# CLINICAL STUDY PROTOCOL

## A Phase 2, Open-Label Study to Evaluate the Safety and Efficacy of APX001 in the Treatment of Patients with Invasive Mold Infections Caused by Aspergillus Species or Rare Molds

**Investigational Product:** APX001
**Protocol Number:** APX001-202
**EudraCT Number:** 2019-001386-33

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**Version Number:** 3.0
**Date:** 29 September 2020

# SIGNATURE PAGE

**A Phase 2, Open-Label Study to Evaluate the Safety and Efficacy of APX001 in the Treatment of Patients with Invasive Mold Infections Caused by Aspergillus Species or Rare Molds**

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

Signature Date

PPD MD
PPD
Amplyx Pharmaceutical, Inc.

# INVESTIGATOR AGREEMENT

By signing below I agree that:

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

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

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

# SYNOPSIS

**TITLE:** A Phase 2, Open-Label Study to Evaluate the Safety and Efficacy of APX001 in the Treatment of Patients with Invasive Mold Infections Caused by Aspergillus Species or Rare Molds

**PROTOCOL NUMBER:** APX001-202

**INVESTIGATIONAL PRODUCT:** APX001

**PHASE:** 2

**INDICATION:** Treatment of patients with invasive mold infections (IMIs) caused by *Aspergillus* species (spp.) or rare molds

**OBJECTIVES:**

The primary objective of this proof-of-concept study is to evaluate the safety and efficacy of APX001 for the treatment of adult patients aged 18 years and above with IMIs caused by *Aspergillus* spp. or rare molds (eg, *Scedosporium* spp., *Fusarium* spp., and Mucorales fungi), who have limited antifungal treatment options.

The secondary objectives of this study are to:

- Evaluate global response at End of Study Treatment (EOST)
- Evaluate safety parameters of APX001
- Evaluate pharmacokinetic (PK) parameters of APX001

**BACKGROUND:**

APX001, a first-in-class small molecule investigational drug candidate, is the water-soluble methyl phosphate prodrug of the active moiety APX001A. APX001 is rapidly converted *in vivo* to APX001A. APX001A has a novel mechanism of antifungal action, with broad spectrum activity against major fungal pathogens including *Candida* spp. and *Aspergillus* spp.

APX001A inhibits the fungal glycosylphosphatidylinositol (GPI)-anchored wall transfer protein 1 (GWT1) enzyme, a highly conserved inositol acylase that catalyzes an early step in the GPI-anchored biosynthesis pathway. This inhibition has pleiotropic effects on the fungal cell due to inhibition of cell wall mannoprotein localization, which compromises cell wall integrity, biofilm formation, germ tube formation, and fungal growth. APX001A does not inhibit phosphatidylinositol glycan anchor biosynthesis class W (PIGW) protein, the closest mammalian ortholog of the fungal GWT1 protein consistent with the potential for a significant target-based therapeutic window.

APX001A has demonstrated broad *in vitro* antifungal activity against *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., *Scedosporium* spp., *Fusarium* spp., and Mucorales fungi, including activity against azole- and echinocandin-resistant strains. APX001A has demonstrated synergy with echinocandins (*Aspergillus*) and azoles (*Candida*). In 5-fluorouracil immunosuppressed mice with IMIs (*Aspergillus fumigatus*, *Scedosporium prolificans*, and

*Fusarium solani*), APX001 demonstrated statistically significantly improved survival rates and reduced pulmonary fungal colony counts. In cyclophosphamide and cortisone acetate immunosuppressed mice with IMIs (*A. fumigatus*, *Scedosporium apiospermum*, *F. solani*, and *Rhizopus* spp.), APX001 demonstrated statistically significantly improved survival rates and reduced fungal burden. Pharmacokinetic-pharmacodynamic (PK-PD) studies in immunosuppressed mice with invasive infections caused by *A. fumigatus* have shown that the area under the concentration-time curve (AUC) divided by the minimal effective concentration (MEC) ratio is the driver of efficacy. The dose regimen employed in this study provides a steady state AUC ≥200 µg·hr/mL, which is associated with efficacy (colony count and survival benefit) in immunocompromised mice with invasive pulmonary aspergillosis (IPA). Additionally, formal PK-PD studies demonstrated that the dose regimen has favorable probability of target attainment (PTA) for the majority of isolates anticipated to be encountered in this study.

In Phase 1 clinical studies of APX001, the safety, tolerability, and PK of single and multiple ascending doses administered intravenously (IV) and orally (PO) have been studied. To date, a total of 197 healthy volunteers and 21 patients with acute myeloid leukemia (AML) have received APX001 across 5 Phase 1 studies (APX001-101, APX001-102, APX001-103, APX001-105, APX001-106). The duration of the multiple-dose regimens in these studies were 7, 14, and 42 days (6 weeks).

**Phase 1 studies in healthy volunteers:** The highest doses administered in 2 dose escalation studies, APX001-101 and APX001-102, were 600 mg IV daily and 1000 mg PO daily for 14 days, respectively. The 6-week dose regimen administered in study APX001-105 is closely matching the dose and duration that will be employed in this protocol. In these 3 Phase 1 studies, all doses of APX001 were safe and well tolerated. The majority of the treatment-emergent adverse events (TEAEs) were mild, transitory, and resolved without intervention. There were no severe or serious adverse events (SAEs) reported and no dose-limiting toxicities were observed. In all 3 Phase 1 studies, no laboratory test results nor results from other safety evaluations (physical examination, electrocardiogram [ECG], vitals) met the criteria for a TEAE nor did any result meet the a priori rules that prevented dose escalation.

In an additional dose escalation study, APX001-106, cohorts of healthy volunteers were administered 750 to 900 mg IV daily for 6 days, preceded by various loading doses. Some of the 900 mg dose regimens that employed high loading doses were not well tolerated. Consequently, at this time the 900 mg dose regimen will not be employed in this study.

APX001 and APX001A PK parameters for both single and multiple APX001 IV and PO doses in all 4 Phase 1 studies in healthy volunteers were linear and dose proportional. In the cohort embedded within the PO dose Phase 1 study APX001-102, APX001 demonstrated a favorable (ie, APX001 was not a strong inhibitor or strong inducer of cytochrome P450 [CYP] enzymes) drug-drug interaction (DDI) profile. The relative bioavailability of the PO APX001 formulation is >90% in both the presence or absence of food, demonstrating that no food effect exists. In addition, the target AUCs anticipated for efficacy against both yeasts and molds have been achieved with both IV and PO dose formulations.

Further details of all the Phase 1 studies can be found in the Investigator's Brochure (IB).

**Phase 1 studies in patients:** Study APX001-103 was conducted in patients with newly diagnosed AML undergoing induction chemotherapy. The objective of this study was to evaluate the safety, tolerability, and PK of IV and PO doses of APX001 in a patient population in which the investigational medicinal product will be studied. There were no treatment-related SAEs reported during the study and none of the TEAEs reported as related to APX001 resulted in drug withdrawal/discontinuation. With the exception of 1 Grade 3 TEAE (hypertension), all TEAEs reported as related to APX001 were of the Common Terminology Criteria for Adverse Events Grades 1 and 2.

All clinically significant abnormal clinical laboratory findings observed in this study, vital signs, ECG, and physical examination findings, can be attributed to the underlying condition of AML and the aggressive induction chemotherapy. Overall, the safety results from this study indicate daily doses of IV or PO APX001 given for 14 days were safe and well tolerated. No evidence of significant or additional risks of APX001 in this patient population was observed and no new safety concerns were identified.

Plasma concentrations and calculated exposures of APX001 and APX001A in study APX001-103 were lower than expected based on PK data from prior Phase 1 studies in healthy volunteers (APX001-101 and APX001-102). Potential factors that might contribute to this observation were thoroughly investigated and are described in the IB. These experiments confirmed that the plasma concentrations of APX001 and/or APX001A are dependent on hematocrit values. The lowered exposures observed in the APX001-103 PK results are most likely due to a dilution effect. When plasma concentrations are adjusted to account for this effect, PK parameters in APX001-103 are similar to those observed in prior healthy volunteer studies.

Further details of all the Phase 1 studies can be found in the IB.

In summary, APX001 has a novel mechanism of action with broad spectrum activity against *Candida* spp. (yeast) and *Aspergillus* spp. (mold), including activity against polyene and azole-resistant strains of *Aspergillus* spp. APX001 has demonstrated efficacy in a number of animal models of IMIs, including *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., and Mucorales fungi. To date, APX001 in both IV and PO formulations has been safe and well tolerated with a favorable DDI profile. APX001 has the potential to be used as a first-line agent for the treatment of IMIs.

**POPULATION:**

This study will enroll male and female patients aged 18 years and above with a confirmed diagnosis of invasive aspergillosis or invasive rare mold infection. Patients will have limited or no treatment options due to documented/anticipated resistance, contraindication, intolerance, or lack of clinical response to standard of care (SOC) antifungal therapy, as advocated by the relevant regional/country treatment guidelines. The study will enroll CCI cohorts, Cohort A [redacted] Up to 40 patients will be enrolled in Cohort A, and these patients will have an IMI which was diagnosed according to the EORTC/MSGERC criteria. CCI [redacted]

Inclusion Criteria:

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

1. Males or females, 18 years or older.
2. Patients with IMI caused by *Aspergillus* spp. Patients who present with IMI due to other filamentous fungi (eg, *Scedosporium* spp., *Fusarium* spp., and Mucorales fungi such as *Mucor* spp. or *Rhizopus* spp.) may also be enrolled.
   - Cohort A: Diagnosis of proven or probable IMI will be defined in accordance with the Revision and Update of the Consensus Definitions of Invasive Fungal Disease from the EORTC/MSGERC .
   - CCI [redacted]
3. Have limited or no treatment options due to documented or anticipated resistance, contraindication, intolerance, or lack of clinical response to SOC antifungal therapy, as advocated by the relevant regional/country treatment guidelines.
4. Patients where the Investigator considers that there is a potential advantage of using APX001 over current SOC (eg, broad spectrum of activity, activity against resistant mold pathogens, IV and PO formulations, favorable DDI profile, favorable hepatic and renal safety profile, wide tissue distribution including brain), and/or where the SOC antifungal therapy carries significant risk of toxicity or treatment failure (eg, emergence of IMI during antifungal prophylaxis, DDI risk, safety/toxicity risk, site of infection not accessible by SOC).
5. Female patients of nonchildbearing potential must be 1 of the following:
   - Surgically sterile (hysterectomy, bilateral tubal ligation, bilateral salpingectomy, and/or bilateral oophorectomy).
   - Postmenopausal (amenorrhea for >12 months without an alternative medical cause).
6. Females of childbearing potential (ie, not postmenopausal or surgically sterilized) must have a negative urine or serum pregnancy test result within 96 hours prior to Baseline (ie, predose on Day 1). Participating females of childbearing potential with male partners, and males with female partner(s) of childbearing potential, must agree to use 2 forms of contraception, 1 of which must be highly effective and the other an acceptable barrier method (male or female condom), throughout the duration of the study and for 90 days following the last study drug administration. Highly effective methods of contraception include the following:
   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (PO, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (PO, injectable, or implantable), intrauterine device, or intrauterine hormone-releasing system.
   - Bilateral tubal occlusion or vasectomized partner.

     **Note:** A vasectomized partner is a highly effective method of contraception, provided that the male partner is the sole sexual partner of the study patient who is a female of childbearing potential and that the vasectomized partner has received medical assessment of surgical success.
   - Sexual abstinence.

**Note:** 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 (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

7. Male patients must agree to abstain from sperm donation and use condoms with spermicide during sexual intercourse between Screening and at least 90 days after administration of the last dose of study drug. Male patients must ensure nonpregnant female partner(s) of childbearing potential comply with the contraception requirements in Inclusion Criterion 6.
8. Patients must be willing to participate in the study, to give written informed consent, and to comply with the study restrictions; where permitted by local regulations, written informed consent from a legal authorized representative will be obtained for patients who are unable to give consent.
9. CCI [redacted]

Exclusion Criteria:

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

1. Refractory hematologic malignancy with no potential to respond to additional chemotherapy.
2. Chronic aspergillosis, aspergilloma, or allergic bronchopulmonary aspergillosis.
3. Treatment with systemic (PO, IV, or inhaled) antifungal therapy with a mold-active azole or polyene for ≥120 hours immediately before initial dosing.

   **Note:** An exception is antifungal prophylaxis, for which there is no restriction on duration, but must be stopped upon commencement of treatment with APX001.

   Additionally, patients with invasive fungal infection caused by a mold with documented resistance to or lack of coverage by the prior SOC in question, as well as patients with polyene-induced renal toxicity or those who have received empirical treatment with echinocandins, may have received >120 hours prior treatment and remain eligible for the study. These patients must be discussed with the Medical Monitor prior to enrollment, and prior treatment in this case should not exceed >168 hours.

4. Evidence of significant hepatic dysfunction, defined as any of the following:
   - Total bilirubin >3 × the upper limit of normal (ULN) unless isolated hyperbilirubinemia or due to documented Gilbert's disease.
   - Alanine transaminase or aspartate transaminase ≥5 × ULN.
   - Severe or moderate hepatic impairment (Child-Pugh Score >6 points) at any time during 2 weeks prior to dosing. The Child-Pugh score of > 6 is applicable only to patients with hepatic dysfunction and cirrhosis.
5. Ongoing medical history of neurological disorders including abnormal movements or seizures.

**Note:** A current CNS mold infection as well as a stable history of peripheral neuropathy will not be considered exclusionary

6. Patient receiving palliative care only.
7. Known hypersensitivity or other serious reaction to APX001 or any ingredient of APX001.
8. Patient is lactating and/or pregnant or intending to be pregnant during the duration of the study.
9. Investigational drug administered within 30 days or 5 terminal half-lives prior to study drug dosing (whichever is longer).

   **Note:** Participation in research protocols for approved agents for the treatment of an underlying condition is permitted.

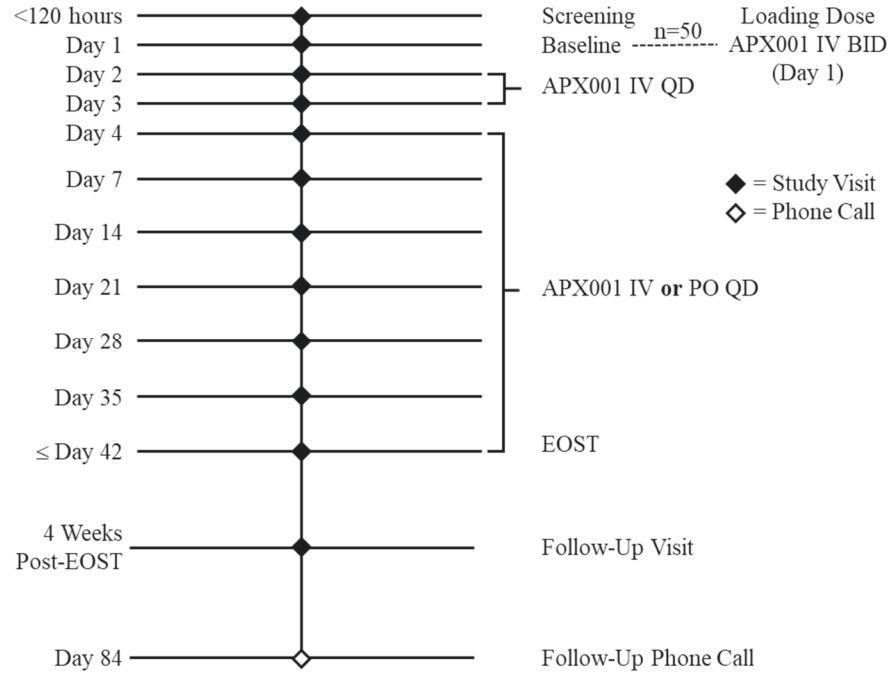
10. Prior participation in this study or any previous study of APX001.
11. Concomitant use of medication that is a strong inducer (ie, rifampin, carbamazepine, phenytoin, rifabutin, efavirenz, nevirapine, phenobarbital, modafinil, St. John's Wort, enzalutamide) of CYP enzymes.
12. Any other condition or laboratory abnormality that, in the opinion of the Investigator or the Sponsor, would put the patient at unacceptable risk for participation in the study or may interfere with the assessments included in the study.
13. Patients on mechanical ventilation
14. Cohort A only: Suspected or confirmed COVID-19 or Influenza A/B infection.
15. Patients with severe renal impairment as determined by estimated glomerular filtration rate (eGFR) <30 mL/min /1.173 $m^2$ calculated by CKD-EPI, including patients on dialysis.
16. Patients with a Karnofsky Performance Status ≤ 30 at screening

**STUDY DESIGN AND DURATION:**

This is a Phase 2, multicenter, open-label, non-comparative study to evaluate the safety and efficacy of APX001 for the treatment of IMIs caused by *Aspergillus* spp. or rare molds (eg, *Scedosporium* spp., *Fusarium* spp., and Mucorales fungi). Patients 18 years of age or older will undergo Screening procedures for up to 5 days, following which eligible patients will participate in the study drug Treatment Period for up to 6 weeks, with a Follow-Up Visit 4 weeks after EOST, and a Follow-Up Phone Call 12 weeks after Day 1 (Day 84). The total duration of a patient's participation in the study will be approximately 12 weeks, inclusive of the follow-up telephone call required on Day 84. Patients who require treatment for longer than 6 weeks can be switched to other licensed antifungal therapy (OLAT) at the discretion of the Investigator and in consultation with the Medical Monitor if the situation allows.

This study will be conducted at up to 40 global sites.

A schematic representing the study's design is included below:




BID = twice daily; EOST = End of Study Treatment; IV = intravenous(ly); PO = oral(ly); QD = once daily.

This study will consist of CCI parallel cohorts. Cohort A will enroll up to 40 patients, CCI [redacted] Each cohort has a single treatment arm consisting of a loading dose of 1000 mg APX001, administered over 3 hours by IV infusion twice daily (BID) within the first 24 hours after initiation of the first infusion. On Days 2 and 3, 600 mg APX001 will be administered over 3 hours by IV infusion once daily (QD). From Day 4 through EOST, the IV dose remains 600 mg APX001 administered over 3 hours by IV infusion QD, or patients may be switched to PO administration of 800 mg APX001 QD. Antiemetics (preferably a 5-$HT_3$ antagonist such as ondansetron or granisetron) should be administered in patients who develop nausea and/or vomiting associated with APX001 administration (both IV and oral), and oral APX001 may be given with food. Additionally, prophylactic antiemetics, (preferably a 5-$HT_3$ antagonist such as ondansetron or granisetron) may be administered prior to dosing (both IV and oral) in patients considered at higher risk of gastrointestinal intolerance. The decision to switch from IV to PO APX001 will be based on the Investigator's discretion and can be done on any day from Day 4 onwards. Patients will remain hospitalized for at least 2 days following the initial switch from IV to PO so that their tolerance to the oral medication may be evaluated and treated as necessary, and patients may be switched between IV and PO as needed. Oral APX001 may be given as an outpatient.

Administration of APX001 should not continue for longer than 6 weeks (inclusive of the loading dose [Day 1]). If an Investigator documents an improvement or resolution in clinical signs and symptoms prior to 6 weeks, eg, if follow-up imaging (as applicable) shows improvement; or a mycological response (if amenable to repeat sampling) is observed, the Investigator may choose to discontinue dosing. Patients will be requested to return for an EOST and a Follow-Up Visit and to agree to a Follow-Up Phone Call.

Dosing is described below:

| Load Dosing Day 1 (Baseline) | Maintenance Dosing Days 2-42 [1] | | |
|---|---|---|---|
| **IV BID** | **IV QD [1]** | **PO QD [1,2]** | **Total Enrolled (n)** |
| 1000 mg | 600 mg | 800 mg | 50 |

1. On Days 2 and 3, APX001 will be administered over 3 hours by IV infusion QD. From Day 4 through EOST, the IV dose remains 600 mg APX001 administered over 3 hours by IV infusion QD, or patients may be switched to PO administration of 800 mg APX001 QD.
2. Patients may switch between IV and PO as needed. Oral APX001 may be given as an outpatient.

BID = twice daily; EOST = End of Study Treatment; IV = intravenous(ly); PO = oral(ly); QD = once daily.

Blood samples (serum and plasma) and other diagnostic specimens (eg, bronchoalveolar lavage [BAL]) will be collected at Screening for pathogen DNA analysis utilizing next-generation sequencing (optional) and/or polymerase chain reaction (PCR) analysis. Urine samples will be collected at Screening for the aspergillosis urine test.

Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected predose and 3 hours post start of infusion on Days 1 (Baseline), 2, 3, 7, and 14; predose on Days 28 and 42; and at any time in clinic at EOST, the Follow-Up Visit, and the Early Termination (E/T) Visit (if applicable). Additionally, for patients who switch to PO dosing, samples should be collected predose and at 3 hours postdose on the initial day of PO dosing, Day 7, and Day 14 and at any time in clinic on Days 28 and 42, at EOST, at the Follow-Up Visit, and at the E/T Visit (if applicable). If the patient switches back to IV dosing, PK samples should be collected predose and at 3 hours post start of infusion on that day as well.

Serum samples for analysis of CCI [redacted] will be collected at Screening; predose on Days 1 (Baseline), 2, and 3; on Days 7, 14, 28, and 42; at EOST; and at the E/T Visit (if applicable).

Serum samples for analysis of C[redacted] will be collected at Screening; predose on Day 1 (Baseline); on Days 14, 28, and 42; at EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable).

Assessment of clinical signs and symptoms will be conducted at Screening; at all visits from Day 1 (Baseline) through EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable).

Radiological assessments (including computed tomography scans of the chest, sinuses, and/or abdomen) will be performed during Screening (SOC scans within 3 days of Screening will be accepted as long as the scans can be provided to the central reader). Computed tomography scans of the chest, sinuses, and/or abdomen will be repeated on Day 14 and at EOST, and if clinically indicated on Days 7, 21, 28, 35, and 42; at the Follow-Up Visit; and at the E/T Visit (if applicable).

Samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) will be collected and processed for culture and susceptibility by the local laboratory at Screening, and as clinically indicated at any visit from Day 1 (Baseline) through EOST, at the Follow-Up Visit, and at the E/T Visit (if applicable). Screening samples for fungal cultures to determine eligibility may have been collected as SOC 120 hours prior to initial dosing. All fungal isolates cultured at the local laboratory will be sent to the central mycology reference laboratory for confirmation of identification and susceptibility testing.

Bronchoalveolar lavage samples will be collected per SOC for culture at the local laboratory and CCI testing at the central laboratory as clinically indicated at any visit from Screening throughout the study.

The safety and tolerability of APX001 will be evaluated through physical examination findings, clinical signs and symptoms, vital signs, changes in clinical laboratory tests, 12-lead ECGs, any other exploration, and monitoring of adverse events and concomitant medications or procedures.

**DOSAGE FORMS AND ROUTE OF ADMINISTRATION:**

On Day 1 (Baseline), a 1000 mg APX001 loading dose will be administered over 3 hours by IV infusion BID within the first 24 hours after initiation of the first infusion.

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

From Day 4 through EOST, APX001 will be administered as either:

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

**Note:** Study drug will not be administered for longer than 6 weeks (inclusive of the loading dose [Day 1]). If an Investigator documents an improvement or resolution in clinical signs and symptoms prior to 6 weeks, eg, if follow up imaging (as applicable) shows improvement; or a mycological response (if amenable to repeat sampling) is observed, the Investigator may choose to discontinue dosing. Patients will be requested to return for an EOST and Follow-Up Visit and to agree to a Follow-Up Phone Call. Patients who still require treatment after EOST should continue on OLAT.

**RATIONALE FOR DOSE AND SCHEDULE SELECTION:**

In a PK-PD IPA study, immunocompromised mice were infected with 6 strains of *A. fumigatus*, inclusive of wild type, azole-resistant, and echinocandin-resistant strains. Groups of animals were dosed with APX001 at different dose fractionations. The AUC from time 0 to 24 hours ($AUC_{(0-24)}$)/MEC ratio was determined to be the PK-PD index that best correlated with antifungal efficacy as assessed by fungal burden (conidial equivalents [CEs] measured by real time quantitative PCR) in lung homogenates. The stasis and 1-logarithm drop endpoints were defined as the quantity of *A. fumigatus* in CEs just prior to APX001 administration compared to CEs at the endpoint of assessment at 96 hours. The median total drug AUC/MEC which achieved stasis and 1-logarithm kill endpoints for each *A. fumigatus* strain were 2801.6 and 5258.2.

The clinical isolates surveillance data from 2017, 2018 and 2019 of APX001A antifungal activity against *Aspergillus* spp. shows that the majority (96%) of *Aspergillus* isolates have MEC values of 0.008 to 0.03 µg/mL. The MEC in 90% of patients ($MEC_{90}$) for *Aspergillus* isolates likely to be found in the clinical patient population under study is 0.03 µg/mL.

One dose regimen of APX001 will be evaluated in this study. In Phase 1 studies in healthy volunteers, the dose regimen in this study was safe and well tolerated. While the study allows a

switch to PO dosing as early as Day 4, the following table describes the estimated total drug $AUC_{(0-24)}$ and PTA for stasis in CE at the $MEC_{90}$ with the companion PO switch at Day 7.

| Load IV BID (Day 1 [Baseline]) | IV Maintenance QD (Days 2-7) | PO Maintenance QD (Days 8-42) | $AUC_{(0-24)}$ (Days 7/14/42) | PTAs at $MEC_{90}$ (stasis [Day 14]) |
|---|---|---|---|---|
| 1000 mg | 600 mg | 800 mg | 195/224/224 | ≥90% |

$AUC_{(0-24)}$ = area under the concentration-time curve from time 0 to 24 hours; BID = twice daily; IV = intravenous(ly); $MEC_{90}$ = minimal effective concentration in 90% of patients; PO = oral(ly); PTA = probability of target attainment; QD = once daily.

The dose regimen employed in this study provides a steady state AUC ≥200 µg·hr/mL, which is associated with efficacy (colony count and survival benefit) in immunocompromised mice with IPA. Additionally, formal PK-PD studies demonstrated that the dose regimen has favorable PTA for the majority of isolates anticipated to be encountered in this study.

Formal PK-PD for invasive rare mold infections (eg, *Fusarium* spp., *Scedosporium* spp., Mucorales fungi) have not yet been conducted. However, immunocompromised animal models of rare mold infections demonstrate colony count and survival benefit at AUCs provided by the dose regimen employed in this study.

**EFFICACY ENDPOINTS:**

Primary:

- All-cause mortality through Day 42.

  **Note:** All-cause mortality will represent the percentage of patients who die after the first dose of study drug through Day 42 from any cause.

Secondary:

- Global response at EOST

CCI [redacted]

**SAFETY VARIABLES:**

Safety assessments will include physical examinations, vital signs, clinical laboratory evaluations, 12-lead ECGs, any other exploration, and adverse events.

**WITHDRAWAL CRITERIA:**

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

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

If a patient must be discontinued from study drug administration for any of the above criteria, the patient will still be encouraged to continue visits and assessments necessary for appropriate safety follow-up.

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 E/T Visit. The reason for patient withdrawal must be documented in the electronic Case Report Form.

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

Withdrawn patients will not be replaced.

The study may be discontinued for any of the following reasons: 5 or more patients in the study (cumulative) experience the same Grade 2 (or higher) related adverse event (laboratory or clinical) which is coded in the same high-level group term per the Medical Dictionary for Regulatory Activities coding, throughout the duration of the study; a recommendation from the Data and Safety Monitoring Board (DSMB) based on other safety signals; lack of study drug availability; inability to enroll the study; or decision by a regulatory authority or the Sponsor.

**DATA REVIEW COMMITTEE:**

A DRC comprised of infectious disease experts will adjudicate the diagnosis of IMI at enrollment. This committee will also provide systematic assessment for clinical, mycological, radiological, and global responses at EOST and at the E/T Visit (if applicable).

Global responses will be classified as complete or partial response (categorized as treatment success), stable response, progression of disease, or death (categorized as treatment failure) according to prespecified criteria. Guidelines for the DRC are described in the DRC Charter.

**DATA AND SAFETY MONITORING BOARD:**

A DSMB comprised of members with pertinent expertise will be responsible for the periodic review of cumulative data from the study 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 patients and those yet to be recruited to the study, as well as the continuing validity and scientific merit of the study. The DSMB may recommend to the Sponsor that dosing in the study be suspended if, in the opinion of the DSMB, further dosing in the study would pose an inappropriate safety risk. Guidelines for what constitutes inappropriate safety risks are described in the DSMB Charter.

**ANALYSIS POPULATIONS:**

Intent-to-Treat Population/Safety Population:

The Intent-to-Treat (ITT)/Safety Population will include all patients who have received at least 1 dose of study drug.

Modified Intent-to-Treat Population:

The modified Intent-to-Treat (mITT) Population will include all patients in the ITT Population who satisfy the following criteria:

- Receive at least 1 dose of study drug
- C**ohort A:** Have a diagnosis of proven or probable IMI confirmed by the DRC
- CCI [redacted]

The mITT Population will be the primary population used for the efficacy analysis.

Per-Protocol Population:

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

- Meet the protocol's key inclusion criteria and exclusion criteria
- Have no major protocol violations

Pharmacokinetic Population:

The PK Population will include all patients who receive any amount of study drug and have evaluable PK data. The PK Population will be used for the PK analysis.

**STATISTICAL ANALYSES:**

Each Cohort will be analyzed and presented separately. There will be no pooling of data across the Cohorts.

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

The efficacy endpoints will be summarized descriptively, and all-cause mortality through Day 42 will be summarized.

Cohort A only: The 1-sided exact binomial test at the alpha = 0.1 level of significance will be used to test the hypothesis that the all-cause mortality at Day 42 is less than 45% (based on historical control data).

The percentage of patients with global response will be summarized.

CCI [redacted]

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

The PK 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 time point of collection. Summary statistics in the tabulation will include the number of observations, mean, standard deviation, percent coefficient of variation, 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:**

Approximately 50 patients will be dosed in this open-label, parallel-group, proof-of-concept study.

Cohort A:

Patients with proven or probable IMI are eligible for inclusion in the mITT Population, which is the primary efficacy population (DRC confirmation required of proven or probable IMI). The sample size calculation is based on the mITT Population from the first dose of APX001 through EOST (up to 6 weeks) for the all-cause mortality primary endpoint. A total of 24 patients in the mITT Population are needed, providing >90% power to detect the difference at a 1-sided significance level of 0.1, assuming an all-cause mortality of 20% for APX001 and 45% for adjusted amphotericin B-treated all-cause mortality from the historical control. Assuming 60% of dosed patients will be eligible to be included in the mITT Population, a dosing of approximately 40 patients allows for statistical testing of proof-of-concept for an estimate of 24 patients in the mITT Population.

CCI [redacted]

**SITES:** Up to 40 global sites

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| AML | Acute myeloid leukemia |
| AUC | Area under the concentration-time curve |
| $AUC_{(0-24)}$ | Area under the concentration-time curve from 0 to 24 hours |
| BAL | Bronchoalveolar lavage |
| BID | Twice daily |
| CBC | Complete blood count |
| CE | Conidial equivalent |
| CFR | Code of Federal Regulations |
| CRA | Clinical research associate |
| CT | Computed tomography |
| CTA | Clinical trial authorization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CVC | Central venous catheter |
| CYP | Cytochrome P450 |
| DDI | Drug-drug interaction |
| DRC | Data Review Committee |
| DSMB | Data and Safety Monitoring Board |
| E/T | Early Termination |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic data capture |
| EIU | Exposure In Utero |
| EORTC | European Organization for Research and Treatment of Cancer |
| EOST | End of Study Treatment |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GPI | Glycosylphosphatidylinositol |
| GWT1 | Glycosylphosphatidylinositol-anchored wall transfer protein 1 |
| IA | Invasive Aspergillosis |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |

| Abbreviation | Definition |
|---|---|
| IMI | Invasive mold infection |
| IMP | Investigational medicinal product |
| INR | International normalized ratio |
| IPA | Invasive pulmonary aspergillosis |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| IV | Intravenous(ly) |
| LAR | Legal authorized representative |
| MEC | Minimal effective concentration |
| $MEC_{90}$ | Minimal effective concentration in 90% of patients |
| mITT | Modified Intent-to-Treat |
| MSG | Mycosis Study Group |
| MycoMEIA | Aspergillosis urine test |
| OLAT | Other licensed antifungal therapy |
| PCR | Polymerase chain reaction |
| PD | Pharmacodynamic |
| PIGW | Phosphatidylinositol glycan anchor biosynthesis class W |
| PK | Pharmacokinetic(s) |
| PO | Oral(ly) |
| PT | Prothrombin time |
| PTA | Probability of target attainment |
| QD | Once daily |
| qPCR | Quantitative polymerase chain reaction |
| SAE | Serious adverse event |
| SOC | Standard of care |
| spp. | Species |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TEAE | Treatment-emergent adverse event |
| ULN | Upper limit of normal |

# 1 INTRODUCTION AND BACKGROUND INFORMATION

APX001, a first-in-class small molecule investigational drug candidate, is the water-soluble methyl phosphate prodrug of the active moiety APX001A. APX001 is rapidly converted *in vivo* to APX001A. APX001A has a novel mechanism of antifungal action, with broad spectrum activity against major fungal pathogens including *Candida* species (spp.) and *Aspergillus* spp.[1,2,3,4,5]

APX001A inhibits the fungal glycosylphosphatidylinositol (GPI)-anchored wall transfer protein 1 (GWT1) enzyme, a highly conserved inositol acylase that catalyzes an early step in the GPI-anchored biosynthesis pathway. This inhibition has pleiotropic effects on the fungal cell due to inhibition of cell wall mannoprotein localization, which compromises cell wall integrity, biofilm formation, germ tube formation, and fungal growth. APX001A does not inhibit phosphatidylinositol glycan anchor biosynthesis class W (PIGW) protein, the closest mammalian ortholog of the fungal GWT1 protein consistent with the potential for a significant target-based therapeutic window.[6,7]

APX001A has demonstrated broad *in vitro* antifungal activity against *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., *Scedosporium* spp., *Fusarium* spp., and Mucorales fungi, including activity against azole- and echinocandin-resistant strains. APX001A has demonstrated synergy with echinocandins (*Aspergillus*)[8] and azoles (*Candida*).[9] In 5-fluorouracil immunosuppressed mice with invasive mold infections (IMIs) (*Aspergillus fumigatus*, *Scedosporium prolificans*, and *Fusarium solani*), APX001 demonstrated statistically significantly improved survival rates and reduced pulmonary fungal colony counts.[8] In cyclophosphamide and cortisone acetate immunosuppressed mice with IMIs (*A. fumigatus*, *Scedosporium apiospermum*, *F. solani*, and *Rhizopus* spp.), APX001 demonstrated statistically significantly improved survival rates and reduced fungal burden.[4] Pharmacokinetic-pharmacodynamic (PK-PD) studies in immunosuppressed mice with invasive infections caused by *A. fumigatus* have shown that the area under the concentration-time curve (AUC) divided by the minimal effective concentration (MEC) ratio is the driver of efficacy.[10,11] The dose regimen employed in this study provides a steady state AUC ≥200 µg·hr/mL, which is associated with efficacy (colony count and survival benefit) in immunocompromised mice with invasive pulmonary aspergillosis (IPA). Additionally, formal PK-PD studies demonstrated that the dose regimen has favorable probability of target attainment (PTA) for the majority of isolates anticipated to be encountered in this study.

In Phase 1 clinical studies of APX001, the safety, tolerability, and PK of single and multiple ascending doses administered intravenously (IV) and orally (PO) have been studied. To date, a total of 197 healthy volunteers and 21 patients with acute myeloid leukemia (AML) have received APX001 across 5 Phase 1 studies (APX001-101, APX001-102, APX001-103, APX001-105, APX001-106). The duration of the multiple-dose regimens in these studies were 7, 14, and 42 days (6 weeks).

Phase 1 studies in healthy volunteers:

The highest doses administered in 2 dose escalation studies, APX001-101 and APX001-102, were 600 mg IV daily and 1000 mg PO daily for 14 days, respectively. The 6-week dose regimen administered in study APX001-105 is closely matching the dose and duration that will be employed in this protocol. In these 3 Phase 1 studies, all doses of APX001 were safe and well

tolerated. The majority of the treatment-emergent adverse events (TEAEs) were mild, transitory, and resolved without intervention. There were no severe or serious adverse events (SAEs) reported and no dose-limiting toxicities were observed. In all 3 Phase 1 studies, no laboratory test results nor results from other safety evaluations (physical examination, electrocardiogram [ECG], vitals) met the criteria for a TEAE nor did any result meet the a priori rules that prevented dose escalation.

In an additional dose escalation study, APX001-106, cohorts of healthy volunteers were administered 750 to 900 mg IV daily for 6 days, preceded by various loading doses. Some of the 900 mg dose regimens that employed high loading doses were not well tolerated. Consequently, at this time the 900 mg dose regimen will not be employed in this study.

APX001 and APX001A PK parameters for both single and multiple APX001 IV and PO doses in all 4 Phase 1 studies in healthy volunteers were linear and dose proportional. In the cohort embedded within the PO dose Phase 1 study APX001-102, APX001 demonstrated a favorable (ie APX001 was not a strong inhibitor or strong inducer of cytochrome P450 [CYP] enzymes) drug-drug interaction (DDI) profile. The relative bioavailability of the PO APX001 formulation is >90% in both the presence or absence of food, demonstrating that no food effect exists. In addition, the target AUCs anticipated for efficacy against both yeasts and molds have been achieved with both IV and PO dose formulations.

Further details of all the Phase 1 studies can be found in the Investigator's Brochure (IB).

Phase 1 studies in patients:

Study APX001-103 was conducted in patients with newly diagnosed AML undergoing induction chemotherapy. The objective of this study was to evaluate the safety, tolerability, and PK of IV and PO doses of APX001 in a patient population in which the investigational medicinal product (IMP) will be studied. There were no treatment-related SAEs reported during the study and none of the TEAEs reported as related to APX001 resulted in drug withdrawal/discontinuation. With the exception of 1 Grade 3 TEAE (hypertension), all TEAEs reported as related to APX001 were of the Common Terminology Criteria for Adverse Events (CTCAE) Grades 1 and 2.

All clinically significant abnormal clinical laboratory findings observed in this study, vital signs, ECG, and physical examination findings, can be attributed to the underlying condition of AML and the aggressive induction chemotherapy. Overall, the safety results from this study indicate daily doses of IV or PO APX001 given for 14 days were safe and well tolerated. No evidence of significant or additional risks of APX001 in this patient population was observed and no new safety concerns were identified.

Plasma concentrations and calculated exposures of APX001 and APX001A in study APX001-103 were lower than expected based on PK data from prior Phase 1 studies in healthy volunteers (APX001-101 and APX001-102). Potential factors that might contribute to this observation were thoroughly investigated and are described in the IB. These experiments confirmed that the plasma concentrations of APX001 and/or APX001A are dependent on hematocrit values. The lowered exposures observed in the APX001-103 PK results are most likely due to a dilution effect. When plasma concentrations are adjusted to account for this effect, PK parameters in APX001-103 are similar to those observed in prior healthy volunteer studies.

Further details of all the Phase 1 studies can be found in the IB.

In summary, APX001 has a novel mechanism of action with broad spectrum activity against *Candida* spp. (yeast) and *Aspergillus* spp. (mold), including activity against polyene and azole-resistant strains of *Aspergillus* spp. APX001 has demonstrated efficacy in a number of animal models of IMIs, including *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., and Mucorales fungi. To date, APX001 in both IV and PO formulations has been safe and well tolerated with a favorable DDI profile. APX001 has the potential to be used as a first-line agent for the treatment of IMIs.

## 1.1 Rationale

The need for improved treatment of invasive fungal diseases remains high, particularly with the growing number of immunocompromised patients, such as AML patients, non-Hodgkin's lymphoma patients, 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 rare molds (eg, *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, have DDIs, may not be available as IV and PO formulations, or have become increasingly ineffective due to the rise of drug resistant fungal strains.

Patients enrolled in this study will have limited or no antifungal treatment options due to documented/anticipated resistance, contraindication, intolerance, or lack of clinical response to standard of care (SOC) antifungal therapy. Under this setting, APX001 may have potential advantages over SOC antifungal therapy and thus supports its preliminary investigation for the treatment of IMIs.

Invasive aspergillosis is a well-described complication of severe influenza pneumonia. Severe influenza in critically ill patients is complicated by IPA in 7-23% of cases and associated with a case fatality rate of more than 50%. Since December 2019 coronavirus disease 2019 (COVID-19) has rapidly spread around the globe, becoming a pandemic threat. Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience major lung damage due to viral replication and the ensuing cytokine storm and complex inflammatory processes. The severe damage to lung tissue can lead to secondary infections. Most recently, cases of invasive pulmonary aspergillosis in patients with COVID-19 pneumonia with ARDS have been reported. Given this, it is important to consider the evaluation of APX001 in the management of these patients. As such, a separate Cohort has been incorporated into the protocol.

## 1.2 Risk/Benefit

### 1.2.1 Potential Risks

Patients participating in this study will receive a drug in clinical development that has not yet been approved by regulatory authorities. It is unknown if patients with invasive infections caused by *Aspergillus* spp. or rare molds will benefit from treatment with APX001. Based on histopathological findings in minipigs administered APX001 orally for 15 weeks, there is a potential that patients receiving treatment with APX001 may be at risk for liver toxicity; male patients may also be at risk for irreversible testicular toxicity (impaired fertility). Based on the findings in Phase 1 and 2 studies, there is a potential that patients receiving treatment with APX001 may develop headache, dizziness, fatigue, nausea, and vomiting. For more information on the APX001 safety profile please refer to the IB.

### 1.2.2 Potential Benefits

APX001 may have potential benefits compared to the current SOC for treatment of invasive infections caused by *Aspergillus* spp. or rare molds. Furthermore, APX001 has a differentiated safety profile, is available as IV and PO formulation, and may have fewer DDIs than the SOC treatments.

Patients with azole-resistant mold infections, including azole-resistant *A. fumigatus* and some rare molds (eg, *Fusarium* spp., *Scedosporium* spp., Mucorales fungi) typically receive IV treatment with a polyene. Polyenes have been associated with risk of nephrotoxicity, electrolyte imbalance, and infusion reactions which can be limiting in patient care.[12] APX001 has broad-spectrum antifungal activity with coverage against azole-resistant molds, and has the potential to be safer and easier to use compared to polyene.

APX001 may provide an advantage over a polyene for the treatment of "breakthrough" infections in patients receiving prophylaxis with mold active triazoles. APX001 has the potential to provide antifungal coverage for *A. fumigatus* and rare molds, without the potential for polyene-induced toxicities. With wide tissue penetration, APX001 may provide a benefit for the treatment of patients with invasive fungal infections in the eye and central nervous system.

APX001 may provide a benefit to patients with invasive fungal infections who are unable to receive treatment with a mold-active azole due to intolerance, toxicity, or clinically significant drug interactions. APX001 has the potential to provide broad-spectrum antifungal coverage, without the risk of hepatic or other azole-associated toxicities, and is expected to be less likely to induce clinically significant drug interactions.

Thus, APX001 is an investigational drug therapy that may fill an unmet need with a unique mechanism of action and no suspected cross-resistance to other mold active antifungals seen in animal models or surveillance to date.

Additionally, in those patients with a COVID-19 pneumonia who develop invasive aspergillosis, APX001 may provide a potential treatment for the secondary IPA infection.

### 1.2.3 Assessment of Potential Risks and Benefits

APX001 is a broad-spectrum antifungal agent, available in both IV and PO formulations, with wide-tissue distribution, including the eye and central nervous system. APX001 has a differentiated safety and DDI profile compared to SOC antifungal therapy. Patients with limited treatment options will be included in this investigational study if they have an invasive infection with *Aspergillus* or a rare mold, and there is a potential advantage of receiving treatment with APX001 compared to the current SOC.

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 proof-of-concept study is to evaluate the safety and efficacy of APX001 for the treatment of adult patients aged 18 years and above with IMIs caused by *Aspergillus* spp. or rare molds (eg, *Scedosporium* spp., *Fusarium* spp., and Mucorales fungi), who have limited antifungal treatment options.

### 2.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate global response at End of Study Treatment (EOST)
- Evaluate safety parameters of APX001
- Evaluate PK parameters of APX001

## 3 STUDY DESCRIPTION

### 3.1 Summary of Study Design

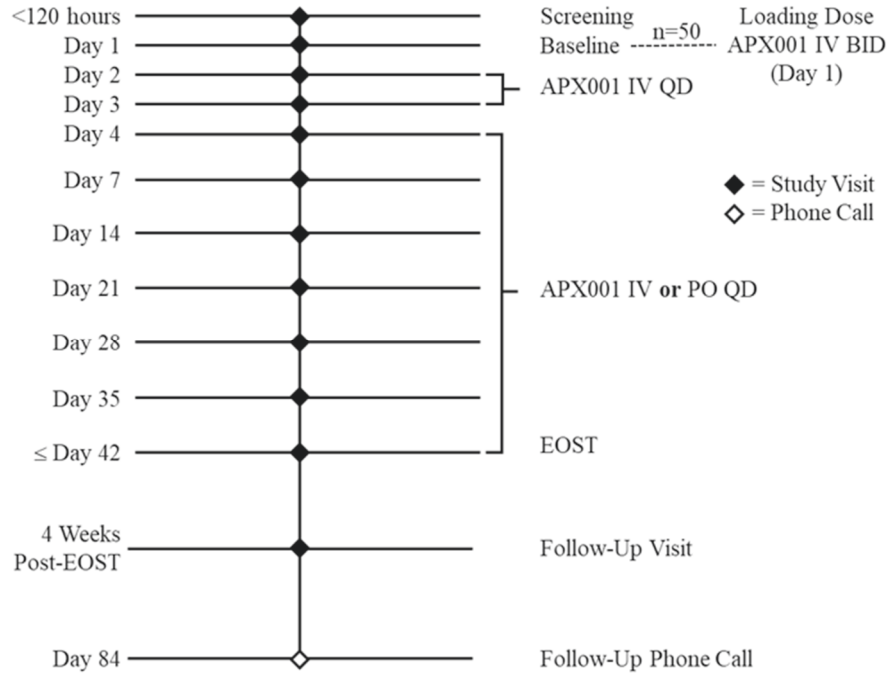
This is a Phase 2, multicenter, open-label, parallel-group, non-comparative study to evaluate the safety and efficacy of APX001 for the treatment of IMIs caused by *Aspergillus* spp. or rare molds (eg, *Scedosporium* spp., *Fusarium* spp., and Mucorales fungi). Patients 18 years of age or older will undergo Screening procedures for up to 5 days, following which eligible patients will participate in the study drug Treatment Period for up to 6 weeks, with a Follow-Up Visit 4 weeks after EOST, and a Follow-Up Phone Call 12 weeks after Day 1 (Day 84). The total duration of a patient's participation in the study will be approximately 12 weeks, inclusive of the follow-up telephone call required on Day 84. Patients who require treatment for longer than 6 weeks can be switched to other licensed antifungal therapy (OLAT) at the discretion of the Investigator and in consultation with the Medical Monitor if the situation allows.

This study will be conducted at up to 40 global sites.

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**




BID = twice daily; EOST = End of Study Treatment; IV = intravenous(ly); PO = oral(ly); QD = once daily.

This study will consist of CCI parallel cohorts. Cohort A will enroll up to 40 patients, CCI [redacted] Each cohort has a single treatment arm consisting of a loading dose of 1000 mg APX001, administered over 3 hours by IV infusion twice daily (BID) within the first 24 hours after initiation of the first infusion. On Days 2 and 3, 600 mg APX001 will be administered over 3 hours by IV infusion once daily (QD). From Day 4 through EOST, the IV dose remains 600 mg APX001 administered over 3 hours by IV infusion QD, or patients may be switched to PO administration of 800 mg APX001 QD. Antiemetics (preferably a 5-$HT_3$ antagonist such as ondansetron or granisetron) should be administered in patients who develop nausea and/or vomiting associated with APX001 administration (both IV and oral), and oral APX001 may be given with food. Additionally, prophylactic antiemetics, (preferably a 5-$HT_3$ antagonist such as ondansetron or granisetron) may be administered prior to dosing (both IV and oral) in patients considered at higher risk of gastrointestinal intolerance. The decision to switch from IV to PO APX001 will be based on the Investigator's discretion and can be done on any day from Day 4 onwards. Patients will remain hospitalized for at least 2 days following the initial switch from IV to PO so that their tolerance to the oral medication may be evaluated and treated as necessary. Patients may be switched between IV and PO as needed. Oral APX001 may be given as an outpatient.

Administration of APX001 should not continue for longer than 6 weeks (inclusive of the loading dose [Day 1]). If an Investigator documents an improvement or resolution in clinical signs and symptoms prior to 6 weeks, eg, if follow-up imaging (as applicable) shows improvement; or a

mycological response (if amenable to repeat sampling) is observed, the Investigator may choose to discontinue dosing. Patients will be requested to return for an EOST and Follow-Up Visit and to agree to a Follow-Up Phone Call.

Table 1 describes dosing for the study.

**Table 1. Patient Enrollment by Dosing Arm**

| Load Dosing Day 1 (Baseline) | Maintenance Dosing Days 2-42 [1] | | |
|---|---|---|---|
| **IV BID** | **IV QD [1]** | **PO QD [1,2]** | **Total Enrolled (n)** |
| 1000 mg | 600 mg | 800 mg | 50 |

1. On Days 2 and 3, APX001 will be administered over 3 hours by IV infusion QD. From Day 4 through EOST, the IV dose remains 600 mg APX001 administered over 3 hours by IV infusion QD, or patients may be switched to PO administration of 800 mg APX001 QD.
2. Patients may switch back and forth between IV and PO as needed. Oral APX001 may be given as an outpatient.

BID = twice daily; EOST = End of Study Treatment; IV = intravenous(ly); PO = oral(ly); QD = once daily.

Blood samples (serum and plasma) and other diagnostic specimens (eg, bronchoalveolar lavage [BAL]) will be collected at Screening for pathogen DNA analysis utilizing next-generation sequencing (optional) and/or polymerase chain reaction (PCR) analysis. Urine samples will be collected at Screening for the aspergillosis urine test (MycoMEIA).

Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected predose and 3 hours post start of infusion on Days 1 (Baseline), 2, 3, 7, and 14; predose on Days 28 and 42; and at any time in clinic at EOST, the Follow-Up Visit; and the Early Termination (E/T) Visit (if applicable). Additionally, for patients who switch to PO dosing, samples should be collected predose and at 3 hours postdose on the initial day of PO dosing, Day 7, and Day 14 and at any time in clinic on Days 28 and 42, at EOST, at the Follow-Up Visit, and at the E/T Visit (if applicable). If the patient switches back to IV dosing, PK samples should be collected predose and at 3 hours post start of infusion on that day as well.

Serum samples for analysis of CCI [redacted] will be collected at Screening; predose on Days 1 (Baseline), 2, and 3; on Days 7, 14, 28, and 42; at EOST; and at the E/T Visit (if applicable).

Serum samples for analysis of C[redacted] will be collected at Screening; predose on Day 1 (Baseline); on Days 14, 28, and 42; at EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable).

Assessment of clinical signs and symptoms will be conducted at Screening; at all visits from Day 1 (Baseline) through EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable).

Radiological assessments (including computed tomography [CT] scans of the chest, sinuses, and/or abdomen) will be performed during Screening (SOC scans within 3 days of Screening will be accepted as long as the scans can be provided to the central reader). Computed tomography scans of the chest, sinuses, and/or abdomen will be repeated on Day 14 and at EOST, and if clinically indicated on Days 7, 21, 28, 35, and 42; at the Follow-Up Visit; and at the E/T Visit (if applicable).

Samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) will be collected and processed for culture and susceptibility by the local laboratory at Screening, and as clinically indicated at any visit from Day 1 (Baseline) through EOST, at the Follow-Up Visit, and at the E/T Visit (if applicable). Screening samples for fungal cultures to determine eligibility may have been collected as SOC within 120 hours prior to initial dosing. All fungal isolates cultured at the local laboratory will be sent to the central mycology reference laboratory for confirmation of identification and susceptibility testing.

Bronchoalveolar lavage samples will be collected per SOC for culture at the local laboratory and CCI testing at the central laboratory as clinically indicated at any visit from Screening throughout the study.

The safety and tolerability of APX001 will be evaluated through physical examination findings, clinical signs and symptoms, vital signs, changes in clinical laboratory tests, 12-lead ECGs, any other exploration, and monitoring of adverse events and concomitant medications or procedures.

### 3.2 Study Indication

APX001 is indicated for the treatment of patients with IMIs caused by *Aspergillus* spp. or rare molds.

## 4 SELECTION AND WITHDRAWAL OF PATIENTS

### 4.1 Inclusion Criteria

This study will enroll male and female patients aged 18 years and above with a confirmed diagnosis of invasive aspergillosis or invasive rare mold infection. Patients will have limited or no treatment options due to documented/anticipated resistance, contraindication, intolerance, or lack of clinical response to SOC antifungal therapy, as advocated by the relevant regional/country treatment guidelines. The study will enroll CCI cohorts, Cohort A CCI Up to 40 patients will be enrolled in Cohort A, and these patients will have an IMI which was diagnosed according to the EORTC/MSGERC criteria. CCI

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

1. Males or females, 18 years or older.
2. Patients with IMI caused by *Aspergillus* spp. Patients who present with IMI due to other filamentous fungi (eg, *Scedosporium* spp., *Fusarium* spp., and Mucorales fungi such as *Mucor* spp. or *Rhizopus* spp.) may also be enrolled.
   - Cohort A: Diagnosis of proven or probable IMI will be defined in accordance with the Revision and Update of the Consensus Definitions of Invasive Fungal Disease from the EORTC/MSGERC (Donnelly et al., 2019)[13] (see APPENDIX D and APPENDIX E).
   - CCI

3. Have limited or no treatment options due to documented or anticipated resistance, contraindication, intolerance, or lack of clinical response to SOC antifungal therapy, as advocated by the relevant regional/country treatment guidelines.
4. Patients where the Investigator considers that there is a potential advantage of using APX001 over current SOC (eg, broad spectrum of activity, activity against resistant mold pathogens, IV and PO formulations, favorable DDI profile, favorable hepatic and renal safety profile, wide tissue distribution including brain), and/or where SOC antifungal therapy carries significant risk of toxicity or treatment failure (eg, emergence of IMI during antifungal prophylaxis, DDI risk, safety/toxicity risk, site of infection not accessible by SOC).
5. Female patients of nonchildbearing potential must be 1 of the following:
    - Surgically sterile (hysterectomy, bilateral tubal ligation, bilateral salpingectomy, and/or bilateral oophorectomy).
    - Postmenopausal (amenorrhea for >12 months without an alternative medical cause).
6. Females of childbearing potential (ie, not postmenopausal or surgically sterilized) must have a negative urine or serum pregnancy test result within 96 hours prior to Baseline (ie, predose on Day 1). Participating females of childbearing potential with male partners, and males with female partner(s) of childbearing potential, must agree to use 2 forms of contraception, 1 of which must be highly effective and the other an acceptable barrier method (male or female condom), throughout the duration of the study and for 90 days following the last study drug administration. Highly effective methods of contraception include the following:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (PO, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (PO, injectable, or implantable), intrauterine device, or intrauterine hormone-releasing system.
    - Bilateral tubal occlusion or vasectomized partner.

      **Note:** A vasectomized partner is a highly effective method of contraception, provided that the male partner is the sole sexual partner of the study patient who is a female of childbearing potential and that the vasectomized partner has received medical assessment of surgical success.
    - Sexual abstinence.

      **Note:** 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 (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
7. Male patients must agree to abstain from sperm donation and use condoms with spermicide during sexual intercourse between Screening and at least 90 days after administration of the last dose of study drug. Male patients must ensure nonpregnant female partner(s) of childbearing potential comply with the contraception requirements in Inclusion Criterion 6.

8. Patients must be willing to participate in the study, to give written informed consent, and to comply with the study restrictions; where permitted by local regulations, written informed consent from a legal authorized representative (LAR) will be obtained for patients who are unable to give consent.
9. CCI [redacted]

## 4.2 Exclusion Criteria

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

1. Refractory hematologic malignancy with no potential to respond to additional chemotherapy.
2. Chronic aspergillosis, aspergilloma, or allergic bronchopulmonary aspergillosis.
3. Treatment with systemic (PO, IV, or inhaled) antifungal therapy with a mold-active azole or polyene for ≥120 hours immediately before initial dosing.

   **Note**: An exception is antifungal prophylaxis, for which there is no restriction on duration but must be stopped upon commencement of treatment with APX001.

   Additionally, patients with invasive fungal infection caused by a mold with documented resistance to or lack of coverage by the prior SOC in question, as well as patients with polyene-induced renal toxicity or those who have received empirical treatment with echinocandins may have received >120 hours prior treatment and remain eligible for the study. These patients must be discussed with the Medical Monitor prior to enrollment, and prior treatment in this case should not exceed >168 hours.

4. Evidence of significant hepatic dysfunction, defined as any of the following:
   - Total bilirubin >3 × the upper limit of normal (ULN) unless isolated hyperbilirubinemia or due to documented Gilbert's disease.
   - Alanine transaminase or aspartate transaminase ≥5 × ULN.
   - Severe or moderate hepatic impairment (Child-Pugh Score >6 points) at any time during 2 weeks prior to dosing. The Child-Pugh score of > 6 is applicable only to patients with hepatic dysfunction and cirrhosis.
5. Ongoing medical history of neurological disorders including abnormal movements or seizures. **Note**: A current CNS mold infection as well as a stable history of peripheral neuropathy will not be considered exclusionary.
6. Patient receiving palliative care only.
7. Known hypersensitivity or other serious reaction to APX001 or any ingredient of APX001.
8. Patient is lactating and/or pregnant or intending to be pregnant during the duration of the study.

9. Investigational drug administered within 30 days or 5 terminal half-lives prior to study drug dosing (whichever is longer).

   **Note**: Participation in research protocols for approved agents for the treatment of an underlying condition is permitted.

10. Prior participation in this study or any previous study of APX001.
11. Concomitant use of medication that is a strong inducer (ie, rifampin, carbamazepine, phenytoin, rifabutin, efavirenz, nevirapine, phenobarbital, modafinil, St. John's Wort, enzalutamide) of CYP enzymes.
12. Any other condition or laboratory abnormality that, in the opinion of the Investigator or the Sponsor, would put the patient at unacceptable risk for participation in the study or may interfere with the assessments included in the study.
13. Patients on mechanical ventilation
14. Cohort A only: Suspected or confirmed COVID-19 or Influenza A/B infection.
15. Patients with severe renal impairment as determined by estimated glomerular filtration rate (eGFR) <30 mL/min /1.173 $m^2$ calculated by CKD-EPI, including patients on dialysis
16. Patients with a Karnofsky Performance Status ≤ 30 at screening

### 4.3 Withdrawal Criteria

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

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

If a patient must be discontinued from study drug administration for any of the above criteria, the patient will still be encouraged to continue visits and assessments necessary for appropriate safety follow-up.

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 E/T Visit. The reason for patient withdrawal must be documented in the electronic Case Report Form (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.

## 4.4 Discontinuation Rules

### 4.4.1 Study Discontinuation Rules

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

Additionally, the study may be discontinued for any of the following reasons: 5 or more patients in the study (cumulative) experience the same Grade 2 (or higher) related adverse event (laboratory or clinical) which is coded in the same high-level group term per the Medical Dictionary for Regulatory Activities coding, throughout the duration of the study; lack of study drug availability; inability to enroll the study; or decision by a regulatory authority or the Sponsor.

### 4.4.2 Patient Discontinuation Rules

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. Whenever feasible, the Investigator should discuss the patient situation with the Medical Monitor prior to discontinuation of the patient.

A patient who has discontinued study drug administration will still be encouraged to continue visits and assessments necessary for appropriate safety follow-up, and to complete the full panel of assessments scheduled for the E/T 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.

### 4.5 Premature Study Termination

The study may be terminated prematurely by the Sponsor or a regulatory authority if there is sufficient reasonable cause. Reasonable cause includes reaching a discontinuation rule (Section 4.4), evidence of inappropriate risk for study patients, lack of study product availability, or reason to conclude that it will not be possible to collect the data necessary to reach the study's objectives and it is therefore not ethical to continue enrollment of more patients.

In addition, an independent DSMB may terminate the study 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.

The Sponsor will promptly inform the Investigators and the regulatory authority(ies) of the termination of the study and the reason(s) for the termination. The Investigators are responsible for promptly informing patients that they must discontinue study drug. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will also be informed promptly and provided the reason(s) for the termination, as specified by the applicable regulatory requirement(s).

## 5 STUDY TREATMENTS

### 5.1 Treatment Groups

Patients in Cohorts A and B will receive the same treatment. Patients will receive a loading dose of 1000 mg APX001, administered over 3 hours by IV infusion BID within the first 24 hours after initiation of the first infusion. On Days 2 and 3, 600 mg APX001 will be administered over 3 hours by IV infusion QD. From Day 4 through EOST, the IV dose remains 600 mg APX001 administered over 3 hours by IV infusion QD, or patients may be switched to PO administration of 800 mg APX001 QD. The decision to switch from IV to PO APX001 will be based on the Investigator's discretion.

### 5.2 Rationale for Dosing

In a PK-PD IPA study, immunocompromised mice were infected with 6 strains of *A. fumigatus*, inclusive of wild type, azole-resistant, and echinocandin-resistant strains. Groups of animals were dosed with APX001 at different dose fractionations. The AUC from time 0 to 24 hours ($AUC_{(0-24)}$)/MEC ratio was determined to be the PK-PD index that best correlated with antifungal efficacy as assessed by fungal burden (conidial equivalent [CEs] measured by real time quantitative PCR [qPCR]) in lung homogenates. The stasis and 1-logarithm drop endpoints were defined as the quantity of *A. fumigatus* in CEs just prior to APX001 administration compared to CEs at the endpoint of assessment at 96 hours. The median total drug AUC/MEC which achieved stasis and 1-logarithm kill endpoints for each *A. fumigatus* strain were 2801.6 and 5258.2.[14]

The clinical isolates surveillance data from 2017,2018, and 2019 of APX001A antifungal activity against *Aspergillus* spp. shows that the majority (96%) of *Aspergillus* isolates have MEC values of 0.008 to 0.03 µg/mL. The MEC in 90% of patients ($MEC_{90}$) for *Aspergillus* isolates likely to be found in the clinical patient population under study is 0.03 µg/mL.

One dose regimen of APX001 will be evaluated in this study. In Phase 1 studies in healthy volunteers, the dose regimen in this study was safe and well tolerated. While the study allows a switch to PO dosing as early as Day 4, Table 2 describes the estimated total drug $AUC_{(0-24)}$ and PTA for stasis in CE at the $MEC_{90}$ with the companion PO switch at Day 7.

**Table 2. Estimated Area Under the Curve and Probability of Target Attainment for the APX001 Dose Regimen**

| Load IV BID (Day 1 [Baseline]) | IV Maintenance QD (Days 2-7) | PO Maintenance QD (Days 8-42) | $AUC_{(0-24)}$ (Days 7/14/42) | PTAs at $MEC_{90}$ (stasis [Day 14]) |
|---|---|---|---|---|
| 1000 mg | 600 mg | 800 mg | 195/224/224 | ≥90% |

$AUC_{(0-24)}$ = area under the concentration-time curve from time 0 to 24 hours; BID = twice daily; IV = intravenous(ly); $MEC_{90}$ = minimal effective concentration in 90% of patients; PO = oral(ly); PTA = probability of target attainment; QD = once daily.

The dose regimen employed in this study provides a steady state AUC ≥200 µg·hr/mL, which is associated with efficacy (colony count and survival benefit) in immunocompromised mice with IPA. Additionally, formal PK-PD studies demonstrated that the dose regimen has favorable PTA for the majority of isolates anticipated to be encountered in this study.

Formal PK-PD for invasive rare mold infections (eg. *Fusarium* spp., *Scedosporium* spp., Mucorales fungi) have not yet been conducted. However, immunocompromised animal models of rare mold infections demonstrate colony count and survival benefits at AUCs provided by the dose regimen employed in this study.

## 5.3 Randomization and Blinding

This is an 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 an aqueous solution formulated at a concentration of 20 mg/mL. The formulation consists of APX001 drug substance, sodium chloride, potassium phosphate (dibasic and monobasic), hydrochloric acid, sodium hydroxide, and water for injection. A 20 or 50 mL sterile glass vial is filled with 17.5 or 35 mL of APX001 injection, respectively, yielding 350 or 700 mg/vial. APX001 injection will be further diluted and administered as an IV infusion. Preparation and dilution instructions will be provided in the Pharmacy Manual.

The formulation of 200 mg tablets consists of APX001 drug substance, microcrystalline cellulose, colloidal silicon dioxide, pregelatinized starch, povidone, anhydrous dibasic calcium phosphate, talc, and magnesium stearate. All tablets are coated with an aqueous coated film system and

purified water. 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

APX001 for IV administration will be delivered via central venous catheter (CVC) or peripheral IV line access according to SOC. APX001 for IV administration must not be infused into the same CVC or peripheral line access that is being used concurrently for the administration of other medications. Volumetric infusion pumps will be used during the administration of APX001 to ensure the prescribed volume is delivered to the patient. The infusion rate and total volume administered will be recorded on the patient's IV bag label and in their source documentation.

A loading dose of 1000 mg APX001 will be administered over 3 hours by IV infusion BID within the first 24 hours after initiation of the first infusion. On Days 2 and 3, 600 mg APX001 will be administered over 3 hours by IV infusion QD. From Day 4 through EOST, the IV dose remains 600 mg APX001 administered over 3 hours by IV infusion QD, or patients may be switched to PO administration of 800 mg APX001 QD.

Patients who have completed a minimum of 3 days of IV APX001 may be switched from IV to PO APX001 if they are able to ingest medication PO and the Investigator deems it is in the patient's best interest to do so. The switch to PO can be done on any day from Day 4 onwards. Patients will remain hospitalized for at least 2 days following the initial switch from IV to PO so that their tolerance to the oral medication may be evaluated and treated as necessary. Oral APX001 may be given with food, and prophylactic antiemetics may be administered. Patients may be switched between IV and PO as needed. Oral APX001 may be given as an outpatient.

Study drug will not be administered for longer than 6 weeks (inclusive of the loading dose [Day 1]). If an Investigator documents an improvement or resolution in clinical signs and symptoms prior to 6 weeks, eg, if follow-up imaging (as applicable) shows improvement; or a mycological response (if amenable to repeat sampling) is observed, the Investigator may choose to discontinue dosing. Patients will be requested to return for an EOST and Follow-Up Visit and to agree to a Follow-Up Phone Call. Patients who still require treatment after EOST should continue on OLAT.

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.

Intravenous APX001 will be administered inpatient by clinic staff while PO APX001 may be administered by clinic staff while hospitalized, or independently by patients at home. The acceptable dosing window for APX001 is ±1 hour on Day 1 (Baseline), and ±2 hours on Day 2 through EOST.

### 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. During the Treatment Period, outpatients will be asked to bring the dosing diary and study drug bottles with them to every clinic visit.

### 5.5.5 Storage and Accountability

APX001 injection will be stored at -20°C and tablets will be stored at 2°C 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 APX001 as a Victim Substrate for Cytochrome P450 Drug-drug Interactions

APX001 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 (eg, rifampin, carbamazepine, phenytoin, rifabutin) are excluded from participating in the study.

Concomitant use of multiple medications that are strong inhibitors of different CYP pathways may increase levels of APX001A, which in consequence may potentially affect the safety risk of APX001 administration. Caution should be advised when coadministering any medication that is a strong inhibitor of any CYP(s), especially if another medication(s) that the patient is taking is also a strong inhibitor of CYP(s).

#### 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 DDIs will depend on the extent of induction or inhibition and therapeutic margin of the specific victim substrate(s).

Coadministration 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.

Refer to https://drug-interactions.medicine.iu.edu/MainTable.aspx for an exhaustive list of CYP enzyme inducers and inhibitors.

### 5.6.2 Restricted Medications and/or Procedures

Eligible patients are prohibited from receiving treatment with systemic (PO, IV, or inhaled) antifungal therapy with a mold-active azole or polyene for ≥120 hours immediately before initial dosing. The exception to this rule applies to patients who receive antifungal prophylaxis, for which there is no restriction on duration but must be stopped upon commencement of treatment with APX001. Additionally, patients with invasive fungal infection caused by a mold with documented resistance to or lack of coverage by the prior SOC in question, as well as patients with polyene-induced renal toxicity or those who have received empirical treatment with echinocandins, may have received >120 hours prior treatment and remain eligible for the study. These patients must be discussed with the Medical Monitor prior to enrollment, and prior treatment in this case should not exceed >168 hours. Once on study, patients may not receive concomitant systemic antifungal therapy for the treatment of aspergillosis while they are receiving APX001.

Patients cannot have received any investigational drug within 30 days or 5 terminal half-lives prior to dosing (whichever is longer). Participation in research protocols for approved agents for the treatment of an underlying condition is permitted.

### 5.6.3 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 through the Follow-Up Visit 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. Use of chemotherapeutic agents earlier than 14 days prior to study drug administration will also 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. Only those patients who have transient loss of capacity (eg, septic shock, sedation) can have an 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 Screening Visit (Day -5 to Day -1)

The following procedures will be performed at the Screening Visit:

- Obtain informed consent.
- Record demographic information.
- Cohort A: Record EORTC/MSGERC classification.
- [redacted]
- Assess disease severity using the Eastern Cooperative Oncology Group Performance Status and Karnofsky Performance Status. Assess P/F ratio (if patient is ventilated).
- Record medical history.
- Perform urine or serum pregnancy test on women of childbearing potential only.
- Perform a complete physical examination including assessment of general appearance, skin, eyes, heart, chest, abdomen, and a neurological examination and measure height and weight.
- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform 12-lead ECG in triplicate.
- Perform clinical laboratory assessments (serum chemistry, hematology [including complete blood count (CBC) with differential], coagulation [including prothrombin time (PT)/international normalized ratio (INR)], and urinalysis).
- Collect blood samples (serum and plasma) and other diagnostic specimens (eg, BAL) for pathogen DNA analysis utilizing next-generation sequencing (optional) and/or PCR analysis, analysis of [redacted] and [redacted]
- Collect urine sample for MycoMEIA.
- Perform CT scan of the chest, sinuses, and/or abdomen.
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate).
- Collect BAL samples per SOC for culture and [redacted] testing as clinically indicated.

- Record prior and concomitant medications.
- Assess adverse events.

### 6.3 Treatment Period (Day 1 up to Day 42)

All patients, including those enrolled on the basis of preliminary mycological evidence as noted in APPENDIX E, will undergo the stated study procedures below. After inclusion into the study, every effort should be made to upgrade the certainty of diagnosis of invasive fungal disease.

#### 6.3.1 Day 1 (Baseline)

The following procedures will be performed on Day 1 (Baseline):

- Perform urine or serum pregnancy test on women of childbearing potential only if the Screening Visit occurred ≥96 hours prior to Day 1 (Baseline).
- Perform a neurological examination (all patients) and a symptom-directed physical examination as clinically indicated (ie, new signs or symptoms and follow-up on earlier findings) and measure weight.
- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform clinical laboratory assessments (serum chemistry, hematology [including CBC with differential], coagulation [including PT/INR], and urinalysis).
- Collect serum samples for analysis of CCI and C predose.
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.
- Collect BAL samples per SOC for culture and CCI testing as clinically indicated.
- Administer a loading dose of 1000 mg APX001 by IV infusion over 3 hours BID within the first 24 hours after initiation of the first infusion.
- Collect plasma PK samples predose and 3 hours post start of infusion.
- Record concomitant medications.
- Assess adverse events.

#### 6.3.2 Day 2

The following procedures will be performed on Day 2:

- Assess clinical signs and symptoms.
- Collect serum sample for analysis of CCI predose.

- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.
- Collect BAL samples per SOC for culture and CCI testing as clinically indicated.
- Administer 600 mg APX001 by IV infusion over 3 hours QD.
- Collect plasma PK samples predose and 3 hours post start of infusion.
- Record concomitant medications.
- Assess adverse events.
- Review accountability for all returned study drug.

### 6.3.3 Day 3

The following procedures will be performed on Day 3:

- Assess clinical signs and symptoms.
- Perform 12-lead ECG in triplicate.
- Collect serum sample for analysis of CCI predose.
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.
- Collect BAL samples per SOC for culture and CCI testing as clinically indicated.
- Administer 600 mg APX001 by IV infusion over 3 hours QD.
- Collect plasma PK samples predose and 3 hours post start of infusion.
- Record concomitant medications.
- Assess adverse events.
- Review accountability for all returned study drug.

### 6.3.4 Day 7 (± Day)

The following procedures will be performed on Day 7 (±1 day):

- Perform a neurological examination (all patients) and a symptom-directed physical examination as clinically indicated (ie, new signs or symptoms and follow-up on earlier findings) and measure weight.
- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform 12-lead ECG in triplicate.

- Perform clinical laboratory assessments (serum chemistry, hematology [including CBC with differential], coagulation [including PT/INR], and urinalysis).
- Perform CT scan if clinically indicated.
- Collect serum sample for analysis of CCI [redacted].
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.
- Collect BAL samples per SOC for culture and CCI [redacted] testing as clinically indicated.
- Administer 600 mg APX001 by IV infusion over 3 hours QD or 800 mg APX001 PO QD.
- Collect plasma PK samples predose and 3 hours post start of infusion or PO dosing.
- Record concomitant medications.
- Assess adverse events.
- Review accountability for all returned study drug.

### 6.3.5 Day 14 (± Day)

The following procedures will be performed on Day 14 (±1 day):

- Perform a neurological examination (all patients) and a symptom-directed physical examination as clinically indicated (ie, new signs or symptoms and follow-up on earlier findings) and measure weight.
- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform 12-lead ECG in triplicate.
- Perform clinical laboratory assessments (serum chemistry, hematology [including CBC with differential], coagulation [including PT/INR], and urinalysis).
- Perform CT scan.
- Collect serum samples for analysis of CCI [redacted] and C [redacted].
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.
- Collect BAL samples per SOC for culture and CCI [redacted] testing as clinically indicated.
- Administer 600 mg APX001 by IV infusion over 3 hours QD or 800 mg APX001 PO QD.
- Collect plasma PK samples predose and 3 hours post start of infusion or PO dosing.
- Record concomitant medications.
- Assess adverse events.

- Review accountability for all returned study drug.

### 6.3.6 Day 21 (± Days)

The following procedures will be performed on Day 21 (±2 days):

- Perform a neurological examination (all patients) and a symptom-directed physical examination as clinically indicated (ie, new signs or symptoms and follow-up on earlier findings) and measure weight.
- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform CT scan if clinically indicated.
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.
- Collect BAL samples per SOC for culture and CCI testing as clinically indicated.
- Administer 600 mg APX001 by IV infusion over 3 hours QD or 800 mg APX001 PO QD.
- Record concomitant medications.
- Assess adverse events.
- Review accountability for all returned study drug.

### 6.3.7 Day 28 (± Days)

The following procedures will be performed on Day 28 (±2 days):

- Perform urine or serum pregnancy test on women of childbearing potential only.
- Perform a neurological examination (all patients) and a symptom-directed physical examination as clinically indicated (ie, new signs or symptoms and follow-up on earlier findings) and measure weight.
- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform clinical laboratory assessments (serum chemistry, hematology [including CBC with differential], coagulation [including PT/INR], and urinalysis).
- Perform CT scan if clinically indicated.
- Collect serum samples for analysis of CCI and C .
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus spirate, tracheal aspirate) as clinically indicated.

- Collect BAL samples per SOC for culture and CCI testing as clinically indicated.
- Administer 600 mg APX001 by IV infusion over 3 hours QD or 800 mg APX001 PO QD.
- Collect plasma PK samples predose for IV dosing or at any time in clinic for PO dosing.
- Record concomitant medications.
- Assess adverse events.
- Review accountability for all returned study drug.

### 6.3.8 Day 35 (± Days)

The following procedures will be performed on Day 35 (±2 days):

- Perform a neurological examination (all patients) and a symptom-directed physical examination as clinically indicated (ie, new signs or symptoms and follow-up on earlier findings) and measure weight.
- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform CT scan if clinically indicated.
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.
- Collect BAL samples per SOC for culture and CCI testing as clinically indicated.
- Administer 600 mg APX001 by IV infusion over 3 hours QD or 800 mg APX001 PO QD.
- Record concomitant medications.
- Assess adverse events.
- Review accountability for all returned study drug.

### 6.3.9 Day 42 (± Days)

If EOST procedures are performed after Day 39, Day 42 procedures will not be required. The following procedures will be performed on Day 42 (±2 days):

- Administer 600 mg APX001 by IV infusion over 3 hours QD or 800 mg APX001 PO QD.
- Record Investigator assessment of global response.
- Assess survival status.
- Perform urine or serum pregnancy test on women of childbearing potential only.
- Perform a complete physical examination including assessment of general appearance, skin, eyes, heart, chest, abdomen, and a neurological examination and measure weight.

- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform 12-lead ECG in triplicate.
- Perform clinical laboratory assessments (serum chemistry, hematology [including CBC with differential], coagulation [including PT/INR], and urinalysis).
- Perform CT scan if clinically indicated.
- Collect serum samples for analysis of CCI and C[redacted].
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.
- Collect BAL samples per SOC for culture and CCI testing as clinically indicated.
- Collect plasma PK samples predose for IV dosing or at any time in clinic for PO dosing.
- Record concomitant medications.
- Assess adverse events.
- Review accountability for all returned study drug.

### 6.4 End of Study Treatment (+2 Days)

The EOST should occur as soon as possible following completion of APX001 dosing and within 2 days of last dose. The following procedures will be performed at EOST (+2 days):

- Record Investigator assessment of global response.
- Assess survival status.
- Perform urine or serum pregnancy test on women of childbearing potential only.
- Perform a complete physical examination including assessment of general appearance, skin, eyes, heart, chest, abdomen, and a neurological examination and measure weight.
- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform 12-lead ECG in triplicate.
- Perform clinical laboratory assessments (serum chemistry, hematology [including CBC with differential], coagulation [including PT/INR], and urinalysis).
- Perform CT scan.
- Collect serum samples for analysis of CCI and C[redacted].
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.

- Collect BAL samples per SOC for culture and CCI testing as clinically indicated.
- Collect plasma PK samples at any time in clinic.
- Record concomitant medications.
- Assess adverse events.
- Review accountability for all returned study drug.

### 6.5 Follow-Up Visit (4 Weeks After End of Study Treatment [±3 Days])

The following procedures will be performed at the Follow-Up Visit (4 weeks after EOST [±3 days]):

- Perform urine or serum pregnancy test on women of childbearing potential only.
- Perform a neurological examination (all patients) and a symptom-directed physical examination as clinically indicated (ie, new signs or symptoms and follow-up on earlier findings) and measure weight.
- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform CT scan if clinically indicated.
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.
- Collect BAL samples per SOC for culture and CCI testing as clinically indicated.
- Collect serum sample for analysis of C [redacted].
- Collect plasma PK samples at any time in clinic.
- Record concomitant medications.
- Assess adverse events.

### 6.6 Follow-Up Phone Call (Day 84 [±3 Days])

The Follow-Up Phone Call will occur 12 weeks (±3 days) after Day 1 (Baseline).

The following procedures will be performed during the Follow-Up Phone Call (Day 84 [±3 days]):

- Assess survival status.

### 6.7 Early Termination Visit and Withdrawal Procedures

For patients who are withdrawn from the study prior to completion, the following procedures will be performed at an E/T Visit:

- Perform urine or serum pregnancy test on women of childbearing potential only.
- Perform a complete physical examination including assessment of general appearance, skin, eyes, heart, chest, abdomen, and a neurological examination and measure weight.
- Assess clinical signs and symptoms.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Perform 12-lead ECG in triplicate.
- Perform clinical laboratory assessments (serum chemistry, hematology [including CBC with differential], coagulation [including PT/INR], and urinalysis).
- Perform CT scan if clinically indicated.
- Collect serum samples for analysis of CCI and C.
- Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) as clinically indicated.
- Collect BAL samples per SOC for culture and CCI testing as clinically indicated.
- Collect plasma PK samples at any time in clinic.
- Record concomitant medications.
- Assess adverse events.

## 7 EFFICACY ASSESSMENTS

### 7.1 Primary Efficacy Endpoint

The primary efficacy parameter is the following:

- All-cause mortality through Day 42.

  **Note:** All-cause mortality will represent the percentage of patients who die after the first dose of study drug through Day 42 from any cause.

Every attempt must be made to record survival status at Day 42 or anytime thereafter for all dosed patients, regardless of their status of treatment, as long as the patient has not withdrawn consent from participation in the study. An in-person assessment is preferred; however, this assessment may also be performed via a telephone call if an in-person visit is not possible.

### 7.2 Secondary Efficacy Endpoint

The secondary efficacy parameter is the following:

- Global response at EOST

[redacted]

### 7.4 Clinical Signs and Symptoms Assessment

Assessment of clinical signs and symptoms will include examination of the following body systems: general appearance including skin, head, eyes, ears, nose, throat, neck, trunk, lymph nodes, respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, neurological, psychological, lymphatic/hematological, and endocrine/metabolic.

### 7.5 Microbiological Assessments

#### 7.5.1 Pathogen DNA

Blood samples and/or other diagnostic specimens (eg, BAL) for pathogen DNA analysis utilizing next-generation sequencing (optional) and/or PCR analysis will be collected at Screening. Polymerase chain reaction analysis will be performed at a central laboratory and potentially at the local laboratory. The Sponsor may provide sites with a validated qPCR kit to use for testing locally. Optional next-generation sequencing of pathogen DNA will be performed by Karius.

#### 7.5.2 Aspergillosis Urine Test

A urine sample will be collected at Screening for an MycoMEIA.

#### 7.5.3 Serum Biomarkers

Serum samples for the analysis of [redacted] will be collected at Screening; predose on Days 1 (Baseline), 2, and 3; on Days 7, 14, 28, and 42; at EOST; and at the E/T Visit (if applicable). Analysis of [redacted] will be reported at the local laboratory as clinically indicated, and an aliquot of the sample will be sent to the central laboratory for analysis.

Serum samples for analysis of [redacted] will be collected at Screening; predose on Day 1 (Baseline); on Days 14, 28, and 42; at EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable). Analysis of [redacted] will be reported at the local laboratory as clinically indicated, and an aliquot of the sample will be sent to the central laboratory for analysis of [redacted].

### 7.5.4 Bronchoalveolar Lavage

Bronchoalveolar lavage samples will be collected per SOC for culture at the local laboratory and CCI testing at the central laboratory as clinically indicated at any visit from Screening throughout the study.

### 7.5.5 Fungal Culture

Samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) will be collected and processed for culture and susceptibility by the local laboratory at Screening, and as clinically indicated at any visit from Day 1 (Baseline) through EOST, at the Follow-Up Visit, and at the E/T Visit (if applicable). Screening samples for fungal cultures to determine eligibility may have been collected as SOC within 120 hours prior to initial dosing. All fungal isolates cultured at the local laboratory will be sent to the central mycology reference laboratory for confirmation of identification and susceptibility testing.

## 7.6 Pharmacokinetic Assessments

Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected predose and 3 hours post start of infusion on Days 1 (Baseline), 2, 3, 7, and 14; predose on Days 28 and 42; and at any time in clinic at EOST, the Follow-Up Visit, and the E/T Visit (if applicable). Additionally, for patients who switch to PO dosing, samples should be collected predose and at 3 hours postdose on the initial day of PO dosing, Day 7, and Day 14 and at any time in clinic on Days 28 and 42, at EOST, at the Follow-Up Visit, and at the E/T Visit (if applicable). If the patient switches back to IV dosing, PK samples should be collected predose and at 3 hours post start of infusion on that day as well.

Optionally, if body fluids are sampled as part of routine patient management (eg, BAL, 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 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 an IMP, whether or not related to the IMP. 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 initial dosing through the Follow-Up Visit. Patients should be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study treatment. Following initial dosing, 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 (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure itself.

Any medical condition already present at initial dosing should be recorded as medical history and not be reported as an adverse event unless the medical condition or signs or symptoms present at Baseline changes in severity, frequency, 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 (eg, ECG) findings that are detected during the study or are present at initial dosing and significantly worsen during the study should be reported as adverse events, as described below. 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. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

### 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, ie, 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 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 CTCAE v5.0. For those adverse event terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- CTCAE Grade 4: Life threatening consequences; urgent intervention indicated
- CTCAE Grade 5: Death related to the adverse event

Causality Assessment:

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

No (not related, unlikely to be related) – 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 (possibly, probably, or definitely 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.

  **Note**: 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.

  **Note:** Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from Baseline. 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 (ie, no place

to stay, live too far away to come for hospital visits, respite care) 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.

  **Note:** Important medical events that do not meet any of the above criteria 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 initial dosing until the Follow-Up Visit must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (After the Follow-Up Visit, any SAE that the Investigator considers related to study drug must be reported to the Medpace Clinical Safety or the Sponsor/designee).

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at Medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.6) 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: Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: Medpace-safetynotification@medpace.com

Medpace SAE reporting line – Europe:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
Email: medpace-safetynotification@medpace.com

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 (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

## 8.4 Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an adverse event or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

## 8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSAR) 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/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

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

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to APX001.

### 8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a study drug given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the study drug is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a study drug, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a study drug by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of study drug are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All adverse events associated with these Special Situation reports should be reported as adverse events or SAEs as well as recorded on the adverse event eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: medpace-safetynotification@medpace.com

Medpace SAE reporting line – Europe:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
Email: medpace-safetynotification@medpace.com

### 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 [including CBC with differential], coagulation [including PT/INR], and urinalysis) will occur at Screening; predose on Days 1 (Baseline), 7, 14, 28, and 42; at EOST; and at the E/T Visit (if applicable).

A urine or serum pregnancy test will be performed at Screening; on Days 1 (Baseline) (if the Screening Visit occurred ≥96 hours prior to Day 1 [Baseline]), 28, and 42; at EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable) for all women of childbearing potential.

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 E for a complete list of clinical laboratory analytes.

### 8.8 Vital Signs

Vital signs will include temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation and will be collected at Screening; predose on Days 1 (Baseline), 7, 14, 21, 28, 35, and 42; at EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable). Patients should be supine for at least 5 minutes prior to measurement of vital signs.

### 8.9 Electrocardiograms

A 12-lead ECG will be obtained in triplicate at Screening, Days 3, 7, 14 and 42, EOST, and the E/T Visit (if applicable). Patients should be supine for at least 5 minutes prior to the collection of 12-lead ECGs.

### 8.10 Physical Examinations

A complete physical examination will be conducted at Screening, Day 42, EOST, and the E/T Visit (if applicable). A complete physical examination will include an assessment of general appearance, skin, eyes, heart, chest, abdomen, and a neurological examination. Components of the neurological examination include cranial nerve, sensory, and motor examination; reflex and gait testing; and coordination assessment. Height will be measured at Screening and weight will be measured at Screening; on Days 1 (Baseline), 7, 14, 21, 28, 35, and 42; at EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable).

A neurological examination (all patients) and a symptom-directed physical examination will be conducted as clinically indicated (ie, new signs or symptoms and follow-up on earlier findings) on Days 1 (Baseline), 7, 14, 21, 28, 35, and at the Follow-Up Visit.

### 8.11 Computed Tomography

Computed tomography scans of the chest, sinuses, and/or abdomen will be performed during Screening (SOC scans within 3 days of Screening will be accepted as long as the scans can be provided to the central reader). Repeat CT scans will be performed on Day 14 and at EOST, and if clinically indicated on Days 7, 21, 28, 35, and 42; at the Follow-Up Visit; and at the E/T Visit (if applicable).

The same CT scanner and imaging protocol used at Screening should be used for subsequent CT scans, if possible. Additional CT scans may be performed during treatment and follow-up if clinically indicated.

## 9 STATISTICS

### 9.1 Analysis Populations

Each Cohort will be analyzed and presented separately. There will be no pooling of data across the Cohorts. Each Cohort will have respective ITT, mITT, PP and PK populations.

Intent-to-Treat Population/Safety Population:

The Intent-to-Treat (ITT)/Safety Population will include all patients who have received at least 1 dose of study drug.

Modified Intent-to-Treat Population:

The modified Intent-to-Treat (mITT) Population will include all patients in the ITT Population who satisfy the following criteria:

- Receive at least 1 dose of study drug
- **Cohort A:** Have a diagnosis of proven or probable IMI confirmed by the DRC
- [redacted]

The mITT Population will be the primary population used for the efficacy analysis.

Per-Protocol Population:

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

- Meet the protocol's key inclusion criteria and exclusion criteria
- Have no major protocol violations

Pharmacokinetic Population:

The PK Population will include all patients who receive any amount of study drug and have evaluable PK data. The PK Population will be used for the PK analysis.

## 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. Each Cohort will be analyzed and presented separately. There will be no pooling of data across the Cohorts.

### 9.2.1 Analysis of Efficacy

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

The efficacy endpoints will be summarized descriptively, and all-cause mortality through Day 42 will be summarized. For Cohort A, the 1-sided exact binomial test at the alpha = 0.1 level of significance will be used to test the hypothesis that the all-cause mortality at Day 42 is less than 45% (based on historical control data).

The percentage of patients with global response will be summarized.

CCI [redacted]

### 9.2.2 Analysis of Safety

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

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

A TEAE is defined as an adverse event that 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, vital sign, and ECG interval data for both actual values and changes from Baseline over time.

Abnormal physical examination findings will be listed.

#### 9.2.2.1 Pharmacokinetic Analysis

The PK 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 time point of collection. Summary statistics in the tabulation will include n, mean, standard deviation, percent coefficient of variation, 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 Data Review Committee

A DRC comprised of infectious disease experts will adjudicate the diagnosis of IMI at enrollment. This committee will also provide systematic assessment for clinical, mycological, radiological, and global responses at EOST and at the E/T Visit (if applicable).

Global responses will be classified as complete or partial response (categorized as treatment success), stable response, progression of disease, or death (categorized as treatment failure) according to prespecified criteria (APPENDIX G). 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 be responsible for the periodic review of cumulative data from the study 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 patients and those yet to be recruited to the study, as well as the continuing validity and scientific merit of the study. The DSMB may recommend to the Sponsor that dosing in the study be suspended if, in the opinion of the DSMB, further dosing in the study would pose an inappropriate safety risk. Guidelines for what constitutes inappropriate safety risks are described in the DSMB Charter.

### 9.2.6 Sample Size Determination

Approximately 50 patients will be dosed in this open-label, proof-of-concept study.

Cohort A:

Patients with proven or probable IMI are eligible for inclusion in the mITT Population, which is the primary efficacy population (DRC confirmation required of proven or probable IMI). The sample size calculation is based on the mITT Population from the first dose of APX001 through EOST (up to 6 weeks) for the all-cause mortality primary endpoint. A total of 24 patients in the mITT Population are needed, providing >90% power to detect the difference at a 1-sided significance level of 0.1, assuming an all-cause mortality of 20% for APX001 and 45% for adjusted

amphotericin B-treated all-cause mortality from the historical control. Assuming 60% of dosed patients will be eligible to be included in the mITT Population, a dosing of approximately 40 patients allows for statistical testing of proof-of-concept for an estimate of 24 patients in the mITT Population.

CCI [redacted]

[redacted]

# 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 following thesauri will be used:

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

# 11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

## 11.1 Ethical Conduct of the Study

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

## 11.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, informed consent form (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 by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines 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, advertisements to be used for patient recruitment, 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.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

## 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 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 original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB 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 subject card to be carried at all times. The subject card will state that the patient is participating in a clinical research study, type of treatment, number of treatment packs received, 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 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, eg, 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 (ie, 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 Medpace 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

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### 12.2.4 Biological Specimens

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### 12.2.5 Mycology Reference Laboratory

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Email: info@jmilabs.com

### 12.2.6 Pharmacokinetic Laboratory

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# APPENDIX A: SCHEDULE OF PROCEDURES

| | Screening | Baseline | Treatment Period[a,b] | | | | | | | | EOST[c,d] | Follow-Up Visit[e] | Follow-Up Phone Call[e] | E/T |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day | -5 to -1 | 1 | 2 | 3 | 7 (±1) | 14 (±1) | 21 (±2) | 28 (±2) | 35 (±2) | 42 (±2)[c] | (+2) | (±3) | 84 (±3) | |
| Informed consent | X | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | |
| IMI classification[f] | X | | | | | | | | | | | | | |
| Disease severity assessment[g] | X | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | |
| Urine or serum pregnancy test[h] | X | X[i] | | | | | | X | | X | X | X | | X |
| Prior/concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Physical examination | X[j] | X[k] | | | X[k] | X[k] | X[k] | X[k] | X[k] | X[j] | X[j] | X[k] | | X[j] |
| Clinical signs and symptoms assessment[l] | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Vital signs[m] | X | X | | | X | X | X | X | X | X | X | X | | X |
| 12-lead ECG[n] | X | | | X | X | X | | | | X | X | | | X |
| Clinical laboratory assessments[o] | X[p] | X | | | X | X | | X | | X | X | | | X |
| Pathogen DNA analysis, PCR, and MycoMEIA [q] | X | | | | | | | | | | | | | |
| CT scan of the chest, sinuses, and/or abdomen[r] | X[s] | | | | X[t] | X | X[t] | X[t] | X[t] | X[t] | X | X[t] | | X[t] |
| Serum collection for [redacted][u] | X | X | X | X | X | X | | X | | X | X | | | X |
| Fungal cultures[v] | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| APX001 administration[w,x] | | X | X | X | X | X | X | X | X | X | | | | |
| Plasma PK sample[y] | | X | X | X | X | X | | X | | X | X | X | | X |
| Adverse events assessment | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| BAL[z] | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Serum collection for | X | X | | | | X | | X | | X | X | X | | X |

| | Screening | Baseline | Treatment Period[a,b] | | | | | | | | EOST[c,d] | Follow-Up Visit[e] | Follow-Up Phone Call[e] | E/T |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day | -5 to -1 | 1 | 2 | 3 | 7 (±1) | 14 (±1) | 21 (±2) | 28 (±2) | 35 (±2) | 42 (±2)[c] | (+2) | (±3) | 84 (±3) | |
| C [redacted][aa] | | | | | | | | | | | | | | |
| APX001 accountability | | | X | X | X | X | X | X | X | X | X | | | X |
| Investigator assessment of global response | | | | | | | | | | X | X | | | |
| Survival status assessment | | | | | | | | | | X | X | | X | |

a. Administration of APX001 should not continue for longer than 6 weeks. If an Investigator documents an improvement or resolution in clinical signs and symptoms prior to 6 weeks, eg, if follow-up imaging (as applicable) shows improvement; or a mycological response (if amenable to repeat sampling) is observed, the Investigator may choose to discontinue dosing. Patients will be requested to return for an EOST and Follow-Up Visit and to agree to a Follow-Up Phone Call.
b. During the Treatment Period, 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. If EOST procedures are performed after Day 39, Day 42 procedures will not be required.
d. The EOST will occur within 2 days of completion of APX001 dosing.
e. The Follow-Up Visit will occur 4 weeks (±3 days) post EOST. The Follow-Up Phone Call will occur 12 weeks (±3 days) after Day 1 (Baseline).
f. Cohort A: Historical patient EORTC/MSGERC classification of proven or probable IMI may be used for study assessment. CCI [redacted]
g. Assess disease severity using the Eastern Cooperative Oncology Group Performance Status and Karnofsky Performance Status. Assess P/F ratio (if patient is ventilated)
h. For females of childbearing potential only.
i. If the Screening Visit occurred ≥96 hours prior to Day 1 (Baseline), perform a urine or serum pregnancy test on women of childbearing potential only.
j. Conduct a complete physical examination. The physical examination includes an assessment of general appearance, skin, eyes, heart, chest, abdomen, and a neurological examination. Measure height only at Screening. Measure weight at each indicated visit.
k. Conduct a neurological examination (all patients) and a symptom-directed physical examination as clinically indicated (ie, new signs or symptoms and follow-up on earlier findings). Measure weight at each indicated visit.
l. Assessment of clinical signs and symptoms includes examination of the following body systems: general appearance including skin, head, eyes, ears, nose, throat, neck, trunk, lymph nodes, respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, neurological, psychological, lymphatic/hematological, and endocrine/metabolic.
m. Vital signs include temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation. Measure vital signs at Screening; at predose on Days 1 (Baseline), 7, 14, 21, 28, 35, and 42; at EOST; at the Follow-up Visit; and at the E/T Visit (if applicable). Patients should be supine for at least 5 minutes prior to measurement of vital signs.
n. Collect 12-lead ECGs in triplicate at Screening, on Days 3, 7, 14 and 42, at EOST, and at the E/T Visit (if applicable). Patients should be supine for at least 5 minutes prior to collection of 12-lead ECGs.
o. Clinical laboratory assessments include serum chemistry, hematology (including CBC with differential), coagulation (including PT/INR), and urinalysis. Collect blood and urine specimens at Screening; at predose on Days 1 (Baseline), 7, 14, 28, and 42; at EOST; and at the E/T Visit (if applicable).

p. Clinical laboratory assessments performed at Screening 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.
q. Collect blood samples (serum and plasma) and other diagnostic specimens (eg, BAL) for pathogen DNA analysis utilizing next-generation sequencing (optional), PCR analysis, and collect urine sample for MycoMEIA.
r. The same CT scanner and imaging protocol used at Screening should be used for subsequent CT scans, if possible. Additional CT scans may be performed during treatment and follow-up if clinically indicated.
s. Standard of care scans within 3 days of Screening will be accepted as long as the scans can be provided to the central reader.
t. Perform CT scan if clinically indicated.
u. Collect serum samples for analysis of CCI at Screening; predose on Days 1 (Baseline), 2, and 3; on Days 7, 14, 28, and 42; at EOST; and at the E/T Visit (if applicable). Analysis of CCI will be reported at the local laboratory and an aliquot of the sample will be sent to the central laboratory for analysis.
v. Collect samples for fungal cultures (eg, from BAL fluid, sputum, bronchial brush, sinus aspirate, tracheal aspirate) at Screening, and collect as clinically indicated at any visit from Day 1 (Baseline) through EOST, at the Follow-Up Visit, and at the E/T Visit (if applicable). Screening samples for fungal cultures to determine eligibility may have been collected as SOC within 120 hours prior to initial dosing. All fungal isolates should be submitted to the central mycology reference laboratory for confirmation of identification and susceptibility testing.
w. On Day 1 (Baseline), administer a loading dose of 1000 mg APX001 by IV infusion BID within the first 24 hours after initiation of the first infusion. On Days 2 and 3, administer 600 mg APX001 by IV infusion QD. From Day 4 through EOST, administer 600 mg APX001 by IV infusion QD, or administer 800 mg APX001 PO QD. Antiemetics (preferably a 5-$HT_3$ antagonist such as ondansetron or granisetron) should be administered in patients who develop nausea and/or vomiting associated with APX001 administration (both IV and oral), and oral APX001 may be given with food. Additionally, prophylactic antiemetics, (preferably a 5-$HT_3$ antagonist such as ondansetron or granisetron) may be administered prior to dosing (both IV and oral) in patients considered at higher risk of gastrointestinal intolerance. The decision to switch from IV to PO APX001 will be based on the Investigator's discretion and can be done on any day from Day 4 onwards. Patients will remain hospitalized for at least 2 days following the initial switch from IV to PO so that their tolerance to the oral medication may be evaluated and treated as necessary. Oral APX001 may be given with food, and prophylactic antiemetics may be administered. Patients may be switched between IV and PO as needed. Oral APX001 may be given as an outpatient. All IV infusions will be administered over 3 hours. APX001 will be administered for a maximum of 6 weeks (inclusive of the loading dose [Day 1]).
x. Intravenous APX001 will be administered inpatient by staff in clinic while PO APX001 will be administered independently by patients at home. The acceptable dosing window for APX001 is ±1 hour on Day 1 (Baseline), and ±2 hours on Day 2 through EOST.
y. Collect plasma PK samples predose and 3 hours post start of infusion on Days 1 (Baseline), 2, 3, 7 and 14; predose on Days 28 and 42; and at any time in clinic at EOST, the Follow-Up Visit, and the E/T Visit (if applicable). Additionally, for patients who switch to PO dosing, samples should be collected predose and at 3 hours postdose on the initial day of PO dosing, Day 7, and Day 14 and at any time in clinic on Days 28 and 42, at EOST, at the Follow-Up Visit, and at the E/T Visit (if applicable). If the patient switches back to IV dosing, PK samples should be collected predose and at 3 hours post start of infusion on that day as well.
z. Collect BAL samples per SOC for culture at the local laboratory and CCI testing at the central laboratory as clinically indicated.
aa. Collect serum samples for analysis of C at Screening; predose on Day 1 (Baseline); on Days 14, 28, and 42; at EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable). Analysis of C will be reported at the local laboratory as per local SOC and an aliquot of the sample will be sent to the central laboratory for analysis.

BAL = bronchoalveolar lavage; BID = twice daily; CBC = complete blood count; CT = computed tomography; E/T = Early Termination; ECG = electrocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EOST = End of Study Treatment; IMI = invasive mold infection; INR = international normalized ratio; IV = intravenous(ly); MSG = Mycosis Study Group; MycoMEIA = Aspergillosis urine test; PCR = polymerase chain reaction; PK = pharmacokinetic(s); PO = oral(ly); PT = prothrombin time; QD = once daily; SOC = standard of care.

# APPENDIX B: CLINICAL SAFETY LABORATORY ANALYTES

**Standard Safety Chemistry Panel**

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

**Hematology**

| | |
|---|---|
| Hematocrit | Hemoglobin |
| Platelets | Red blood cell count |

White blood cell count and differential [1]

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

**Coagulation**

| | |
|---|---|
| Prothrombin time | International normalized ratio |

**Urinalysis**

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

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

**Other Tests**

Urine or serum pregnancy test [1]

1. Women of childbearing potential only.

# APPENDIX C: FUNGAL AND OTHER LABORATORY ANALYTES

**Serum Biomarker**

| | |
|---|---|
| CCI | C |

**Bronchoalveolar Lavage**

| | |
|---|---|
| CCI | Fungal culture |

**Other Fungal Diagnostics**

| | |
|---|---|
| Next-generation sequencing (optional) and/or polymerase chain reaction analysis of pathogen DNA (blood and/or other diagnostic specimens) | Aspergillosis urine test |

# APPENDIX D: REVISION AND UPDATE OF THE CONSENSUS DEFINITIONS OF PROVEN INVASIVE FUNGAL DISEASE FROM THE EORTC/MSGERC

| Analysis and Specimen | Molds[1] |
|---|---|
| Microscopic analysis: sterile material | Histopathologic, cytopathologic, or direct microscopic examination[2] of a specimen obtained by needle aspiration or biopsy in which hyphae are seen accompanied by evidence of associated tissue damage |
| **Culture** | |
| Sterile material | Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a paranasal or mastoid sinus cavity specimen, and urine |
| Blood | Blood culture that yields a mold[3] (eg, *Fusarium* species) in the context of a compatible infectious disease process |
| Serology | Not applicable |
| Tissue Nucleic Acid Diagnosis | Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue |

1. If culture is available, append the identification at the genus or species level from the culture results.
2. Tissue and cells submitted for histopathologic or cytopathologic studies should be stained using Grocott-Gomori methenamine silver stain or periodic acid Schiff stain to facilitate inspection of fungal structures. Whenever possible, wet mounts of specimens from foci related to invasive fungal disease should be stained with a fluorescent dye (eg, calcofluor or blankophor).
3. Recovery of *Aspergillus* species from blood cultures rarely indicates endovascular disease and almost always represents contamination.

# APPENDIX E: REVISION AND UPDATE OF THE CONSENSUS DEFINITIONS OF PROBABLE INVASIVE FUNGAL DISEASE FROM THE EORTC/MSGERC

| **A diagnosis of probable IFD requires at least 1 Host Factor, 1 Clinical Criterion, and Mycological Evidence as described below:** |
|---|
| **Host Factors** |
| • Recent history of neutropenia (<0.5 × $10^9$ neutrophils/L [<500 neutrophils/$mm^3$] for >10 days) temporally related to the onset of fungal disease |
| • Hematologic malignancy |
| • Receipt of an allogeneic stem cell transplant |
| • Receipt of a solid organ transplant |
| • Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days |
| • Treatment with other recognized T cell immunosuppressants, such as calcineurin inhibitors, TNF-α blockers, lymphocyte-specific monoclonal antibodies, or immunosuppressive nucleoside analogues during the past 90 days |
| • Treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib |
| • Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency) |
| • Acute GVHD Grade III or IV involving the gut, lungs, or liver that is refractory to first line treatment with steroids |
| **Clinical Criteria** |
| Pulmonary aspergillosis<br>The presence of one of the following 4 signs on CT:<br>• Dense, well-circumscribed lesion(s) with or without a halo sign<br>• Air-crescent sign<br>• Cavity<br>• Wedge-shaped and segmental or lobal consolidation |
| Other pulmonary mold diseases<br>The presence of one of the following 5 signs on CT:<br>• Dense, well-circumscribed lesion(s) with or without a halo sign<br>• Air-crescent sign<br>• Cavity<br>• Wedge-shaped and segmental or lobal consolidation<br>• Reverse halo sign |
| Tracheobronchitis<br>• Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis |
| Sino-nasal diseases<br>• Acute localized pain (including pain radiating to the eye)<br>• Nasal ulcer with black eschar<br>• Extension from the paranasal sinus across bony barriers, including into the orbit |
| Central nervous system infection<br>1 of the following 2 signs:<br>• Focal lesions on imaging<br>• Meningeal enhancement on magnetic resonance imaging or CT |
| BAL = bronchoalveolar lavage; CSF = cerebrospinal fluid; CT = computed tomography; GVHD = graft versus host disease; IFD = invasive fungal disease; PCR = polymerase chain reaction; spp. = species; STAT 3 = signal transducer and activator of transcription 3; TNF = tumor necrosis factor. |

| **Mycological Evidence*** |
|---|
| • Any mold (*Aspergillus*, *Fusarium*, *Scedosporium* species., or Mucorales) recovered by culture from sputum, BAL, bronchial brush, or aspirate<br>• Microscopical detection of fungal elements in sputum, BAL, bronchial brush, or aspirate indicating a mold |
| Tracheobronchitis<br>• *Aspergillus* recovered by culture of BAL or bronchial brush<br>• Microscopical detection of fungal elements in BAL or bronchial brush indicating a mold |
| Sino-nasal diseases<br>• Mold recovered by culture of sinus aspirate samples<br>• Microscopical detection of fungal elements in sinus aspirate samples indicating a mold |
| Aspergillosis only<br>CCI antigen<br>Antigen detected in plasma, serum, BAL, or CSF<br>Any 1 of the following:<br>• Single serum or plasma: ≥1.0<br>• BAL fluid: ≥1.0<br>• Single serum or plasma: ≥0.7 and BAL fluid ≥0.8*<br>• CSF: ≥1.0<br>*Aspergillus* PCR*<br>Any 1 of the following:<br>• Plasma, serum, or whole blood: 2 or more consecutive PCR tests positive<br>• BAL fluid: 2 or more duplicate PCR tests positive<br>• At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid<br>Aspergillus species recovered by culture from sputum, BAL, bronchial brush, or aspirate |

*Patients with the following preliminary mycological evidence may be entered into the study:

1. A single serum or plasma CCI ≥0.7 or CCI in BAL fluid ≥0.8 pending the results of a second CCI test collected prior to dosing.
2. A single positive PCR for *Aspergillus* from plasma, serum, whole blood, or BAL pending the results of a second PCR test collected prior to dosing.
3. A positive result from the Karius test which indicates the presence of cell-free DNA for *Aspergillus* or other rare molds.
4. A positive result from IMMY's sōna *Aspergillus* Lateral Flow Device pending the results of a CCI or PCR test for *Aspergillus*.

After inclusion into the study, every effort should be made to upgrade the certainty of diagnosis of IFD.
BAL = bronchoalveolar lavage; CSF = cerebrospinal fluid; CT = computed tomography; GVHD = graft versus host disease; IFD = invasive fungal disease; PCR = polymerase chain reaction; spp. = species; STAT 3 = signal transducer and activator of transcription 3; TNF = tumor necrosis factor.
(Donnelly et al.,2019)

# APPENDIX F: CCI [redacted] DIAGNOSTIC CRITERIA FOR INVASIVE ASPERGILLOSIS

| |
|---|
| **Proven Invasive Pulmonary Aspergillosis**<br>Idem EORTC/MSGERC criteria (refer to APPENDIX D) |
| **Putative invasive pulmonary aspergillosis**<br>A diagnosis of putative IPA requires at least 1 mycological finding, 1 clinical criterion and 1 radiological finding |
| **Host Factor (must be present in all CCI [redacted] patients)** |
| • SARS-Cov-2 and/or influenza A/B lower respiratory tract infection |
| **Mycological Criteria (one or more of the following must be present)** |
| • Aspergillus-positive sputum or tracheal aspirate (only in the presence of findings of plaque, pseudomembrane or ulcer in bronchoscopy *or* in conjunction with cavitation in an area of pulmonary consolidation |
| • Aspergillus-positive culture from BAL fluid |
| • CCI [redacted] antigen in serum or plasma ≥ 0.5 |
| • CCI [redacted] antigen in BAL fluid: ≥1.0 |
| **Clinical Criteria (one of the following signs and symptoms must be present)** |
| • Fever refractory to at least 3 days of appropriate antibiotic therapy |
| • Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause |
| • Dyspnea |
| • Hemoptysis |
| • Pleuritic friction rub chest pain |
| • Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support |
| **Radiological Criteria (must be present)** |
| • Abnormal medical imaging by CT scan of the lungs |

BAL = bronchoalveolar lavage; CT = computed tomography; EORTC/MSGERC = European Organization for the Research and Treatment of Cancer/Mycosis Study Group Education and Research Consortium

Modified from Blot et al., 2012 and Schauwvlieghe et al., 2018

# APPENDIX G: RESPONSE CRITERIA

## General Criteria for Global Responses to Antifungal Therapy

| Outcome, Response | Criteria |
|---|---|
| **Success** | |
| Complete response | Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease and radiological abnormalities, and mycological evidence of eradication of disease |
| Partial response | Survival within the prespecified period of observation, improvement in attributable symptoms and signs of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden, as assessed by a quantitative and validated laboratory marker |
| **Failure** | |
| Stable response[1] | Survival within the prespecified period of observation and minor or no improvement in fungal disease, but no evidence of progression, as determined on the basis of a composite of clinical, radiological, and mycological criteria |
| Progression of fungal disease | Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria |
| Death | Death during the prespecified period of evaluation, regardless of attribution |

(Segal B, 2008)

1. In certain invasive fungal diseases (eg, invasive mold diseases), stabilization of fungal disease during periods of severe immunocompromise provides evidence of efficacy of treatment and may be a reasonable short-term therapeutic goal until immune recovery occurs.

## Clinical Response

| Clinical Response to Treatment will be Categorized as One of the Following 4 Possible Outcomes: | |
|---|---|
| Complete response | Resolution of all attributable symptoms, signs, and/or bronchoscopic abnormalities present at Baseline |
| Partial response | Major improvement (usually nearly complete) in attributable symptoms, signs, and/or bronchoscopic abnormalities present at Baseline |
| Stable disease | Minor or no improvement in attributable symptoms, signs, and/or bronchoscopic abnormalities present at Baseline, but patient continued on therapy without deterioration |
| Failure | Deterioration in attributable symptoms, signs, and/or bronchoscopic abnormalities necessitating alternative antifungal therapy or resulting in death |

## Radiological Response

| **Radiological Response to Treatment will be Categorized as One of the Following 4 Possible Outcomes:** | |
|---|---|
| Complete response | Resolution (normalization of X-ray, CT scan, etc.) of all radiological abnormalities *attributed to aspergillosis* compared to Baseline |
| Partial response | Major improvement of radiological abnormalities *attributed to aspergillosis* compared to Baseline |
| Stable disease | Minor or no improvement of radiological abnormalities *attributed to aspergillosis* compared to Baseline |
| Failure | Worsening of radiological abnormalities *attributed to aspergillosis* compared to Baseline |

CT = computed tomography.

## Mycological Response

| **Mycological Response to Treatment will be Categorized as One of the Following 4 Possible Outcomes:** | |
|---|---|
| Eradication | Absence of *Aspergillus* in a relevant clinical specimen (culture negative and absence of fungal elements by microscopy or histopathology, as appropriate) |
| Presumed eradication | Inferred in patients with complete clinical and imaging response for whom an invasive procedure for obtaining the relevant clinical specimen is not performed |
| Persistence | Any evidence based on culture, microscopy, or histopathology for the presence of *Aspergillus* |
| Indeterminate | Inadequate data available for categorization as eradication, presumed eradication, or persistence |

# APPENDIX H: DRUG-INDUCED LIVER INJURY CRITERIA

**For patients with normal liver transaminases and bilirubin at baseline:**

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

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

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

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

**For patients with elevations in baseline transaminases or bilirubin:**

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

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

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

- If baseline measurements were <2x ULN, discontinue if ALT or AST increases to >5x baseline measurements.
- If baseline average measurements >2x ULN, discontinue if ALT or AST increases to >3x baseline measurements.
- Discontinue if ALT or AST increase >2x baseline measurements AND the increase is accompanied by a concomitant increase in TBL to >2x baseline measurements or the INR concomitantly increases by >0.2.

- For any patients who present with a constellation of syndromes indicative of liver disease as per the Investigator's overall assessment (ie, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]).

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

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