Fosmanogepix Clinical Protocol C4791010 (APX001-202)

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

Statistical Analysis Plan (SAP)

Version: 1

Date: 14 November 2022

[redacted]

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APPENDICES

1. VERSION HISTORY

Associated Protocol Amendment	Rationale	Specific Changes
Original 29 Sep 2020	N/A	N/A

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

2. INTRODUCTION

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

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4791010, (Amendment 3.0, dated 29Sept2020). 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.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

2.2.1. Primary Objective

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

2.2.2. Secondary Objectives

The secondary objectives of this study are to:

- *Evaluate global response at End of Study Treatment (EOST).*
- *Evaluate safety parameters of fosmanogepix.*
- *Evaluate pharmacokinetic (PK) parameters of fosmanogepix and manogepix.*

2.2.3. Primary Estimand(s)

Not applicable. This is an open-label single arm Phase 2 study.

2.2.4. Secondary Estimand(s)

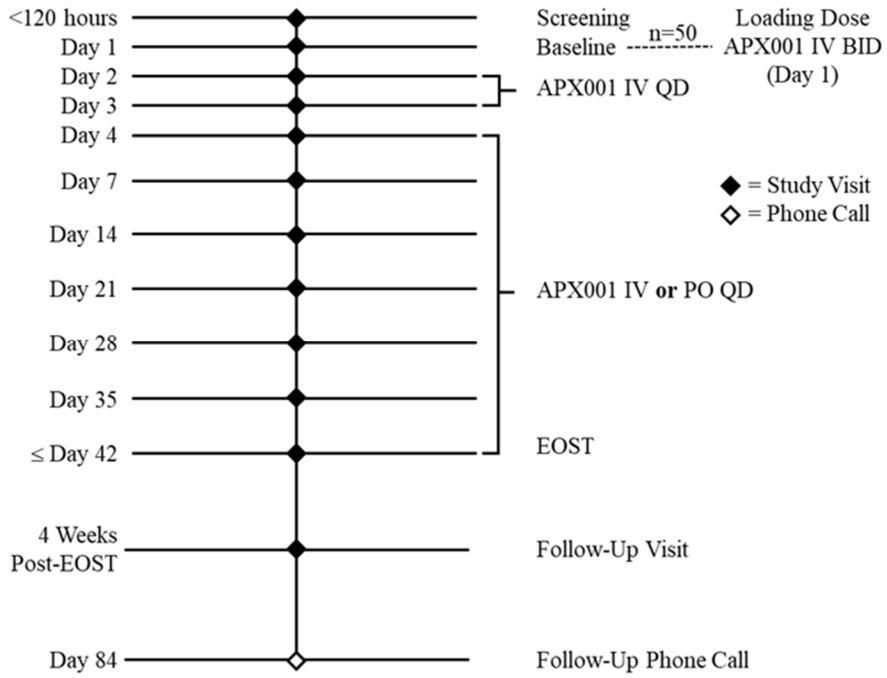
Not applicable. This is an open-label single arm Phase 2 study.

2.3. Study Design

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

This study will be conducted at up to 40 global sites. The study will enroll male and female patients aged 18 years and above with a confirmed diagnosis of invasive aspergillosis or invasive rare mold infection. Patients will have limited or no treatment options due to documented/anticipated resistance, contraindication, intolerance, or lack of clinical response to standard of care (SOC) antifungal therapy. The study will enroll two cohorts, Cohort A and B. Up to 40 patients will be enrolled in Cohort A, and these patients will have an IMI which was diagnosed according to the EORTC/MSGERC criteria. CCI [redacted] *Further details of the study design can be found in the protocol.*

Figure 1. Study Design



2.4. Sample Size Determination

Approximately 50 patients will be dosed in this open-label, parallel-group study, and will be enrolled in one of 2 cohorts, as follows:

Cohort A (~40 participants):

Patients with proven or probable IMI are eligible for inclusion in the mITT Population, which is the primary efficacy population (DRC confirmation required of proven or probable IMI).

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

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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Efficacy Endpoint(s)

The primary efficacy parameter is all-cause mortality through Day 42.

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

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

3.2. Secondary Efficacy Endpoint(s) Assessed by DRC

The secondary efficacy parameter for this study is Global Response at EOST/ET. Global response will be classified as follows according to prespecified criteria, as determined by the DRC **(**Guidelines for the DRC are described in the DRC Charter):

- Complete Response: Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease and radiological abnormalities, and mycological evidence of eradication of disease).

- Partial Response: Survival within the prespecified period of observation, improvement in attributable symptoms and signs of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden, as assessed by a quantitative and validated laboratory marker categorized as treatment success.

- Stable Response: Survival within the prespecified period of observation and minor or no improvement in fungal disease, but no evidence of progression, as determined based on a composite of clinical, radiological, and mycological criteria, progression of disease, or death (categorized as treatment failure).

- Progression of fungal disease: Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria.

- Death: Death during the prespecified period of evaluation, regardless of attribution. *If any patient has missing global response at EOST, it will be presented as 'Indeterminate' in the summary.*

Treatment outcomes for Global Response based on DRC assessment at EOST are defined as follows:

- Treatment success: Complete response or partial response.
- Treatment failure: Stable response, progression of fungal disease and death.

3.2.1. Other Secondary Endpoints

Other secondary endpoints include:

- Safety parameters of fosmanogepix (see Section 3.6).
- Pharmacokinetic (PK) parameters of fosmanogepix/manogepix (see Section 3.4).

3.2.1.1. Clinical Response

Clinical response based on DRC Assessment at EOST will be categorized as follows:

- Complete response: Resolution of all attributable symptoms, signs, and/or bronchoscopic abnormalities present at Baseline.
- Partial response: Major improvement (usually nearly complete) in attributable symptoms, signs, and/or bronchoscopic abnormalities present at Baseline.
- Stable response: Minor or no improvement in attributable symptoms, signs, and/or bronchoscopic abnormalities present at Baseline, but patient continued on therapy without deterioration.
- Failure: Deterioration in attributable symptoms, signs, and/or bronchoscopic abnormalities necessitating alternative antifungal therapy or resulting in death.

3.2.1.2. Radiological Response

Radiological Response based on DRC Assessment at EOST will be categorized as follows:

- Complete response: Resolution (normalization of X-ray, CT scan, etc.) of all radiological abnormalities attributed to aspergillosis compared to Baseline.
- Partial response: Major improvement of radiological abnormalities attributed to aspergillosis compared to Baseline.
- Stable disease: Minor or no improvement of radiological abnormalities attributed to aspergillosis compared to Baseline.

- Failure: Worsening of radiological abnormalities attributed to aspergillosis compared to Baseline.

3.2.1.3. Mycological Response

Mycological Response based on DRC Assessment at EOST will be categorized as follows:

- Eradication: Absence of *Aspergillus* (or other mold) in a relevant clinical specimen (culture negative and absence of fungal elements by microscopy or histopathology, as appropriate).

- Presumed eradication: Inferred in patients with complete clinical and imaging response for whom an invasive procedure for obtaining the relevant clinical specimen is not performed.

- Persistence: Any evidence based on culture, microscopy, or histopathology for the presence of *Aspergillus* (or other mold).

- Indeterminate: Inadequate data available for categorization as eradication, presumed eradication, or persistence.

3.2.1.4. Investigator Assessment of Global Response

Global response based on investigator assessment at EOST are as follows:

- Complete Response: Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease and radiological abnormalities, and mycological evidence of eradication of disease).

- Partial Response: Survival within the prespecified period of observation, improvement in attributable symptoms and signs of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden, as assessed by a quantitative and validated laboratory marker categorized as treatment success.

- Stable Response: Survival within the prespecified period of observation and minor or no improvement in fungal disease, but no evidence of progression, as determined based on a composite of clinical, radiological, and mycological criteria, progression of disease, or death (categorized as treatment failure).

- Progression of fungal disease: Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria.

- Death: Death during the prespecified period of evaluation, regardless of attribution. *If any patient has missing global response at EOST, it will be presented as 'Indeterminate' in the summary.*

- Treatment Outcomes for Global Response based on Investigator Assessment at EOST:
    - Treatment success: Complete response or partial response.
    - Treatment failure: Stable response, progression of fungal disease and death.

3.2.1.5. Investigator Assessment of Clinical Response

Clinical response based on investigator assessment at EOST are as follows:

- Complete response: Resolution of all attributable symptoms, signs, and/or bronchoscopic abnormalities present at Baseline.
- Partial response: Major improvement (usually nearly complete) in attributable symptoms, signs, and/or bronchoscopic abnormalities present at Baseline.
- Stable response: Minor or no improvement in attributable symptoms, signs, and/or bronchoscopic abnormalities present at Baseline, but patient continued on therapy without deterioration.
- Failure: Deterioration in attributable symptoms, signs, and/or bronchoscopic abnormalities necessitating alternative antifungal therapy or resulting in death.

3.2.1.6. Investigator Assessment of Radiological

Radiological response based on investigator assessment are as follows:

- Complete response: Resolution (normalization of X-ray, CT scan, etc.) of all radiological abnormalities attributed to aspergillosis compared to Baseline.
- Partial response: Major improvement of radiological abnormalities attributed to aspergillosis compared to Baseline.
- Stable disease: Minor or no improvement of radiological abnormalities attributed to aspergillosis compared to Baseline.
- Failure: Worsening of radiological abnormalities attributed to aspergillosis compared to Baseline.

3.2.1.7. Investigator Assessment of Mycological Response

Mycological Response based on Investigator Assessment at EOST as Follows:

- Eradication: Absence of *Aspergillus* in a relevant clinical specimen (culture negative and absence of fungal elements by microscopy or histopathology, as appropriate).

- Presumed eradication: Inferred in patients with complete clinical and imaging response for whom an invasive procedure for obtaining the relevant clinical specimen is not performed.

- Persistence: Any evidence based on culture, microscopy, or histopathology for the presence of *Aspergillus.*

- Indeterminate: Inadequate data available for categorization as eradication, presumed eradication, or persistence.

3.2.1.8. Clinical Signs and Symptoms

Clinical signs and symptoms included Cough, Dyspnea, Pleuritic Chest Pain, Fever, Hemoptysis, Visual Disturbance, Skin Lesion, Headache, Sinus Pain, Joint Pain and/or swelling. Clinical signs and symptoms were assessed as absent, mild, moderate, severe or not done. ("Not done" is recorded at the symptoms level).

3.2.1.9. Next-generation Sequencing of Cell-free Pathogen DNA

DNA sequencing was performed by a reference genetic laboratory (Karius) to facilitate the identification of infecting pathogens; a subject level listing will be provided.

3.2.1.10. CCI [redacted] Levels

CCI [redacted] levels were assessed at local LAB (investigator site) and central LAB. Subject level listing of CCI [redacted] for local LAB and central LAB will be provided.

3.2.1.11. Fungal Culture

Fungal cultures were assessed at local clinical labs (investigator site). Isolated pathogens were sent to a central LAB (JMI Labs) for confirmatory identification and susceptibility testing. Subject level listing by subject by pathogen will be provided for local LAB and central LAB results.

3.2.1.12. Radiology Assessments

Radiology assessments were performed at screening, Day 14 and at EOST, and if clinically indicated on Days 7, 21, 28, 35, and 42; at the Follow-Up Visit; and at the E/T Visit (if applicable). Subject level listing of imaging will be provided.

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[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

3.4. Pharmacokinetic Assessments

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

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

3.5. Baseline Variables

Baseline data will be collected according to the schedule of procedures in the protocol.

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

For microbiological data, baseline pathogen(s) are *Aspergillus* spp. or rare molds (eg, *Scedosporium* spp., *Fusarium* spp., *Lomentospora* spp., and Mucorales fungi, etc.) isolated from the last positive fungal culture sample collected prior to the first dose of study drug.

3.6. Safety Endpoints

Safety assessments will include treatment-emergent adverse events and serious adverse events, including deaths, vital signs (temperature, systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation), clinical laboratory evaluations (serum chemistry, hematology, coagulation, urinalysis), 12-lead ECGs, physical examination including specific neurology assessments.

3.7. 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. Any adverse event that started on or after the administration of study drug will be considered a treatment emergent adverse event (TEAE). AEs will be captured from the time of initial dosing through the Follow-Up Visit. Events that occur after Day 42 (maximum duration of treatment with fosmanogepix) but prior to and including the Follow-Up visit will be considered treatment

emergent. All AEs will be coded to system organ class (SOC) and preferred term (PT) using the MedDRA.

3.8. Clinical Laboratory Evaluations

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

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

A urine or serum pregnancy test will be performed at Screening; on Days 1 (Baseline) (if the Screening Visit occurred ³96 hours prior to Day 1 [Baseline]), 28, and 42; at EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable) for all women of childbearing potential.

3.9. Vital Signs

Vital signs will include temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation and will be collected at Screening; predose on Days 1 (Baseline), 7, 14, 21, 28, 35, and 42; at EOST; at the Follow-Up Visit; and at the E/T Visit (if applicable).

3.10. Electrocardiograms

A 12 lead ECG will be obtained in triplicate at Screening, Days 3, 7, 14 and 42, EOST, and the E/T Visit (if applicable).

3.11. Physical Examinations

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

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

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Population	Description	Applicable Analysis
ITT	All participant entered to the study	
Modified Intent-to-Treat (mITT)	The modified Intent-to-Treat (mITT) Population will include all patients in the ITT Population who satisfy the following criteria: Receive at least 1 dose of study drug. Cohort a: have a diagnosis of proven or probable IMI confirmed by the DRC.	The mITT Population will be the primary population used for the efficacy analyses
compliance	The Per-Protocol Population will include all patients in the mITT Population who satisfy the following criteria: • Meet the protocol's key inclusion criteria and exclusion criteria. • Receive at least 80% of the intended doses; and • Have no major protocol violations, ie, not received any prohibited concomitant medications per the protocol that would impact the efficacy of study drug.	Per protocol analyses will not be performed due to the small size of the study and due to design of study (eg, open label). This has been documented in the study log.
Safety	All participants who receive at least 1 dose of study intervention.	For all safety endpoints
PK population	The PK Population will include all patients who receive any amount of study drug and have evaluable PK data.	For PK parameters

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. General Considerations

The mortality rate will be analyzed at Day 42 CCI [redacted] with Day 42 being primary. Key secondary endpoints and global response at EOST will be summarized descriptively. CCI [redacted] at each scheduled visit and change from baseline will be summarized with descriptive statistics. CCI [redacted] at each scheduled visit and change from baseline will be summarized with descriptive statistics. The above analyses will be conducted in the mITT population for Cohort A. At the time this analysis plan was written, all subjects were enrolled in Cohort A CCI [redacted]

5.2. Hypotheses and Decision Rules

The primary hypothesis for Cohort A is that the mortality rate at Day 42 is <45% based on 1-sided exact binomial test at the alpha = 0.1 level of significance.

The hypothesis will be as follows:

H_0: $\pi \geq 45\%$

H_a: $\pi < 45\%$

where π is the all-cause mortality through Day 42. 1-sided 90% confidence interval (CI) or two-sided 80% CIs will be provided. It can be concluded that the all-cause mortality at Day 42 is less than 45% (based on historical control data) if the upper limit of the CI is lower than 45%.

5.3. General Methods

5.3.1. Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

5.3.2. Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the CRF.

5.3.3. Definition of Baseline

For microbiological data, baseline pathogen(s) are *Aspergillus* spp. or rare molds (eg, *Scedosporium* spp., *Fusarium* spp., *Lomentospora* spp., and Mucorales fungi, etc.) isolated from the last positive fungal culture sample collected 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 first dose of study drug.

5.3.4. Summary Statistics

Summary statistics will be presented for Cohort A only. 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.

5.3.5. Analyses for Binary Endpoints

For all binary endpoints, proportion of participants and 95% CI will be presented.

5.3.6. Analyses for Continuous Endpoints

For continuous endpoints, mean (SD), median, max, min will be presented.

5.3.7. Analyses for Categorical Endpoints

For categorical endpoints, number and percentage will be presented with the associated sample size.

5.4. Methods to Manage Missing Data

Patients who dropped out or had missing outcome data will be included in the denominator for efficacy analyses. If any patient has missing global response, clinical response, radiological response, or mycological response from the DRC or Investigator at EOST, it will be presented as missing in the summary.

In cases of missing or incomplete dates (eg, 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 electronic Case Report Form (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.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

All-cause mortality through Day 42 will be summarized for Cohort A using descriptive statistics.

6.2. Main Analysis

All-cause mortality through Day 42 is calculated as the percentage of patients who die after the first dose of study drug through Day 42 from any cause using the mITT population.

For Cohort A only, the 1-sided exact binomial test at the alpha = 0.1 level of significance will be used to test the hypothesis as below:

H0: $\pi \geq 45\%$

Ha: $\pi < 45\%$

where π is the all-cause mortality through Day 42. 1-sided 90% confidence interval (CI) or two-sided 80% CIs will be provided. It can be concluded that the all-cause mortality at Day 42 is less than 45% (based on historical control data) if the upper limit of the CI is lower than 45%.

6.3. Secondary Endpoint(s)

Global response at EOST. Global responses will be classified as complete or partial response (categorized as treatment success), stable response, progression of fungal disease, or death (categorized as treatment failure) by the Investigator and adjudicated by the DRC.

Number and percentage of patients in the mITT Populations with global responses at EOST as determined by the DRC will be tabulated for Cohort A. Two-sided 80% exact binomial CIs of the treatment success rate will be presented for Cohort A only.

Global response will also be summarized descriptively as, complete response, partial response, stable response, progression of fungal disease, death at EOST, ET and EOST/ET (LOCF).

6.4. Other Endpoint(s)

6.4.1. Clinical Responses

Clinical responses will be assessed by DRC and by investigator will be classified as complete response, partial response, stable response, and failure. Number and percentage of patients in the mITT Populations with clinical responses at EOST as determined by the DRC will be tabulated for Cohorts A. Two-sided 80% exact binomial CIs of the treatment success (complete and partial response) rate will be presented for Cohort A.

Clinical responses at EOST as determined by the Investigator will be tabulated in the same manner.

6.4.2. Radiological Response

Radiological responses will be assessed by DRC and by investigator and will be be classified as (complete response, partial response, stable response, and failure.

Number and percentage of patients in the mITT Populations with radiological responses at EOST as determined by the DRC will be tabulated for Cohort A. -Two-sided 80% exact binomial CIs of the treatment success (complete and partial response) rate will be presented for Cohort A.

Radiological responses at EOST as determined by the Investigator will be tabulated in the same manner.

6.4.3. Mycological Response

Mycological responses will be assessed by DRC and by investigator and will be classified as eradication, presumed eradication, persistence, or indeterminate.

Number and percentage of patients in the mITT Populations with mycological responses at EOST as determined by the DRC will be tabulated for Cohort A. Two-sided 80% exact binomial CIs of the treatment success (eradication and presumed eradication) rate will be presented for Cohort A.

Mycological responses at EOST as determined by the Investigator will be tabulated in the same manner.

6.4.4. Clinical Signs and Symptoms

Clinical signs and symptoms will be summarized at Baseline and study visit. Number and percent of participant with each clinical signs and symptoms of absent, mild, moderate, severe, or not done will be presented.

6.4.5. Next Generation Sequencing of Cell-free Pathogen DNA

DNA sequencing was to be performed by a reference genetic laboratory (Karius) to facilitate the identification of infecting pathogens; subject level listing will be provided.

6.4.6. CCI Levels

A subject level listing of CCI for (local lab investigator site) and (central LAB) will be provided.

6.4.7. Fungal Culture

A subject level listing by pathogen will be provided for local (investigator site) and central laboratory results.

6.4.8. Radiology Assessments

A subject level listing of imaging results will be provided.

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6.6. Pharmacokinetic Assessment

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

6.7. Subset Analyses

The following sub-group analysis will be provided for primary and key secondary endpoint:

- Primary endpoint: Day 42 mortality by baseline pathogen.
- Secondary endpoint: global response at EOST by baseline pathogen.
- Primary endpoint: Day 42 mortality by limited treatment option criteria.
- Secondary endpoint: global response at EOST by limited treatment criteria.
- Primary endpoint: Day 42 mortality by participant who switch to 400 mg BID fosmanogepix dose vs. maintained with 800 mg of fosmanogepix dose QD.
- Secondary endpoint: global response at EOST by participant who switch to 400 mg BID fosmanogepix dose vs. maintained with 800 mg of fosmanogepix dose QD.

[redacted]

6.8. Baseline and Other Summaries and Analyses

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

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years vs. ≥65 years).
- Sex.
- Race.
- Ethnicity.
- Height (cm).
- Weight (kg).
- Body mass index (BMI) (kg/m^2).
- eGFR (ml/min /1.73 m^2) calculated by CKD-EPI equation and categories (<30, 30-<60, 60-<90 and ≥90).

- Eastern cooperative oncology group (ECOG) status (0, 1, 2, 3, 4, and 5).
- Severity of disease assessed by Karnofsky performance status and categories (≤30 vs. >30).
- Hospitalization status (ICU, non-ICU, emergency room, or other).
- Diagnosis of IMI per DRC (possible IMI, probable IMI, proven IMI, and not categorized).
- Site of IMI as below:
    - Cerebral.
    - Cutaneous abscess.
    - Eye.
    - Intraabdominal.
    - Pulmonary.
    - Renal.
    - Sinuses.
    - Thrombus.
    - Urogenital.
    - Other.
- Limited Treatment Options Criteria:
    - Documented or anticipated resistance.
    - Contraindication to soc.
    - Intolerance to soc.
    - Lack of clinical response to soc.
    - No treatment options.

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by Cohort A for the ITT/Safety Population, mITT, Populations.

6.8.1. Baseline Infection Characteristics

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

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

6.8.2. Medical History

Medical history will be coded to SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA, Version 25.0). Counts and percentages of patients with medical history by SOC and PT will be summarized for Cohort A based on the ITT/Safety Population and mITT Population. Medical history will be listed by patient.

6.8.3. Study Conduct and Participant Disposition

Patient disposition will be summarized for the ITT/Safety Population and mITT Population by Cohort A. The following patient disposition categories will be included in the summary:

- Patients who received 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 the impacts of the covid-19 pandemic.
- Patients who completed the study through Day 42.
- Patients who did not complete the study through Day 42.
- Patients who completed the study through the follow-up visit (4 weeks after EOST).
- patients who did not complete the study (and reason**).**

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

6.8.4. Protocol Deviations

The number of patients with at least one protocol deviation, and the number of patients with at least one deviation in each category defined in the study protocol deviation plan. Deviations will be presented for Cohort A by category for important protocol deviations based on the ITT/Safety Population and mITT Population. In addition, the protocol deviations related to COVID-19 pandemic will be categorized and summarized separately. Protocol deviations will also be listed by patient.

6.8.5. Study Drug Exposure and Compliance

Study drug includes both intravenous and oral fosmanogepix. Days of exposure to study drug will be calculated as follows:

- Days of exposure Overall (IV + oral dose) as the last dose date of study drug - first dose date of study drug +1.
- Days of exposure IV dose only (as the last dose date of IV - the first dose date of IV) - number of days that participant was switched to oral dose.
- Day of exposure oral dose only (as the last date of oral dose - first date of oral dose) - number of days that the participant was in IV dose.

Descriptive statistics with count and percentage of participants with overall (oral + iv dose), oral dose and iv dose, for cohort a based on the ITT/safety population and mITT population will be provided 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. In addition for oral dose, for participant who switch from 800 mg/day QD to 400 mg BID, number and presence of participant will be provided.

For patients who did not switch from intravenous (IV) to oral dose, the compliance rate for IV 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 IV dose of study drug to the date of the last IV dose of study drug.

The overall study drug compliance will be the oral dose compliance plus the IV dose compliance.

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

> %"compliance"= ("total amount of doses received * " 100)/"expected doses per day * the total number of medication days"

The compliance rate will be summarized with descriptive statistics overall (Oral + IV) dose, oral dose, and IV dose for Cohort A for the ITT/Safety Population and mITT Population. In addition, contingency tables will be provided to show the number and percentage of patients with compliance in the following categories: <80% and ≥80%.

6.8.6. Prior and Concomitant Medications and Nondrug Treatments

Prior and Concomitant medications will be coded by class and preferred term using the World Health Organization (WHO) Drug Dictionary.

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 class and preferred term by Cohort A for the ITT/Safety Population and mITT Population:

- Prior medications.
- Concomitant medications.
- Prior systemic mold antifungals.
- Other Licensed Antifungal Treatments that were optionally prescribed by investigator after 6 week of study drug treatment (this data has been collected in the prior antifungal module).
- Concomitant systemic mold antifungals.

In addition, duration of prior systemic antifungals prior to first dose of study drug will be tabulated in the following categories: 1 day, 2 days, 3 days, 4 days, 5 days, and >5 days.

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

6.8.7. Safety Summaries and Analyses

Safety data will be summarized based on the Safety Population for Cohort A.

6.8.8. Adverse Events

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 TRSAEs).
- Any TEAEs leading to discontinuation of study drug.
- Any TRAEs leading to discontinuation of study drug.
- Any AEs leading to death.

The number and percentage of patients who experienced at least one TEAE will be presented by SOC and PT. TEAEs, TRAEs, study drug withdrawals due to TEAEs and TRAEs, 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 TRAEs by SOC and PT.

Although a patient may have two or more TEAEs, the patient is counted only once within a SOC and PT category. The same patient may contribute to two or more PTs in the same SOC category.

A list of patients who have SAEs, a list of patients who discontinue from study drug due to TEAEs or TRAEs, and a list of death due to AEs will be provided. All AEs will be listed.

6.8.9. Laboratory Data

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.

6.8.10. 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.

6.8.11. 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. The average of the triplicates at each visit will be used in the summary. All 12-lead ECG findings will be listed by patient.

6.8.12. Physical Examination

Physical examination including neurological findings will be listed by patient.

7. INTERIM ANALYSIS

No interim analysis is planned for this study.

7.1. Data Review Committee

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

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

7.2. Data And Safety Monitoring Board

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

8. REFERENCES

Not Applicable.

APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary endpoint: Mortality rate at Day 42.	Primary	mITT	All observed data.	Cohort A: One-sided exact binomial test at the alpha = 0.1 level of significance:
Secondary Endpoint: Global response at EOST	Secondary	mITT	All observed data	Cohort A: Two-sided 80% exact binomial CI
Clinical responses	Other	mITT	All observed data	Cohort A: Two-sided 80% exact binomial CI
Radiological response	Other	mITT	All observed data	Cohort A: Two-sided 80% exact binomial CI
Mycological response	Other	mITT	All observed data	Cohort A: Two-sided 80% exact binomial CI
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

The following table defines the visit windows and labels to be used for reporting:

Visit Number	Visit Label	Definition [Day window]
1	Screening	Day -5 to -1
2	Baseline	Day 1
3	Day 2	= Day 2
4	Day 3	= Day 3
5	Day 7	= Day 7, with a window of ±1 days, (ie, days 6 to 8)
6	Day 14	= Day 14, with a window of ±1 days, (ie, days 13 to 16)
7	Day 21	= Day 21, with a window of ±2 days, (ie, days 19 to 23)
8	Day 28	= Day 28, with window from 26 to 30
9	Day 35	= Day 35, with window from 33 to 37
10	Day 42	= Day 42, with window from 40 to 44
11	EOST[2]	End of study treatment (Date of last treatment) +2 days
12	FU	(Date of FU) ±3 days
13	FU Phone call	Day 84 ±3 days

Appendix 3. List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AspUTest	Aspergillosis urine test
ATC	Anatomical therapeutic chemical
BAL	Bronchoalveolar lavage
BID	Twice daily
BMI	Body mass index
CBC	Complete blood count
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSR	Clinical study report
CT	Computed tomography
DRC	Data Review Committee
DSMB	Data and Safety Monitoring Board
E/T	Early Termination
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EORTC	European Organization for Research and Treatment of Cancer
EOST	End of Study Treatment
IA	Invasive Aspergillosis
IMI	Invasive mold infection
INR	International normalized ratio
ITT	Intent-to-Treat
IV	Intravenous(ly)
LLN	Lower limit of normal
LTO	Limited Treatment Option
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MSG	Mycosis Study Group
OLAT	Other licensed antifungal therapy
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PO	Oral(ly)
PT	Prothrombin time
QD	Once daily
qPCR	Quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
spp.	Species
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
ULN	Upper limit of normal
WHO	World Health Organization