifungal treatment is permitted. Once on study, patients may not receive concomitant systemic antifungal therapy for the treatment of candidemia while they are receiving APX001.

Patients cannot have received any investigational drug within 30 days prior to dosing.

5.6.3 Step-down Antifungal Therapy

The IDSA clinical practice guidelines for treatment of Candidiasis recommend that the total duration of therapy for candidemia is 14 days after documented clearance of *Candida* spp. from the bloodstream (i.e., first consecutive negative blood culture) and resolution of symptoms attributable to candidemia. Hence, the duration of antifungal treatment required to treat patients with candidemia in this study will be driven by the time to clearance of candidemia. In 3 randomized controlled trials in candidemia and invasive Candidiasis, the median time to bloodstream infection clearance after receiving appropriate antifungal therapy was 2 to 3 days. Therefore, patients enrolled in this study may need a few additional days of fluconazole therapy for a total duration of antifungal treatment of approximately 16 to 17 days. Likewise, any patients who have deep-seated sites of infections diagnosed after enrollment, while they can continue to receive APX001 study drug treatment per protocol, will require additional days of fluconazole therapy.

If appropriate, additional antifungal drug therapy with fluconazole (unless susceptibility results warrant alternative antifungal therapy) can be administered beyond 14 days of APX001. The recommended dose of fluconazole is 800 mg QD on the first day followed by 400 mg QD, for a maximum of 7 days.

5.6.4 Documentation of Prior and Concomitant Medication Use

All prior medications received by the patient 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 patients (or the patient's LAR) prior to any study-specific procedures being performed. Patients with a positive blood culture taken as SOC with yeast suspected to be *Candida* spp. or a positive rapid diagnostic method may sign the ICF and undergo Screening procedures, but must have a confirmed *Candida* spp. blood culture to be dosed. Only those patients who have transient loss of capacity (e.g., septic shock, mechanical ventilation, sedation) can have a LAR sign consent. These patients, upon return of their capacity, will then be consented and allowed to make their own informed medical decisions. Patients with permanent loss of capacity will not be eligible for study participation.

6.2 Eligibility (≤96 Hours Prior to Baseline)

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

- Collect blood culture and confirm positive for *Candida* spp.
- Collect blood sample for rapid diagnostic test positive for candidemia (if a rapid diagnostic test is available and used routinely for diagnosis of candidemia; the test must be Sponsor-approved and subsequent confirmatory blood culture is also required)

Screening is triggered by the early identification of *Candida* spp. (or yeast) in blood drawn as SOC within a 96-hour window prior to first dose. Isolates of *Candida* spp. from the SOC culture must be submitted to the mycology reference laboratory for confirmation of identification and susceptibility testing.

6.3 Screening (≤96 Hours Prior to Baseline)

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 dilated fundoscopic examination
- Perform clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis)
- Perform urine pregnancy test (for females of childbearing potential only)

- Collect blood cultures for *Candida* spp. (2 consecutive sets [1 aerobic and 1 anaerobic blood culture bottle per set] of blood cultures from 2 separate sites [1 from a central venous catheter (CVC) and 1 peripheral venipuncture, or 2 peripheral venipunctures, if a CVC is not applicable])
- Collect other cultures and histopathology from other sites, as clinically indicated to assess the site(s) and extent of candidemia infection
- Perform imaging tests as clinically indicated to assess the site(s) and extent of candidemia infection
- Record prior/concomitant medications
- Record adverse events

6.4 Treatment Period

6.4.1 Baseline (Day 1 Pre-Dose)

Baseline procedures are to be completed pre-dose on the same day as 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)
- 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
- Intravascular catheter management and log of the line changes; any indwelling intravascular catheters should be removed and catheter tips cultured prior to starting APX001 dosing; entrance site tissue should also be cultured if it appears infected
- 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, the body site that corresponds to the entry site of candidemia (e.g., central venous catheter entry site), and a neurological examination.
- Collect blood culture for *Candida* spp. and blood for *Candida* spp. testing by T2MR assay
- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety])
- Collect other cultures and histopathology from other sites, as clinically indicated to monitor the site(s) and extent of candidemia infection
- Perform imaging tests, as clinically indicated to monitor the site(s) and extent of candidemia infection

- Collect serum samples for analysis of (1,3)-β-D-glucan
- Record concomitant medications
- Record adverse events

6.4.2 Study Drug Treatment

During Study Drug Treatment, twice weekly visits are required with a maximum window of ±2 days. 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.

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

- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight; collect twice weekly (daily Days 2 to 4 while inpatient)
- Intravascular catheter management log; all changes to be recorded until EOT while inpatient, and as clinically indicated thereafter or for outpatients
- Perform clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis); collect twice weekly
- Perform urine pregnancy test (for females of childbearing potential only); every 30 days if required by local regulations
- Perform focused, symptom-based physical examination including a neurological examination, once weekly
- Collect blood cultures for *Candida* spp. and blood for *Candida* spp. testing by T2MR assay; daily on Days 2 through 4 (minimum), continuing until 2 negative blood culture results on 2 consecutive tests are reported
- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety]); collect twice weekly
    - Optional: If body fluids are sampled as part of routine patient management (e.g., bronchoalveolar lavage, lumbar puncture, paracentesis, vitreal 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
- Collect other cultures and histopathology from other sites, as clinically indicated to monitor the site(s) and extent of candidemia infection
- Perform imaging tests as clinically indicated to monitor the site(s) and extent of candidemia infection
- Administer study drug; administered as a 3-hour IV loading dose BID on 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 a maximum of 14 days (inclusive of the loading dose [Study Day 1])

- Record concomitant medications
- Assess adverse events

6.4.3 End of Study Drug Treatment

The EOST occurs after completion of APX001 dosing. The following procedures will be performed at EOST:

- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight
- Intravascular catheter management log
- Perform dilated fundoscopic examination (only required in those patients who had positive fundoscopic findings at Screening, or as clinically indicated)
- 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 focused, symptom-based physical examination including a neurological examination
- Collect blood culture for *Candida* spp. and blood for *Candida* spp. testing by T2MR assay
- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety])
    - Optional: If body fluids are sampled as part of routine patient management (e.g., bronchoalveolar lavage, lumbar puncture, paracentesis, vitreal 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.
- Collect other cultures and histopathology from other sites, as clinically indicated to monitor the site(s) and extent of candidemia infection
- Perform imaging tests as clinically indicated to monitor the site(s) and extent of candidemia infection
- Collect serum sample for analysis of(1,3)-β-D-glucan
- Evaluate treatment outcome
- Record concomitant medications
- Assess adverse events

6.4.4 End of Antifungal Treatment

After completion of 14 days study drug therapy, if further antifungal treatment is indicated to complete treatment of candidemia in accordance with standard practice guidelines, fluconazole (unless susceptibility results warrant alternative antifungal therapy) may commence for up to a further 7 days. If applicable, an assessment of efficacy will also be made at the end of this antifungal treatment.

The EOT for patients completing the study is ≤7 days after completion of 14 days of APX001 dosing. If EOT is within 48 hours of EOST, asterisked procedures (*) do not need to be repeated, unless clinically indicated. The following procedures will be performed at EOT:

- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight
- Intravascular catheter management log
- Perform dilated fundoscopic examination (only required in those patients who had positive fundoscopic findings at Screening, or as clinically indicated)*
- 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 focused, symptom-based physical examination including a neurological examination*
- Collect blood culture for *Candida* spp.
- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety])
    - Optional: If body fluids are sampled as part of routine patient management (e.g., bronchoalveolar lavage, lumbar puncture, paracentesis, vitreal 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.
- Collect other cultures and histopathology from other sites, as clinically indicated to monitor the site(s) and extent of candidemia infection
- Perform imaging tests as clinically indicated to monitor the site(s) and extent of candidemia infection*
- Evaluate treatment outcome
- Record concomitant medications
- Assess adverse events

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

6.5.1 Follow-up 2 Weeks After End of Antifungal Treatment (+2 Days)

The following procedures will be performed at the Follow-up visit 2 weeks (+2 days) after EOT:

- 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 focused, symptom-based physical examination including a neurological examination
- Collect blood culture for *Candida* spp.
- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety])
- Collect other cultures and histopathology from other sites, as clinically indicated to monitor the site(s) and extent of candidemia infection
- Perform imaging tests as clinically indicated to monitor the site(s) and extent of candidemia infection
- Evaluate treatment outcome
- Record concomitant medications
- Assess adverse events

6.5.2 Follow-up 4 Weeks After End of Antifungal Treatment (+4 Days)

The following procedures will be performed at the Follow-up visit 4 weeks (+4 days) after EOT:

- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight
- Intravascular catheter management log as clinically indicated
- Perform dilated fundoscopic examination (only required in those patients who had positive fundoscopic findings at Screening, or as clinically indicated)
- 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 focused, symptom-based physical examination including a neurological examination
- Collect blood culture for *Candida* spp.
- Collect other cultures and histopathology from other sites, as clinically indicated to monitor the site(s) and extent of candidemia infection
- Perform imaging tests as clinically indicated to monitor the site(s) and extent of candidemia infection
- Evaluate treatment outcome
- Record concomitant medications
- Assess adverse events

6.6 Early Termination Visit and Withdrawal Procedures

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

- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight
- Intravascular catheter management log
- Perform dilated fundoscopic examination (only required in those patients who had positive fundoscopic findings at Screening, or as clinically indicated)
- 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 focused, symptom-based physical examination including a neurological examination
- Collect blood culture for *Candida* spp. and blood for *Candida* spp. testing by T2MR assay
- Collect plasma sample for PK (APX001 [prodrug] and APX001A [active moiety])
- Collect other cultures and histopathology from other sites, as clinically indicated to monitor the site(s) and extent of candidemia infection
- Perform imaging tests as clinically indicated to monitor the site(s) and extent of candidemia infection
- 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 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 Mycological Outcomes at EOST, EOT, and 2 and 4 weeks after EOT
- Percentage of patients with Treatment Success at EOT, and 2 and 4 weeks after EOT as determined by the DRC
- Overall survival at Study Day 30
- Number of patients with TEAEs

7.3 Exploratory Efficacy Endpoints

The exploratory efficacy parameters include the following:

- Change in serum (1,3)-β-D-glucan levels from Baseline (pre-dose) to EOST
- Correlation of blood culture and T2MR assay *Candida* spp. results from Baseline (pre-dose) through EOST

7.4 Definitions for Efficacy Assessments

7.4.1 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.
- Alive at EOST
- No concomitant use of any other systemic antifungal therapies through EOST

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

Mycological Outcome:

- Eradication is defined as a negative blood culture(s) for *Candida* spp. in the absence of concomitant antifungal therapy through EOST.

7.4.2 At End of Antifungal Treatment (EOT)

After completion of 14 days study drug therapy, if further antifungal treatment is indicated to complete treatment of candidemia in accordance with standard practice guidelines, fluconazole (unless susceptibility results warrant alternative antifungal therapy) may commence for up to a

further 7 days. If applicable, an assessment of efficacy will also be made at the end of this antifungal treatment at EOT.

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

- Two consecutive blood cultures negative for *Candida* spp.
- Alive at EOT
- No additional systemic antifungal therapies (except for protocol-allowed step-down treatment [e.g., fluconazole]) through EOT

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

Mycological Outcome:

- Eradication is defined as a negative blood culture(s) for Candida spp. in the absence of additional antifungal therapy (except for protocol-allowed step-down treatment [e.g., fluconazole]) through EOT.

7.4.3 At Follow-up (2 Weeks and 4 Weeks After End of Antifungal Treatment)

- Recurrence (mycological) is defined as a mycologically confirmed infection based on blood culture with the same Baseline *Candida* spp. during the 4 weeks after EOT.
- Relapse (DRC Assessment) is defined as re-occurrence of *Candida* in blood culture during the Follow-up Period, or diagnostic parameters indicative of recurrence or late spread of the *Candida* infection.

7.5 Microbiological Assessments

7.5.1 Blood Cultures

A blood culture positive for *Candida* spp. drawn within 96 hours of APX001 dosing is required for eligibility as part of SOC. During screening, 2 consecutive sets (1 aerobic and 1 anaerobic blood culture bottle per set) of blood cultures from 2 separate sites (1 from a CVC and 1 peripheral venipuncture, or 2 peripheral venipunctures, if a CVC is not applicable) are required before the initiation of APX001 dosing. The screening cultures may be drawn on the day of dosing. Blood cultures (minimum of 1 set) for *Candida* spp. will also be performed at Baseline (pre-dose), during Study Drug Treatment, at EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination. During the Study Drug Treatment Period, daily blood cultures are required on Study Days 1 through 4; thereafter, blood cultures may be stopped after negative results on 2 consecutive days are obtained. *Candida* spp. isolates from the blood cultures performed at the local laboratory must be submitted to the mycology reference laboratory for confirmation of identification and susceptibility testing.

If a Sponsor-approved rapid diagnostic test for candidemia is used to identify potentially eligible patients, subsequent confirmatory blood cultures are required prior to dosing. Likewise, *Candida* spp. isolates from these blood cultures are to be submitted to the mycology reference laboratory. Results from any further rapid diagnostic tests performed as per local SOC must be captured in the eCRF.

7.5.2 Cultures From Other Sites of Infection

Any *Candida* spp. cultured from a normally sterile site, from intravascular catheter tip(s), or from a sample indicative of deep-seated invasive Candidiasis discovered after dosing with APX001, should be sent to the mycology reference laboratory for confirmation of identification and susceptibility testing.

7.5.3 *Candida* Spp. Testing by T2 Magnetic Resonance Assay

Each time a blood culture is collected for the protocol, an additional blood sample will be collected for *Candida* spp. testing by T2MR assay at Baseline, during Study Drug Treatment, and through EOST or Early Termination. A central laboratory will perform the T2MR assay.

7.5.4 Intravascular Catheter Management and Log

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. 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 patient 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. Patients 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 change 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.

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

The severity of infusion site reactions adverse events will be graded using the definitions in Table 1.

Table 1. Infusion Site Reaction Adverse Event Severity Grading Table

Event	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-Threatening)
Infusion/injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Infusion/injection site reaction is defined as a disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an infusion/injection.				

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 an 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] 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] or call the Medpace Clinical Safety SAE reporting line (phone number listed below), and fax the completed paper SAE form 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.

Safety Contact Information: [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.

Expedited reporting of suspected unexpected serious adverse reactions related to APX001 will not be necessary. Listings of cases related to APX001 will be included in the Development Safety Update Report.

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.

8.5.2 Subject Stopping Rule

Study treatment for an individual patient may be discontinued for lack of clinical and/or microbiological response, 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, EOT, and 2 and 4 weeks after EOT, 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] 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 Screening, Baseline (pre-dose), twice weekly during Study Drug Treatment, at EOST, EOT, and 2 and 4 weeks after EOT, 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 2 through 4, and twice weekly thereafter during Study Drug Treatment, at EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination. Height will be collected (from the patient's medical record) at Baseline.

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, EOT, and 4 weeks after EOT, 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 focused, symptom-based physical examination to include a neurological examination will be performed once weekly during study treatment, EOST, EOT, and 2 and 4 weeks after EOT, 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, EOT, and 2 weeks after EOT, or Early Termination.

Optionally, if body fluids are sampled as part of routine patient management (e.g., bronchoalveolar lavage, lumbar puncture, paracentesis, vitreal 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.

8.13 Dilated Fundoscopic Examination

A dilated fundoscopic examination will be performed at Screening for all patients and at EOST, EOT, and 4 weeks after EOT, or Early Termination for those patients who had positive fundoscopic findings at Screening, or as clinically indicated.

8.14 Imaging Tests

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

8.15 Other Cultures and Histopathology

Other cultures and histopathology should be performed to assess the site(s) and extent of candidemia infection as clinically indicated.

8.16 Intravascular Catheter/Device Management Log

The management of intravascular catheters, intravascular devices, and, if applicable, any drains will be recorded, including any associated microbiology results.

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 within 96 hours of the start of treatment with APX001

Per-Protocol Population

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

- Received at least 1 dose of study drug
- Have a confirmed diagnosis of candidemia within 96 hours of the start of treatment with APX001
- Did not exceed prior antifungal treatment (per eligibility)
- Meet the protocol's key inclusion and exclusion criteria (to be defined in the study's Statistical Analysis Plan)
- Have no major protocol violations (to be defined in the study's Protocol Deviation Plan)

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

9.2.2 Analysis of Safety

All safety analyses will be performed on the Safety Population. Safety data will be patient 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.

9.2.2.1 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.

9.2.3 Interim Analysis

No interim analysis is planned for the study.

9.2.4 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 candidemia 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.

9.2.5 Data and Safety Monitoring Board

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. 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.

9.2.6 Sample Size Determination

A sample size of approximately 20 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 patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients 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 patients. 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 patients, 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 patients 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 patient or patient'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 patient 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 Subject Card

On enrollment in 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. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient 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 patient liability insurance for all patients 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, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

12.2 Address List

12.2.1 Sponsor

Amplyx Pharmaceuticals, Inc.
12730 High Bluff Drive, Suite 160
San Diego, CA 92130
Telephone: +1-858-345-1755
Fax: +1-858-345-1346

12.2.2 Contract Research Organization

[redacted]

12.2.3 Drug Safety

[redacted]

12.2.4 Biological Specimens

[redacted]

[redacted]

[redacted]

12.2.5 Mycology Reference Laboratory

[redacted]

12.2.6 Pharmacokinetic Laboratory

[redacted]

13 REFERENCES

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2. Tsay S, Welsh RM, Adams EH, et al. Notes from the field: ongoing transmission of candida auris in health care facilities - United States, June 2016-May 2017. MMWR Morb Mortal Wkly Rep. 2017;66(19):514-15.
3. Castanheira M, Duncanson FP, Diekema DJ, et al. Activities of E1210 and comparator agents tested by CLSI and EUCAST broth microdilution methods against Fusarium and Scedosporium species identified using molecular methods. Antimicrob Agents Chemother. 2012;56(1):352-7.
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6. Watanabe NA, Miyazaki M, Horii T, et al. E1210, a new broad-spectrum antifungal, suppresses Candida albicans hyphal growth through inhibition of glycosylphosphatidylinositol biosynthesis. Antimicrob Agents Chemother. 2012;56(2):960-71.
7. McLellan CA, Whitesell L, King OD, et al. Inhibiting GPI anchor biosynthesis in fungi stresses the endoplasmic reticulum and enhances immunogenicity. ACS Chem Biol. 2012;7(9):1520-8.
8. Hata K, Horii T, Miyazaki M, et al. Efficacy of oral E1210, a new broad-spectrum antifungal with a novel mechanism of action, in murine models of candidiasis, aspergillosis, and fusariosis. Antimicrob Agents Chemother. 2011;55(10):4543-51.
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APPENDIX A: SCHEDULE OF PROCEDURES

Procedure	Eligibility	Screening (≤96 Hours of Baseline) [a]	Treatment Period[b]				Follow-up		Early Termination
			Baseline (Day 1 Pre-Dose)	Study Drug Treatment (≤14 Days)	End of Study Drug Treatment (EOST)[c]	End of Antifungal Treatment (EOT)[e,f]	Follow-up 2 Weeks After EOT +2 Days	Follow-up 4 Weeks After EOT +4 Days	
Informed consent		X[g]							
Inclusion/exclusion criteria		X	X						
Medical history		X							
Demographics		X							
APACHE II score			X						
Vital signs/temperature[h]		X	X	X	X	X	X	X	X
Intravascular catheter/device management log (including any drains, if applicable)		X[i]	X[i]	X	X	X[j]	X[k]	X[k]	X
Dilated fundoscopic examination		X			X[l]	X[d,l]		X[l]	X[l]
Clinical safety laboratory tests[m]		X	X	X	X	X[d]	X	X	X
12-lead electrocardiogram			X		X	X[d]		X	X
Urine pregnancy test (for females of childbearing potential only)		X	X	X[n]	X	X[d]	X	X	X
Physical examination[o]			X	X	X	X[d]	X	X	X
Blood sample for *Candida* spp. culture and testing by T2MR assay[r,s]	X	X[q]	X[p,q]	X[p,q]	X[p,q]	X[q]	X[q]	X[q]	X[p,q]

APPENDIX A: SCHEDULE OF PROCEDURES (CONTINUED)

Procedure	Eligibility	Screening (≤96 Hours of Baseline) [a]	Treatment Period[b]				Follow-up		Early Termination
			Baseline (Day 1 Pre-Dose)	Study Drug Treatment (≤14 Days)	End of Study Drug Treatment (EOST)[c]	End of Antifungal Treatment (EOT)[e,f]	Follow-up 2 Weeks After EOT +2 Days	Follow-up 4 Weeks After EOT +4 Days	
Blood samples for rapid diagnostic test[t]	X								
Pharmacokinetic sample[u]			X	X	X	X	X		X
Other cultures and histopathology[k,v]		X	X	X	X	X	X	X	X
Imaging tests[k,v]		X	X	X	X	X[d]	X	X	X
Serum sample[w]			X		X				X
Evaluation of treatment outcome					X	X	X	X	X
Study drug administration[x]				X					
Fluconazole treatment[y]						X			
Prior/concomitant medications		X	X	X	X	X	X	X	X
Adverse event evaluation		X	X	X	X	X	X	X	X

a. To be completed within 96 hours from blood sampling time for culture positive for *Candida* spp.
b. During Study Drug Treatment, twice weekly visits are required with a maximum window of ±2 days. 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.
c. End of Study Drug Treatment (EOST) occurs after completion of APX001 dosing.
d. Assessments performed at EOST do not need to be repeated at End of Antifungal Treatment (EOT), if <48 hours apart, unless clinically indicated.
e. The EOST may be the same as EOT for those patients that do not have a step-down (i.e., fluconazole or other protocol approved step-down).
f. The EOT occurs up to a maximum of 21 days after Baseline (includes up to 14 days of APX001 administration and up to 7 days of fluconazole administration or other protocol approved step-down).
g. To be obtained prior to the initiation of any protocol-specific procedure outside of SOC.
h. 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 2 to 4, and twice weekly thereafter during Study Drug Treatment, EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination. Height will be collected (from the patient's medical record) at Baseline.
i. 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.
j. Intravascular catheters logged until EOT.

k. As clinically indicated. If obtained, results should be recorded in the eCRF.
l. Only required in those patients who had positive fundoscopic findings at Screening, or as clinically indicated.
m. 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, hematology, coagulation, and urinalysis) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, at EOST, EOT, and 2 and 4 weeks after EOT, 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.
n. Urine pregnancy test (for females of childbearing potential only) every 30 days if required by local regulations.
o. 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 focused, symptom-based physical examination to include a neurological examination will be performed once weekly during study drug treatment, EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination.
p. Each time a blood culture is collected, an additional blood sample will be drawn for subsequent analysis of the correlation of blood culture and T2MR assay *Candida* spp. results from Baseline (pre-dose) through EOST or Early Termination. A central laboratory will perform the T2MR assay.
q. Two consecutive sets of blood cultures during screening within 96 hours before the initiation of APX001 study treatment; 1 set thereafter.
r. All *Candida* spp. isolates must be submitted to the mycology reference laboratory for confirmation of identification and susceptibility testing.
s. During Study Drug Treatment, daily blood cultures on Study Days 1 through 4 (minimum), continuing until 2 consecutive blood cultures negative for *Candida* spp. are reported.
t. Optional rapid diagnostic test, if available and used routinely for candidemia diagnosis; test (e.g., T2MR assay) must be Sponsor-approved; a subsequent confirmatory blood culture must also be performed to confirm *Candida* spp.
u. Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, EOST, EOT, 2 weeks after EOT, or Early Termination. Optional: If body fluids are sampled as part of routine patient management (e.g., bronchoalveolar lavage, lumbar puncture, paracentesis, vitreal 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.
v. Other cultures, histopathology, and imaging tests to assess the site(s) and extent of candidemia infection, if applicable. If performed, these will be analyzed at the local study site.
w. Serum samples for (1,3)-β-D-glucan levels will be collected at Baseline (pre-dose) and EOST, or Early Termination (if applicable).
x. 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 a maximum of 14 days (inclusive of the loading dose [Study Day 1]).
y. After completion of 14 days study drug therapy, if further antifungal treatment is indicated to complete treatment of candidemia in accordance with standard practice guidelines, fluconazole (unless susceptibility results warrant alternative antifungal therapy) may commence for up to a further 7 days.

APACHE = Acute Physiology and Chronic Health Evaluation; BID = twice daily; eCRF = electronic Case Report Form; EOST = End of Study Drug Treatment; EOT = End of Antifungal 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
Calcium	Chloride
Creatine kinase	Creatinine
Estimated glomerular filtration rate	Gamma-glutamyl transferase
Glucose	Inorganic phosphorus
Lactate dehydrogenase	Lipase
Potassium	Sodium
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

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

<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-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