STATISTICAL ANALYSIS PLAN

Protocol Title:	**An Open-Label Study to Evaluate the Efficacy and Safety of APX001 in Patients with Candidemia and/or Invasive Candidiasis Caused by *Candida auris***
Protocol Number:	APX001-203
Protocol Version/Date:	Version 4.0, 8 April 2020
Investigational Product:	APX001
Phase:	2
Sponsor:	Amplyx Pharmaceuticals, Inc. PPD PPD United States
SAP Version/Date:	Version 1.0, 8 February 2021

SIGNATURE PAGE

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This Statistical Analysis Plan is prepared by:

PPD

PPD
Reason: Approved
Date: Feb 8, 2021 16:39 EST

08-Feb-2021

PPD

PPD

Medpace, Inc.

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
PPD PPD Reason: Approved Date: Feb 8, 2021 16:49 EST PPD PhD PPD Medpace, Inc.	08-Feb-2021
PPD PPD Reason: Approved Date: Feb 8, 2021 16:57 EST PPD MD PPD Medpace, Inc.	08-Feb-2021
PPD PPD Reason: Approved Date: Feb 9, 2021 18:52 PST PPD MD PPD Amplyx Pharmaceutical, Inc.	09-Feb-2021

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
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 Drug Treatment
ICF	Informed Consent Form
ITT	Intent-to-Treat
IV	Intravenous(ly)
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 APX001-203. 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 patients aged 18 years and above, with candidemia and/or invasive candidiasis caused by *Candida auris*, who have limited antifungal treatment options.

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 successful Mycological Outcomes at End of Study Drug Treatment (EOST), and 2 and 4 weeks after EOST;
- Evaluate the percentage of patients with Treatment Success 2 and 4 weeks after EOST;
- Evaluate all-cause mortality at Study Day 30;
- Evaluate safety parameters, including number of patients with treatment-emergent adverse events (TEAEs); and
- Evaluate pharmacokinetic (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 treatment of candidemia and/or invasive candidiasis caused by *C. auris* in patients aged 18 years and over with limited antifungal treatment options. Approximately 4-6 sites will be selected from the Republic of South Africa and Panama. The Study Drug Treatment Period will be up to a maximum of 42 days (inclusive of the loading dose [Study Day 1]). There will be a Follow up Period of 4 weeks (+4 days) after EOST. The total duration of participation in the study is up to approximately 10.5 weeks (inclusive of the Screening Period [≤168 hours prior to Baseline]). Patients must have had *C. auris* confirmed in culture <120 hours (for candidemia) or <168 hours (for invasive candidiasis without candidemia) prior to qualification and dosing in the study.

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

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

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

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

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

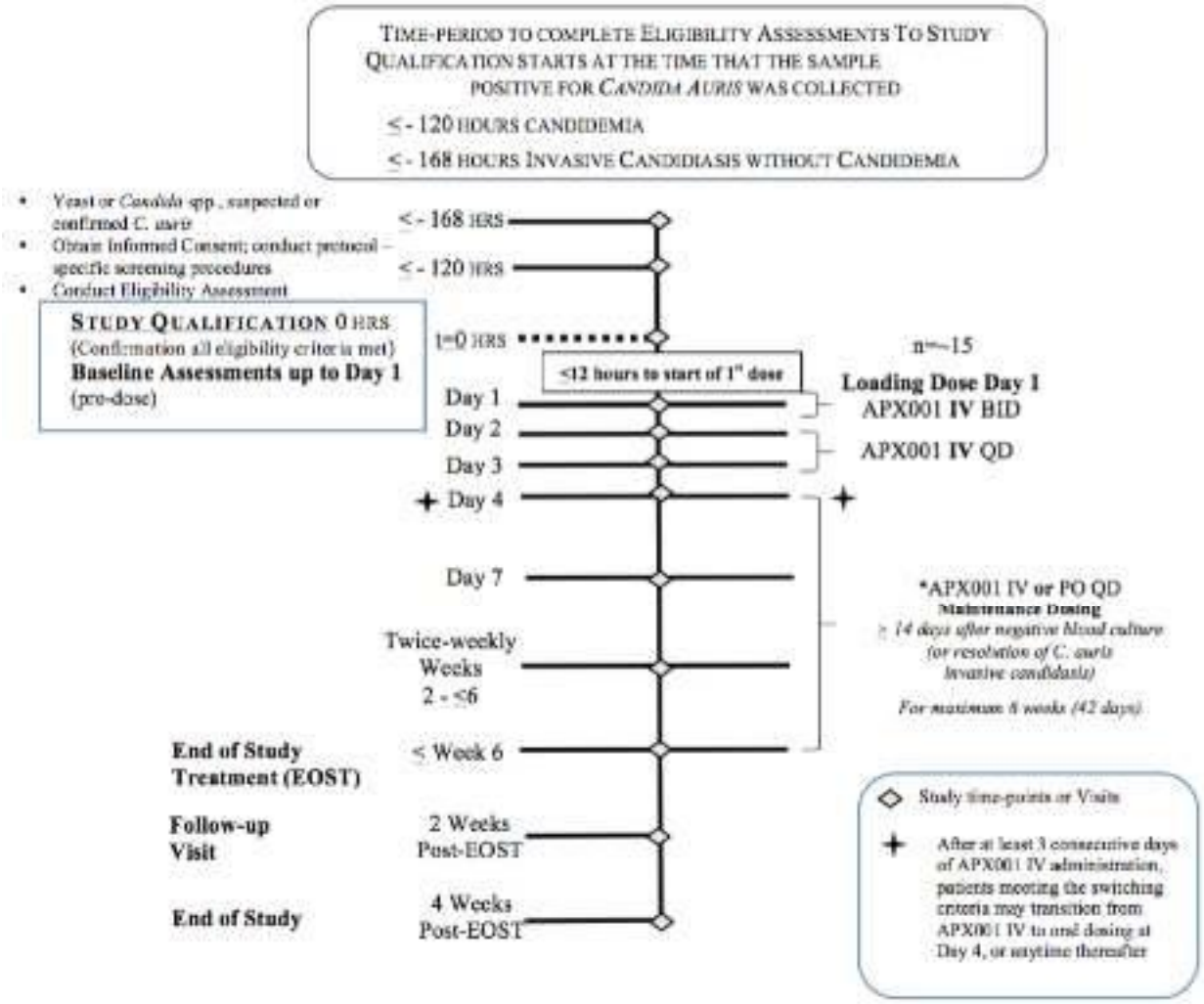
In the event of an inadequate response/failure on APX001 study treatment, the study drug may be discontinued and alternative antifungal treatment instituted.

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

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

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

A schematic representing the study's design is below and a complete schedule of procedures for the study is found in Table 1:



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

TABLE 1: SCHEDULE OF PROCEDURES

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

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

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

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

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

3 INDEPENDENT DATA REVIEW COMMITTEE (DRC)

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

4 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.

5 SAMPLE SIZE DETERMINATION

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

6 STUDY ENDPOINTS

6.1 Primary Efficacy Endpoints

The primary efficacy parameter is percentage of patients with Treatment Success at EOST as determined by the DRC.

6.2 Secondary Efficacy Endpoints

The secondary efficacy parameters include the following:

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

- All-cause mortality 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.

6.4 Definitions for Efficacy Assessments

6.4.1 At EOST

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

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

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

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

Successful Mycological Outcomes:

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

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

6.4.2 At Follow-up (2 Weeks and 4 Weeks After EOST)

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

- Unavailable for follow-up, or unevaluable at follow up for other reasons

Additional DRC assessment categories are provided in the DRC Charter

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

6.4.3 Microbiological Assessments

6.4.3.1 Blood Cultures

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

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

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

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

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

6.4.3.2 Cultures from Other Sites of Infection

For patients with invasive candidiasis, a tissue culture or aspirate/fluid sample confirmed positive for *Candida auris* that has been collected aseptically from a normally sterile site is required for inclusion in the study. Study qualification will occur within 168 hours of a confirmed positive tissue culture or aspirate/fluid collection. Isolates of all *Candida* spp. from SOC eligibility cultures and baseline and follow-up cultures must be submitted to the mycology reference laboratory for confirmation of identification and susceptibility testing. Tissue culture or aspirate/fluid samples for *Candida* spp. will be collected at Baseline (pre-dose), and where amenable to sampling during Study Drug Treatment, at EOST, and 2 and 4 weeks after EOST, or Early Termination. Collection of culture or aspirate/fluid samples may be stopped after at least one negative tissue culture or aspirate/fluid sample.

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

6.4.3.3 Intravascular Catheter Management and Log

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

6.4.4 Pharmacokinetic Assessments

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

6.4.5 Safety Endpoints

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

6.4.5.1 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.

6.4.5.2 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 Baseline (pre-dose), twice weekly during Study Drug Treatment, at EOST, and at 2 and 4 weeks after EOST, or Early Termination. If clinically indicated and at the discretion of the Investigator, or if a suspected adverse event is identified, clinical laboratory assessments may be conducted at any time during the study and compared to Baseline. 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

C-Reactive Protein	Chloride
Calcium	Creatinine
Creatine kinase	Gamma-glutamyl transferase
Estimated glomerular filtration rate	Inorganic phosphorus
Glucose	Lipase
Lactate dehydrogenase	Sodium
Potassium	Uric acid
Total protein	

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

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

Coagulation

Prothrombin time	International normalized ratio

Urinalysis

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

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

Other Tests

Urine pregnancy test (females of childbearing potential only)

6.4.5.3 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 1 through 4 and twice weekly thereafter during Study Drug Treatment for outpatients (daily while inpatient), EOST, and 2 and 4 weeks after EOST, or Early Termination. Height will be collected (from the patient's medical record) at Baseline only.

6.4.5.4 APACHE II Score

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

6.4.5.5 Electrocardiograms

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

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

6.4.5.7 Dilated Fundoscopic Examination

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

6.4.5.8 Imaging Tests

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

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 auris* isolated from the last positive blood sample collected within 120 hours (for candidemia) or last positive culture from a specimen (e.g., tissue, aspirate/fluid) sampled from a normally sterile site within 168 hours (for invasive candidiasis without candidemia) prior to qualification for the study.

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

7.2.4 Per-Protocol (PP) Population

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

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

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 documented.

The analysis based on PP Population specified in the following sections will be performed only if MITT and PP Population are not identical.

7.3 Patient Data and Study Conduct

7.3.1 Patient Disposition

Patient disposition will be summarized for the ITT/Safety Population and MITT Population 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 the study drug;
- Patients who did not complete the study drug (and reason);
- Patients who did not complete the study drug due to COVID-19;
- Patients who completed the study;
- Patients who did not complete the study (and reason); and
- Patients who did not complete the study due to COVID-19.

For patients who did not complete 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 deviation category defined in the study protocol deviation plan will be presented in total based on the ITT/Safety Population and MITT Population. In addition, the protocol deviations related to COVID-19 will be categorized and summarized separately.

In addition, number of patients with visits not completed, in-person partially completed, and performed virtually due to COVID-19 will be summarized for the ITT/Safety Population. The number of patients with visits performed out of window due to COVID-19 will also be tabulated.

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;
- Childbearing potential;
- 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 ITT/Safety Population, 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 and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA, Version 22.0). Counts and percentages of patients with medical history by system organ class and preferred term will be summarized in total based on the ITT/Safety Population and MITT Population.

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 (March 2019G 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/Safety Population and MITT Population:

- Prior medications;
- Concomitant medications;
- Prior systemic antifungals; and
- Concomitant systemic antifungals.

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

7.3.7 Study Drug Exposure and Compliance

Study drug includes both intravenous and oral dose. 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/Safety and MITT Populations with descriptive statistics and with counts and percentages of patients with exposure in the following categories:

- ≤14 days
- >14 to ≤28 days
- >28 to ≤42 days
- >42 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/Safety and MITT 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%.

7.4 Efficacy Assessment

The efficacy analysis will be performed based on MITT Population. The analysis will be repeated on PP Population if MITT and PP Population are not identical.

7.4.1 Primary Efficacy Endpoints

The primary efficacy parameter is percentage of patients with 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 of the treatment success rate 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 Endpoints

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 Sustained, Clinical Relapse, and Other [Non-Relapse]) at 2 and 4 weeks after EOST as determined by the DRC will be presented descriptively, along with the 95% two-sided exact binomial confidence interval for the sustained treatment success rate.

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

Number and percentage of patients in the MITT and PP Populations with Sustained Treatment Success at 2 and 4 weeks after EOST 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 and Presumed Eradication at EOST 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 EOST will be summarized descriptively.

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 through study Day 30.

The number of percentage of patients alive or dead through 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 one.. Patients who were not known to die, or were 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 EOST failure according to DRC classifications (i.e. because (i) Blood cultures and/or cultures from other sites did not become negative at EOST, (ii) *Candida* infection spread to other sites, (iii) Additional antifungals given, (iv) Patient died, (v) Patient withdrew from study but did not die, or (vi) Other), will be summarized descriptively at the EOST visit for the MITT and PP populations. Once a patient has failed treatment, they are subsequently evaluated only for survival and for relevant safety parameters.

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 EOST for the MITT and PP populations. Once a patient has relapsed, or has been assessed as a non-sustained success for any reason, they are subsequently evaluated only for survival and for relevant safety parameters.

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

Factors that can affect outcome, such as intravascular catheter management (timely removal of lines), will be also be summarized descriptively.

7.4.3 Exploratory Efficacy Endpoints

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.

7.4.4 Other Efficacy Data

All other efficacy data will be listed by patient.

7.5 Pharmacokinetic Assessment

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

7.6 Safety Assessment

Safety data will be summarized based on the ITT/Safety Population.

7.6.1 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 22.0. Treatment-emergent adverse events (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; and
- Any AEs leading to death.

The overview of AEs will be repeated for the subsets of AEs occurring during the treatment period and AEs occurring after the treatment period in the same manner above.

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.

A list of patients who have 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.

7.6.2 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
- 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.

7.6.3 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.

7.6.4 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.

7.6.5 Physical Examinations

Physical examination findings will be listed by patient.

7.6.6 Other Safety Assessments

Other safety assessments will be listed by patient.

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 and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.