Statistical Analysis Plan
(SAP)

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

Protocol Number: APX001-201
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SAP APPROVAL FORM

Document Title:	Statistical Analysis Plan
Protocol Number:	APX001-201
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This Statistical Analysis Plan has been reviewed and approved by:

Approved by: Mei Chen, PhD

11-May-2020
Date

11-May-2020
Date

11th May 2020

Michael Hodges, MD
Chief Medical Officer
Amplyx Pharmaceutical, Inc.

Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
ALP	Alkaline phosphatase
APACHE	Acute Physiology and Chronic Health Evaluation
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BID	Twice daily
BMI	Body mass index
CSR	Clinical study report
CVC	Central venous catheter
DRC	Data Review Committee
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOST	End of Study Treatment
EOT	End of Antifungal Treatment
ICF	Informed Consent Form
ITT	Intent-to-Treat
IV	Intravenous(ly)
LAR	Legal authorized representative
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat
PK	Pharmacokinetic(s)
PO	Oral(ly)
PP	Per-Protocol
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
spp.	Species
T2MR	T2 magnetic resonance
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number APX001-201 (Version 3.0, June 3, 2019). The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2. STUDY OVERVIEW

2.1. Study Objectives

2.1.1. Primary Objective

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

2.1.2. Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the time to first negative blood culture;
- Evaluate the percentage of patients with Mycological Outcomes at the End of Study Drug Treatment (EOST), End of Antifungal Treatment (EOT), and 2 and 4 weeks after EOT;
- Evaluate the percentage of patients with Treatment Success at EOT, and 2 and 4 weeks after EOT;
- Evaluate overall survival at Study Day 30;
- Evaluate safety parameters, including number of patients with Treatment-emergent adverse events (TEAEs); and
- Evaluate Pharmacokinetic(s) (PK) parameters of APX001.

2.2. Study Design

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

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

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

All patients (or the patient's legal authorized representative [LAR]) will sign an Informed Consent Form (ICF) before any protocol specified procedures that are not indicated by SOC may be conducted. Inclusion/exclusion criteria assessments, medical history, demographics, and Acute Physiology and Chronic Health Evaluation (APACHE) II score will be collected before dosing.

On Study Day 1 (or over the first 24 hours if started in the evening), a 1000 mg APX001 loading dose will be administered over 3 hours by intravenous (IV) infusion Twice daily (BID). On Study Days 2 and 3 of study drug, a 600 mg APX001 maintenance dose will be administered over 3 hours by IV infusion once daily (QD). On Study Day 4 and onward, the APX001 maintenance dose will be administered as either 600 mg APX001 IV infusion QD over 3 hours or 700 mg oral (PO) QD. Patients who have completed a minimum of 3 days of IV APX001, are clinically stable as determined by the Investigator, able to swallow tablets, and have no further growth of the infecting organism 48 hours following the most recent blood culture, may switch from IV to PO dosing on Study Day 4 and onward. Study drug will be administered for a maximum of 14 days. At the Investigator's discretion, patients requiring a longer duration of antifungal therapy will be switched to fluconazole (unless susceptibility results warrant alternative antifungal therapy), to adhere to the IDSA clinical practice guidelines for the treatment of Candidiasis.

Candida spp. bloodstream infection will be monitored by daily blood culture during Study Drug Treatment until 2 consecutive blood cultures are negative, and at EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination. Simultaneously drawn blood samples will be collected for *Candida* testing by T2 magnetic resonance (T2MR) assay at Baseline, during Study Drug Treatment, and EOST, or Early Termination. Other cultures, histopathology, and imaging tests to assess the site(s) and extent of candidemia infection at other sites will be conducted as clinically indicated, and the results should be recorded in the electronic Case Report Form (eCRF). The management of intravascular catheters, intravascular devices, and, if applicable, any drains will be recorded, including any associated microbiology results.

Patients will be monitored for safety throughout the duration of the study. Safety assessments will include vital signs, clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis), physical examinations (including neurological assessment), prior and concomitant medication reporting, and adverse event reporting. A 12-lead electrocardiogram (ECG) will be performed at Baseline (pre-dose), EOST, EOT, and 4 weeks after EOT, or Early Termination. A dilated fundoscopic examination will be performed at Screening for all patients and EOST, EOT,

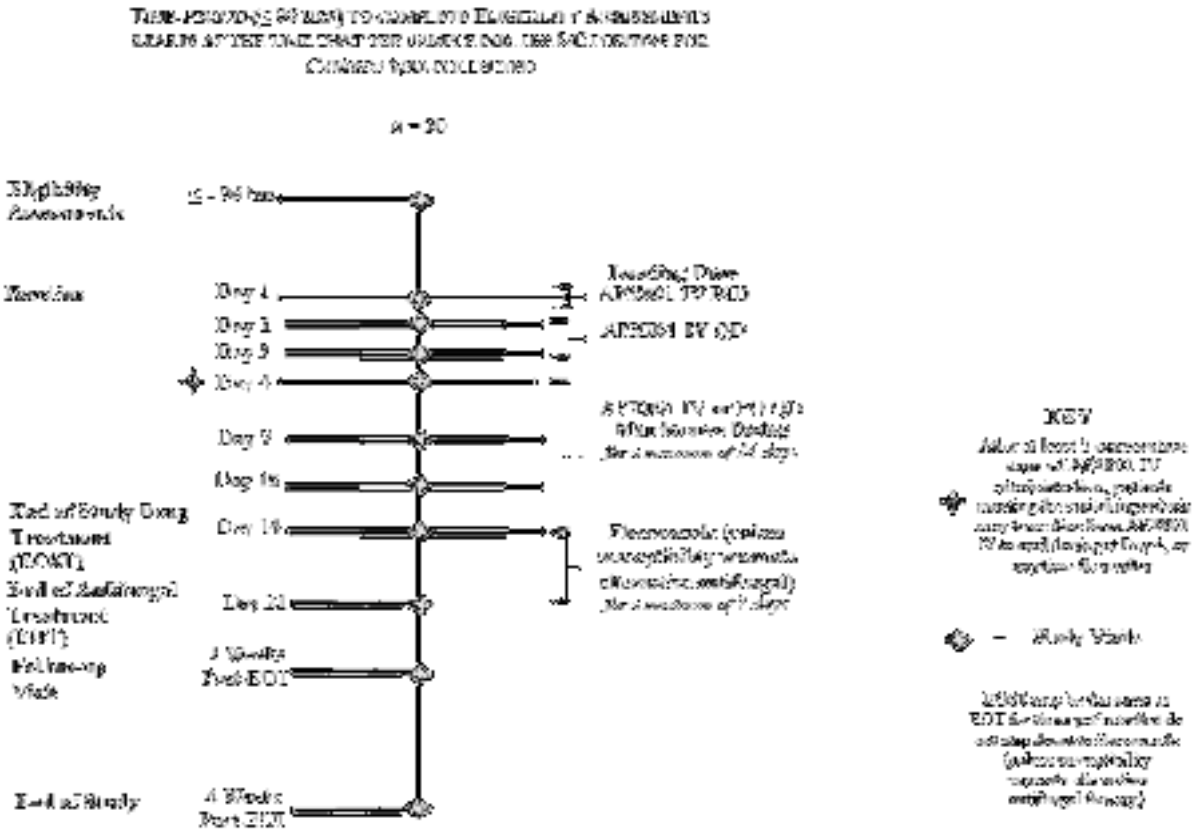
and 4 weeks after EOT, or Early Termination for those patients who had positive fundoscopic findings at Screening, or as clinically indicated. A urine pregnancy test (for females of childbearing potential only) will be performed at Screening and Baseline (pre-dose), every 30 days during treatment if required by local regulations, EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination.

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

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

The evaluation of treatment outcome will be assessed at EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination. The end of study will occur after the last visit of the last patient on the study.

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



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

Table 1 presents the schedule of procedures of the study.

Table 1: Schedule of Procedures

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

Table 1: Schedule of Procedures (Continued)

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

a. To be completed within 96 hours from blood sampling time for culture positive for *Candida* spp.
b. During Study Drug Treatment, twice weekly visits are required with a maximum window of ±2 days. Outpatients will be asked to record daily dosing on a diary and bring the diary and study drug bottles with them to every clinic visit.
c. End of Study Drug Treatment (EOST) occurs after completion of APX001 dosing.
d. Assessments performed at EOST do not need to be repeated at End of Antifungal Treatment (EOT), if <48 hours apart, unless clinically indicated.
e. The EOST may be the same as EOT for those patients that do not have a step-down (i.e., fluconazole or other protocol approved step-down).
f. The EOT occurs up to a maximum of 21 days after Baseline (includes up to 14 days of APX001 administration and up to 7 days of fluconazole administration or other protocol approved step-down).
g. To be obtained prior to the initiation of any protocol-specific procedure outside of SOC.
h. Vital signs will include temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight. Vital signs will be collected at Screening, Baseline (pre-dose), daily on Study Days 2 to 4, and twice weekly thereafter during Study Drug Treatment, EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination. Height will be collected (from the patient's medical record) at Baseline.
i. If possible, all indwelling intravascular catheters should be removed and the catheter tips cultured prior to starting APX001 dosing. The entrance site should also be cultured if it appears infected. Any removed catheter tip should be sent for culture.
j. Intravascular catheters logged until EOT.

k. As clinically indicated. If obtained, results should be recorded in the eCRF.
l. Only required in those patients who had positive fundoscopic findings at Screening, or as clinically indicated.
m. Screening laboratory assessments to determine eligibility will be performed at the local laboratory and may have been collected as SOC within the previous 24 hours. Laboratory assessments collected after Screening will be sent to the central laboratory for analysis. Clinical safety laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, at EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination. If clinically indicated and at the discretion of the Investigator, or if a suspected adverse event is identified, clinical laboratory assessments may be conducted at any time during the study and compared to Baseline.
n. Urine pregnancy test (for females of childbearing potential only) every 30 days if required by local regulations.
o. A complete physical examination will be conducted at Baseline (pre-dose). Complete physical examination will include an assessment of general appearance, skin, eyes, heart, chest, abdomen, the body site that corresponds to the entry site of candidemia (e.g., central venous catheter entry site), if applicable, and a neurological examination. Components of the neurological examination include cranial nerve, sensory and motor examination, reflex and gait testing, and coordination assessment. A focused, symptom-based physical examination to include a neurological examination will be performed once weekly during study drug treatment, EOST, EOT, and 2 and 4 weeks after EOT, or Early Termination.
p. Each time a blood culture is collected, an additional blood sample will be drawn for subsequent analysis of the correlation of blood culture and T2MR assay *Candida* spp. results from Baseline (pre-dose) through EOST or Early Termination. A central laboratory will perform the T2MR assay.
q. Two consecutive sets of blood cultures during screening within 96 hours before the initiation of APX001 study treatment; 1 set thereafter.
r. All *Candida* spp. isolates must be submitted to the mycology reference laboratory for confirmation of identification and susceptibility testing.
s. During Study Drug Treatment, daily blood cultures on Study Days 1 through 4 (minimum), continuing until 2 consecutive blood cultures negative for *Candida* spp. are reported.
t. Optional rapid diagnostic test, if available and used routinely for candidemia diagnosis; test (e.g., T2MR assay) must be Sponsor-approved; a subsequent confirmatory blood culture must also be performed to confirm *Candida* spp.
u. Plasma samples for PK (APX001 [prodrug] and APX001A [active moiety]) will be collected at Baseline (pre-dose), twice weekly during Study Drug Treatment, EOST, EOT, 2 weeks after EOT, or Early Termination. Optional: If body fluids are sampled as part of routine patient management (e.g., bronchoalveolar lavage, lumbar puncture, paracentesis, vitreal fluid collection, abscess drainage), within approximately 2 hours of blood sampling for PK, these samples may be stored for future analysis of APX001 and APX001A levels.
v. Other cultures, histopathology, and imaging tests to assess the site(s) and extent of candidemia infection, if applicable. If performed, these will be analyzed at the local study site.
w. Serum samples for (1,3)-β-D-glucan levels will be collected at Baseline (pre-dose) and EOST, or Early Termination (if applicable).
x. Study drug will be administered as an IV loading dose over 3 hours BID on Study Day 1 (or over the first 24 hours if started in the evening); on Study Days 2 and 3 study drug will be administered over 3 hours by IV QD; on Study Day 4 and onward, PO administration of the study drug may be considered if the patient meets the IV to PO switch criteria. Study drug will be administered for a maximum of 14 days (inclusive of the loading dose [Study Day 1]).
y. After completion of 14 days study drug therapy, if further antifungal treatment is indicated to complete treatment of candidemia in accordance with standard practice guidelines, fluconazole (unless susceptibility results warrant alternative antifungal therapy) may commence for up to a further 7 days.

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

3. SAMPLE SIZE DETERMINATION

A sample size of approximately 20 patients will be recruited in this open-label study. No formal statistical assessment for sample size determination has been performed. This sample size is considered adequate to provide the necessary data to evaluate the efficacy and safety of APX001.

4. INDEPENDENT DATA REVIEW COMMITTEE (DRC)

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

5. DATA SAFETY MONITORING BOARD (DSMB)

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

6. STUDY ENDPOINTS

6.1. Primary Efficacy Endpoints

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

6.2. Secondary Efficacy Endpoints

The secondary efficacy parameters include the following:

- Time to first negative blood culture;
- Percentage of patients with Mycological Outcomes at EOST, EOT, and 2 and 4 weeks after EOT;
- Percentage of patients with Treatment Success at EOT, and 2 and 4 weeks after EOT as determined by the DRC;

- Overall survival at Study Day 30; and
- Number of patients with TEAEs.

6.3. Exploratory Efficacy Endpoints

The exploratory efficacy parameters include the following:

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

6.4. Definitions for Efficacy Assessments

6.4.1. At End of Study Drug Treatment (EOST)

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

- Two consecutive blood cultures negative for *Candida* spp.;
- Alive at EOST; and
- No concomitant use of any other systemic antifungal therapies through EOST.

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

Mycological Outcome:

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

6.4.2. At End of Antifungal Treatment (EOT)

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

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

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

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

Mycological Outcome:

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

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

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

6.5. Microbiological Assessments

6.5.1. Blood Cultures

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

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

6.5.2. Cultures from Other Sites of Infection

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

6.5.3. Candida Spp. Testing by T2 Magnetic Resonance Assay

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

6.5.4. Intravascular Catheter Management and Log

If possible, all indwelling intravascular catheters should be removed and the catheter tips cultured prior to starting APX001 dosing. The entrance site should also be cultured if it appears infected. Intravascular catheter management should be managed at the site level as per local SOC.

6.6. Safety Endpoints

Safety assessments will include adverse events, vital signs, clinical laboratory evaluations, physical examination, and ECGs.

6.6.1. Adverse Events

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

6.6.2. Clinical Laboratory Evaluations

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

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

Standard Safety Chemistry Panel

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

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

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

Coagulation

International normalized ratio

Urinalysis

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

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

Other tests

Urine pregnancy test (females of childbearing potential only)

6.6.3. Vital Signs

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

6.6.4. APACHE II Score

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

6.6.5. Electrocardiograms

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

6.6.6. Physical Examinations

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

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

6.6.7. Pharmacokinetics

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

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

6.6.8. Dilated Fundoscopic Examination

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

6.6.9. Imaging Tests

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

6.6.10. Other Cultures and Histopathology

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

6.6.11. Intravascular Catheter/Device Management Log

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

7. STATISTICAL METHODOLOGY

7.1. General Considerations

7.1.1. Summary Statistics

Summary statistics will be presented in total. 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.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g. standard deviation) will be displayed to two decimal places greater than the original value.

7.1.2. Handling of Dropouts and Missing Data

Subjects who dropped out or had missing outcome data will be included in the denominator for efficacy analyses. A clinical failure occurring at an earlier time point will be carried forward to the subsequent visits.

In cases of missing or incomplete dates (e.g. Adverse event [AE] and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original eCRF will be presented in the data listings.

Missing values for other variables will not be imputed and only observed values will be used in data analyses and summaries.

7.1.3. Baseline Definition

For microbiological data, baseline pathogen(s) are *Candida spp.* isolated from the last positive blood sample collected within 96 hours prior to the first dose of study drug.

For all efficacy and safety endpoints, baseline is defined as the last measurement or assessment prior to the first dose of study drug.

7.2. Analysis Populations

7.2.1. Enrolled Population

The Enrolled Population is defined as all screened patients excluding screen failures.

7.2.2. Intent-to-Treat (ITT) Population/Safety Population

The ITT Population/Safety Population will include all patients who have received at least 1 dose of APX001.

7.2.3. Modified Intent-to-Treat (MITT) Population

The MITT Population will include all patients who satisfy the following criteria:

- Receive at least 1 dose of study drug; and
- Have a confirmed diagnosis of candidemia (blood culture positive for *Candida* spp.) within 96 hours of the start of treatment with APX001

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

7.2.4. Per-Protocol (PP) Population

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

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

Based on the above criteria, the validity listings will be provided to identify which patients to be excluded from the PP Population. After the study team's review, the decision to exclude a patient from the PP Population will be finalized and a list of patients with major protocol deviations leading to exclusion from the PP Population will be finalized and documented.

7.3. Patient Data and Study Conduct

7.3.1. Patient Disposition

Patient disposition will be summarized for the Enrolled Population and ITT Populations in total. The following patient disposition categories will be included in the summary:

- Patients who received study drug;
- Patients who did not receive study drug;

- Patients who completed 14 days of study drug;
- Patients who did not complete 14 days of study drug (and reason);
- Patients who took protocol-allowed step-down further antifungal treatment;
- Patients who did not take protocol-allowed step-down further antifungal treatment;
- Patients who completed the study; and
- Patients who did not complete the study (and reason).

For patients who did not complete 14 days of study drug and patients who did not complete study, a summary will be provided by reason of discontinuation. In addition, the total number of patients for each defined population will be tabulated.

7.3.2. Protocol Deviations

The number of patients with at least one reportable protocol deviation, and the number of patients with at least one reportable deviation in each category defined in the study protocol deviation plan will be presented in total based on the Enrolled Population and ITT Population.

Protocol deviations will also be listed by patient.

7.3.3. Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years);
- Sex;
- Race;
- Ethnicity;
- Height (cm);
- Weight (kg);
- Body mass index (BMI) (kg/m2);
- APACHE II score and categories (<10, 10-19, 20-30, or >30); and
- ICU vs. non-ICU.

Demographic and Baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate in total for the Enrolled Population, ITT, MITT, and PP Populations.

7.3.4. Baseline Infection Characteristics

All baseline pathogens will be summarized with counts and percentages of patients in total for the MITT and PP Populations.

Details of organism identification and antifungal susceptibility results including MICs of all antimicrobials tested will be listed by patient. Both data from local and central microbiological laboratories will be listed.

7.3.5. Medical History

The primary underlying condition leading to candidemia and other medical history will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA, Version 20.1).

Counts and percentages of patients with primary underlying condition and other medical history by SOC and PT will be summarized in total based on the ITT and MITT Populations.

All medical history will be listed by patient.

7.3.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization (WHO) Drug Dictionary (September 2017 B3 Version).

Prior medications are medications used before the first dose of study drug. Concomitant medications are medications that were taken on or after first dose of study drug.

The number and percentages of patients who receive the following prior and concomitant medications will be summarized by ATC class and preferred term in total for the ITT and MITT Populations:

- Prior medications;
- Concomitant medications;
- Prior antifungals;
- Protocol-allowed step-down fluconazole or alternative concomitant antifungals; and
- Additional concomitant antifungals except for protocol-allowed step-down antifungals.

All prior and concomitant medications and procedures will be listed by patient.

7.3.6. Dosing and Extent of Exposure

7.3.6.1. Study Drug

Days of exposure to study drug will be summarized for intravenous and oral dose in overall. Days of exposure to study drug will be calculated as the last dose date of study drug – first dose date of study drug + 1. Overall days of exposure to study drug will be summarized in total based on the ITT, MITT, and PP Populations with descriptive statistics and with counts and percentages of patients with exposure in the following categories:

- ≤7 days;
- >7 to ≤14 days; and

- >14 days

For patients who switch from intravenous to oral dose, the compliance rate for oral dose will be calculated as the total amount of doses received divided by the total amount of doses expected then multiplied by 100. The total amount of expected doses is the number of medication days multiplied by the expected doses per day. Number of medication days is the total number of days from the date of the first oral dose of study drug to the date of the last oral dose of study drug.

Percent compliance with oral study drug will be calculated using the following formula:

$$\%\text{compliance} = \frac{\text{total amount of doses received} * 100}{\text{expected doses per day} * \text{total number of medication days}}$$

The compliance rate for oral dose will be summarized with descriptive statistics in total for the ITT, MITT, and PP Populations. In addition, contingency tables will be provided to show the number and percentage of patients in each treatment group with compliance in the following categories: <80% and ≥80%.

7.3.6.2. Overall Antifungal Treatment

After completion of 14 days study drug therapy, if further antifungal treatment is indicated to complete treatment of candidemia in accordance with standard practice guidelines, fluconazole (unless susceptibility results warrant alternative antifungal therapy) may commence for up to a further 7 days.

The overall duration of antifungal treatment (study drug + protocol-allowed step-down further antifungal treatment) is defined as the last dose date of step-down further antifungal treatment − first dose date of study drug + 1. If patient did not take any step-down further antifungal treatment, the duration of antifungal treatment will be the same as duration of study drug.

The overall duration of antifungal treatment will be summarized in total based on the ITT, MITT, and PP Populations with descriptive statistics and with counts and percentages of patients with exposure in the following categories:

- ≤14 days;
- >14 to ≤21 days; and
- >21 days

The number and percentage of patients who took protocol-allowed step-down further antifungal treatment will also be tabulated based on the ITT, MITT, and PP Populations.

7.4. Efficacy Analysis

7.4.1. Primary Efficacy Analysis

The primary efficacy endpoint is Treatment Success at EOST as determined by the DRC.

The number and percentage of patients with Treatment Success or Treatment Failure at EOST determined by the DRC will be summarized descriptively in total for the MITT Population. The 95% two-sided exact binomial confidence interval will also be presented.

Additional analyses of the primary efficacy endpoint will be performed for the PP Population in the same manner.

7.4.2. Secondary Efficacy Analysis

Descriptive statistics will be provided for secondary efficacy endpoints as the following.

7.4.2.1. Treatment Outcome

Number and percentage of patients in the MITT and PP Populations with treatment outcomes (Treatment Success and Treatment Failure) at EOT as determined by the DRC will be presented descriptively, along with the 95% two-sided exact binomial confidence interval.

Number and percentage of patients in the MITT and PP Populations with treatment outcomes (Treatment Success Sustained, Clinical Relapse, and Other [Non-Relapse]) at 2 and 4 weeks after EOT as determined by the DRC will be presented descriptively, along with the 95% two-sided exact binomial confidence interval.

Number and percentage of patients in the MITT and PP Populations with treatment outcomes (Treatment Success and Treatment Failure) at EOST and EOT as determined by the Investigator will be tabulated, along with the 95% two-sided exact binomial confidence interval.

7.4.2.2. Mycological Outcome

The number and percentage of patients in the MITT and PP Populations with Eradication at EOST and EOT will be summarized descriptively, along with the 95% two-sided exact binomial confidence interval.

The number and percentage of patients in the MITT and PP Populations with Recurrence at 2 and 4 weeks after EOT as determined by the Investigator will be summarized descriptively, along with the 95% two-sided exact binomial confidence interval.

7.4.2.3. Time to First Negative Blood Culture

Time to first negative blood culture is defined as the number of days from first dose date of study drug to the date of first negative blood culture plus 1.

Time to first negative blood culture will be summarized in total using descriptive statistics for the MITT and PP Population.

In addition, the Kaplan-Meier estimate of the median time to first negative blood culture and the associated 95% confidence interval will be presented. Patients without a negative blood culture at post-baseline visits will be censored at the last assessment date.

7.4.2.4. Overall Survival at Study Day 30

Overall survival at Study Day 30 is defined as patient alive by study day 30.

The number of percentage of patients alive or dead by Study Day 30 will be summarized for the MITT and PP Population.

Time to death is defined as the number of days from first dose date of study drug to the date of death from any cause plus 1. Patients without death or lost to follow-up will be censored on the last date the patient is known to be alive. The Kaplan-Meier estimate of the median time to death and the associated 95% confidence interval will be presented.

7.4.2.5. DRC Assessments

Reasons for treatment failure according to DRC classifications (i.e. blood cultures did not become negative, or additional antifungals given, or died, or withdrew from study but did not die) will be summarized descriptively at EOST and EOT visits for the MITT and PP populations.

Reasons for relapse or other reasons for not having an outcome of sustained success at follow-up according to DRC classifications, will be summarized descriptively at 2 and 4 weeks after EOT for the MITT and PP populations.

Reasons for death according to DRC classifications (i.e. candidemia probably contributory, candidemia probably not contributory, or not known) will be tabulated for the MITT and PP populations.

7.4.3. Exploratory Efficacy Analysis

Change in serum (1,3)-β-D-glucan levels from Baseline (pre-dose) to EOST will be summarized in total with descriptive statistics for the MITT Population.

Correlation of blood culture and T2MR assay Candida spp. results from Baseline (pre-dose) through EOST will be explored. The number and percentage of patients with different Candida spp. isolated from blood culture and Candida spp. results from T2MR assay will be summarized by each visit from Baseline (pre-dose) through EOST for the MITT Population.

7.4.4. Other Efficacy Data

All other efficacy data will be listed by patient.

7.5. Safety Analysis

All safety analyses will be performed on the Safety Population.

7.5.1. Adverse Events

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using the MedDRA, Version 20.1. TEAEs are defined as AEs that start on or after the administration of study drug.

An overview of AEs will be provided including counts and percentages of patients (and event counts) with the following:

- Any AEs;
- Any TEAEs (overall and by maximum severity);

- Any study drug-related TEAEs (overall and by maximum severity);
- Any serious AEs (SAEs);
- Any treatment-emergent SAEs (TESAEs);
- Any study drug-related treatment-emergent SAEs (TESAEs);
- Any TEAEs leading to discontinuation of study drug;
- Any study drug-related TEAEs leading to discontinuation of study drug;
- Any AEs leading to discontinuation of study;
- Any study drug-related TEAEs leading to discontinuation of study; and
- Any AEs leading to death.

The number and percentage of patients who experienced at least one TEAE will be presented by system organ class and preferred term. Drug-related TEAEs, study drug withdrawals due to TEAEs, and all SAEs will be summarized in the same manner.

Summaries will be provided by worst grade for the number and percentage of patients with TEAEs and for patients with drug-related TEAEs by system organ class and preferred term.

Although a patient may have two or more TEAEs, the patient is counted only once within a System Organ Class and Preferred Term category. The same patient may contribute to two or more preferred terms in the same System Organ Class category or to two different System Organ Class categories.

A list of patients who have serious adverse events (SAEs), a list of patients who discontinue from study drug due to TEAEs, and a list of death due to AEs will be provided. All adverse events will be listed.

7.5.2. Clinical Laboratory Tests

Central laboratory test results (chemistry, hematology, coagulation, and urinalysis) at each scheduled visit and change from baseline will be summarized with descriptive statistics.

Shift tables from baseline to each scheduled post-baseline visit will be provided for selected chemistry parameters (ALT, AST, ALP, Total Bilirubin, Creatinine, and Creatinine Kinase) and hematology parameters (Hematocrit, Hemoglobin, Platelets, White blood cell count and differential). For chemistry parameters, the following categories will be used: < the lower limit of normal (LLN), normal, >ULN to ≤2×ULN, >2×ULN to ≤3×ULN, >3×ULN to ≤5×ULN, >5×ULN, and missing. For hematology parameters, the following categories will be used: low, normal, high, and missing.

The number and percentage of patients with the following potentially clinically significant abnormal liver function tests at any post-baseline visit will be summarized:

- ALT ≥3×ULN;
- ALT ≥5×ULN;

- ALT ≥10×ULN;
- AST ≥3×ULN;
- AST ≥5×ULN;
- AST ≥10×ULN;
- ALT or AST ≥3×ULN;
- Total Bilirubin >1.5×ULN;
- Total Bilirubin >2×ULN;
- ALP ≥1.5×ULN;
- ALP ≥2×ULN;
- ALT or AST ≥3×ULN and Total Bilirubin >1.5×ULN;
- ALT or AST ≥3×ULN and Total Bilirubin >2×ULN; and
- Potential Hy's Law cases: ALT or AST ≥3×ULN and Total Bilirubin >2×ULN, and ALP ≤ 2×ULN

A listing of patients with any post-baseline clinically significant abnormal liver function tests will be presented.

All clinical laboratory data will be listed. Values outside the normal ranges will be flagged.

7.5.3. Vital Signs

Descriptive statistics will be provided for vital sign data (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and oxygen saturation) presented as both actual values and changes from baseline over time.

A listing of all vital signs will be provided by patient.

7.5.4. Electrocardiograms

Descriptive statistics will be provided for 12-lead ECG interval data (Heart rate, PR, QRS, QT, and RR) and changes from baseline for each scheduled visit.

All 12-lead ECG findings will be listed by patient.

7.5.5. Physical Examinations

Physical examination findings will be listed by patient.

7.5.6. Other Safety Assessments

Other safety assessments will be listed by patient.

7.6. Pharmacokinetic Analyses

All pharmacokinetic analyses will be performed by another vendor and described in a standalone PK analysis plan.

A listing of the PK concentrations by patient will be provided.

8. INTERIM ANALYSIS

No interim analysis is planned for this study.

9. CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

No changes or plans to deviate from the analysis described in the protocol have been made.

10. PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in patient data listings which will be sorted by patient as applicable. Detailed Programming Specifications will be provided in a separate document.