STATISTICAL ANALYSIS PLAN

Version 1.0, dated 17-Oct-2019

A Phase 2, Open-Label, Non-Comparative, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Isavuconazonium Sulfate for the Treatment of Invasive Aspergillosis (IA) or Invasive Mucormycosis (IM) in Pediatric Subjects

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AC	Adjudication Committee
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Intervals
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variation
ECG	Electrocardiogram
EOS	End of Study
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
GM	Galactomannan
hCG	Human chorionic gonadotropin
HLT	High Level Term
IA	Invasive Aspergillosis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFD	Invasive Fungal Disease
IM	Invasive Mucormycosis
INR	International normalized ratio
IV	Intraveneous
K-M	Kaplan-Meier
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
N	Sample Size
PD	Protocol Deviation
PK	Pharmacokinetic
PKAS	Pharmacokinetics Analysis Set
PPK	Population Pharmacokinetics
PT	Preferred Term
PTT	Partial thromboplastin time
QTc	Corrected Q-T Interval
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation

Abbreviations	**Description of abbreviations**
AC	Adjudication Committee
SOC	System Organ Class
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings and Figures
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

List of Key Terms

Terms	Definition of terms
Adverse Event	An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject who has been administered a pharmaceutical product (remark: this means any investigational medicinal product) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
Baseline	Baseline is the time point prior to the first dose of study medication. The last measurements/evaluation prior to first dose of therapy is considered the baseline measure/evaluation.
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug is usually given to a subject, and continues until the last assessment after completing administration of the test drug as stated in the protocol regarding V5 (End of Trial).
Screening	Process for retrieving candidates for the study. Process for checking the eligibility of subjects usually done during the "pre-investigational period". Screening evaluations will be performed on the same day of study enrollment.
Screening failure	Evaluated subject but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive randomized or open label study treatment or decided not to participate anymore (withdrew consent) prior to completing pre-investigational treatment period.

Serious Adverse Event	An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: results in death; a life-threatening adverse drug experience (subject is at immediate risk of death.); insubject hospitalization or prolongation of existing hospitalization, not associated with planned study procedures; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect in the offspring of a subject who received study drug or a medically important events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes procedures for executing the statistical analysis to fulfill the objectives of the study.

Changes to the planned analyses in the final SAP will be justified in the Clinical Study Report (CSR).

2 STUDY OBJECTIVE(S) AND DESIGN

2.1 Study Objective(s)

Safety Objective: To evaluate the safety and tolerability of isavuconazonium sulfate in pediatric subjects.

Efficacy Objective: To assess the efficacy of isavuconazonium sulfate for the treatment of invasive Aspergillosis (IA) or invasive Mucormycosis (IM) in pediatric subjects.

Pharmacokinetic Objective: To evaluate the pharmacokinetics of isavuconazole by monitoring the plasma concentrations in pediatric subjects during treatment with isavuconazonium sulfate.

2.2 Study Design

This is a phase 2, open-label, non-comparative, multicenter study to assess the safety, efficacy and pharmacokinetics of isavuconazonium sulfate in pediatric subjects for the treatment of IA or IM.

An approved informed consent form (ICF) must be obtained from the subject's parent or legal guardian, and, if required, child assent prior to any study related procedures being performed.

Approximately 30 centers in the United States (US) and European Union (EU) are planned to enroll approximately 30 subjects ages 1 to < 18 years of age

The subjects will enter into screening anytime between days -5 to day 1 (predose). All subjects will be assigned to open-label treatment. Treatment will begin on day 1 and then subjects are followed for 60 days after the last dose for safety. Treatment will be administered until the subject has a successful outcome as judged by the investigator or for a maximum duration of 84 days (IA) or 180 days (IM), whichever occurs first.

After successful screening, all subjects will receive a loading regimen of isavuconazonium sulfate, which consists of a dose every 8 hours (± 2 hours) on days 1 and 2 (for a total of 6 doses), followed by once daily maintenance dosing for up to 84 days (IA) or day 180 (IM) of dosing. The first maintenance dose should start 12 to 24 hours after the administration of the last loading dose. Subsequent maintenance doses will be administered once daily (24 hours ± 2 hours from the previous maintenance dose).

Blood sampling for the analysis of trough levels will be obtained from all subjects. The samples should ideally be drawn immediately prior to the next dose of study medication, but must be taken no earlier than 1 hour prior to the next dose on days 7, 14, 21, 42 and 84 or end of treatment (EOT). **In addition to the above, 24-hour pharmacokinetic samples will be obtained on any day between day 14 and day 42, while the subject is still receiving study drug, for subjects that consent to participation in the 24-hour pharmacokinetic assessment.** No additional samples are taken from IM subjects between day 84 through day 180.

Throughout the study, safety and tolerability will be assessed by the recording of AEs, vital signs, electrocardiograms (ECGs) and safety laboratory evaluations. All subjects will complete 2 follow-up visits (via telephone at the discretion of the investigator), 30 and 60 days, after the subject's day 84 (IA) /day 180 (IM) or EOT visit.

If subject discontinues study drug prior to day 84 or day 180 (for IM), all EOT procedures must be completed. If subject continues to allow consent, end of study (EOS) information will be collected 30 and 60 days after EOT.

Details of the schedule of clinical assessments are available in the protocol.

2.3 Randomization

This is an open-label study with no randomization.

3 SAMPLE SIZE

The sample size of approximately 30 subjects is planned. No formal sample size calculation was performed.

Evaluable subjects are subjects that have received at least 1 dose of study drug. Every effort will be made to achieve at least 5 evaluable subjects per age cohort: 1 to < 12 years of age and 12 to < 18 years of age. The sponsor reserves the right to stop enrollment if the cohort

requirements are not achieved. There will be no replacements for any subject that is enrolled but later determined to be non-eligible.

4 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

The determination of whether subjects are included or excluded from the safety and efficacy analysis sets may require using data which will arrive after database hard-lock.

4.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who are enrolled and receive at least one dose of study drug. This will be the primary analysis set for efficacy analyses.

4.2 Modified Full Analysis Set

The modified FAS (mFAS) will consist of the subset of the FAS subjects who have either probable or proven IA or IM diagnosis at baseline or up to 10 days after first dose. Subjects with a possible diagnosis of IA or IM will not be included in this subset. The mFAS will be a secondary analysis set for efficacy analyses. Select demographic and baseline characteristics may also be summarized for the mFAS.

4.3 Safety Analysis Set

The safety analysis set (SAF) will consist of all subjects who are enrolled and receive at least 1 dose of study drug. For this study, the SAF is the same as the FAS. For the statistical summary of the safety data, the SAF will be used.

4.4 Pharmacokinetics Analysis Set

The pharmacokinetic analysis set (PKAS) consists of all subjects who took at least 1 dose of study drug and who have at least 1 plasma concentration. Inclusion of subjects in the PKAS with missing data or major protocol deviations will be considered by the pharmacokineticist on a case-by-case basis.

The PKAS will be used for all summaries and analyses of the pharmacokinetic data.

5 ENDPOINTS

5.1 Safety Endpoints

Safety endpoints will include adverse events (AEs), vital signs, electrocardiogram (ECGs) and laboratory parameters.

5.2 Efficacy Endpoints

5.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be all-cause mortality through day 42. Any death that occurred after first dose of study through day 42 will be included. Any lost to follow-up between first dose and day 42 will be considered a death.

5.2.2 Secondary Efficacy Endpoint(s)

5.2.2.1 Key Secondary Endpoint(s)

The key secondary efficacy endpoints will be all-cause mortality through day 84 and EOT. Any death that occurred after first dose of study drug through day 84 and EOT will be included. Any lost to follow-up between first dose and day 84 and EOT will be considered a death.

5.2.2.2 Additional Secondary Endpoints

Additional secondary efficacy endpoints will include:

- Adjudication Committee (AC) and Investigator assessment of clinical, radiological and mycological response through day 42, day 84 and EOT.
- AC assessment of overall response at day 42, day 84 and EOT

5.3 Other Endpoints

Other endpoints encompass pharmacokinetic variables, including plasma trough (pre-dose) levels on days 7, 14, 21, 42 and 84 or EOT.

6 STATISTICAL METHODOLOGY

6.1 General Considerations

Continuous data will be summarized descriptively including the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized by frequencies and percentages with 95% confidence interval (CI). Efficacy data will be summarized by type of infection including IA, IM and mixed IA/IM infected subjects. Safety summaries will also be presented for by type of infection. The IA group will comprise subjects with IA infection without known IM infection; the IM group will comprise subjects with IM without known IA infection; and the IA/IM group will comprise subjects with mixed IA/IM infection. Analysis Windows will be used and, for those parameters with weekly data collection, are illustrated below in Section 6.9. For those parameters collected less often appropriate windows will be defined. Note that, IM and IA/IM infected subjects will be reported to conclusion of treatment and 60 day follow-up although day 180 is not considered an endpoint analysis. Kaplan Meier (K-M) analyses for mortality will incorporate all survival data to day 240 if IM subjects are included.

All data summarization and analyses will be performed using SAS® Version 9.1.3 or higher. Specifications for table, figures and data listing formats can be found in the Tables, Listings, and Figures (TLF) specifications.

6.2 Study Population

In general, data such as subject disposition, demographics and baseline characteristics will be summarized for FAS population.

6.2.1 Disposition of Subjects

Disposition of subjects will be summarized for all subject.

Number of subjects who complete or prematurely discontinue from treatment or study (i.e., follow up period) will be summarized. For each discontinuation, the primary reason reported by the investigator will be summarized. Number and percentage of subjects for each analysis population will be summarized.

6.2.2 Protocol Deviations

The number and percentage of subjects with the following protocol deviation (PD) criteria will be summarized for each criterion. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion.

Some unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

6.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized descriptively for FAS and mFAS. Descriptive statistics for age, weight, body mass index (BMI) and height at study entry will be presented. Frequency tabulations for sex, ethnicity, age cohorts and race will be presented.

Please note that all Physical Examination Data will be reported in listing. For Post-Baseline visits, recorded abnormal findings/conditions that have worsened from Screening/Baseline, and are clinically significant, will be recorded on the Adverse Events form.

6.2.4 Underlying Diseases or Conditions

All primary underlying diseases and risk factors will be reported using the FAS and mFAS populations. Primary underlying disease diagnosis will be listed with full status of disease diagnosis, timing, severity and/or resolution level. This data will be tabled using Medical Dictionary for Regulatory Activities (MedDRA) codes and listed alphabetically. The number and percentage of subjects will be summarized by diagnosis [system organ class/preferred

term (PT)] and presentation status (New Diagnosis, Remission and Relapse). The summary will also include solid organ transplant and bone marrow or other progenitor cell transplant by type.

6.2.5 Baseline IFI

The descriptive summary includes subjects in each category of fungal infection site and fungal culture organism(s) by genus at baseline using the FAS and mFAS populations. Baseline will include all data collected from Day -28 to Day 10, as relavant. These include Host factors, Clinical factors, Mycological Criterion and Other invasive fungal disease (IFD) signs.

In addition, categorization of patient's fungal infection will include Proven, Probable or Possible. This categorization is evaluated again on Day 10. Day 10 may provide more information than baseline given time for additional confirmatory laboratory results for subjects that may upgrade or downgrade fungal diagnosis. For example, a final baseline evaluation of subject status Proven, Probable or Possible will be determined using the combination of data collected.

6.2.6 Previous and Concomitant Medications

Prior, concomitant and post medications will be summarized by therapeutic subgroup (Anatomical Therapeutic Chemical [ATC] 2nd level) and chemical subgroup (ATC 4th level) and preferred World Health Organization (WHO) using the FAS and mFAS populations. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups. Systemic antifungal therapies will be reported separately.

Previous medications are defined as medications that subjects started and ended prior to first administration of study medication. Analysis Windows will be used, See below Section 6.9. Concomitant medications are defined as any medications that subjects took after the first dose of study medication and through 60 days post EOT. Medications that started prior to first administration of study drug and continued while study drug was given will be counted in both previous and concomitant medications.

6.2.7 Infectious Disease History

History of all fungal, viral and bacterial infections within 14 days prior to screening will be reported among FAS and mFAS. The data will be coded using MedDRA. The number and percent of subjects in each PT will be presented in alphabetic order. All medical history will be included in the listings.

6.3 Study Drug Exposure and Compliance

Study drug exposure will be descriptively summarized for the SAF and mFAS population. Extent of exposure is defined as the number of days between the start and the end date of study drug, where the duration will be calculated by: (end date – start date+1). Additionally

average daily mg dose and average daily mg/kg doses, for LD and maintenance, IV and Oral summaries will be presented using descriptive statistics for continuous data.

The number and percent of subjects with an extent of exposure will be summarized within the following day ranges: >0 to ≤ 2 days, >2 to ≤ 7 days, >7 to ≤ 14 days, >14 to ≤ 21 days, >21 to ≤ 42 days, >42 to ≤ 56 days, >56 to ≤ 84 days, and >84 days. In addition, cumulative exposure will be summarized by the number and percent of subjects for the following categories: ≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 42 days, ≥ 56 days and ≥ 84 days.

6.4 Analysis of Efficacy

Efficacy variables will be summarized for IA, IM and IA/IM disease groups using FAS and mFAS populations. No formal inferential analyses will be performed. Frequencies, percentages, min/max and 95% CIs will be part of the description/summary of the data.

6.4.1.1 Analysis for Primary Efficacy Endpoint(s)

The primary efficacy endpoint will be all-cause mortality through day 42. Any death that occurred after first dose of study drug through day 42 will be included where each subject will be either classified as a dead or alive. Subjects who died on or before day 42, as well as subjects who are lost to follow-up before day 42 will be counted as deaths. The crude all-cause mortality rate will be calculated by dividing the number of deaths by the number of FAS subjects, and a 2-sided exact 95% CI will be calculated.

6.4.1.2 Other Analysis of Primary Efficacy Endpoint(s)

All-cause mortality rate over time will be estimated using Kaplan-Meier method. This analysis will generate a survival function from Day 1 through Day 42. A subject without reported death will be censored on the patient's last assessment day. The cumulative probabilities of mortality rates (100%-survival rates) by Day 42 will be presented.

6.4.1.3 Sensitivity Analysis for Primary Efficacy Endpoint

The primary efficacy endpoint will be analyzed as in Section 6.4.1.1 using the mFAS population. In addition mFAS patients taking excluded concomitant medications used to treat IFDs will be eliminated for analysis of primary endpoint.

A secondary sensitivity analysis will apply a condition on the crude success rate of overall outcome of treatment evaluated by the AC on Day 42. Patients who die before or on Day 42 will be considered failures even if the DRC considers them successes. The crude success rate of overall outcome of treatment evaluated by the AC at Day 42 incorporating this condition will be summarized. A 95% CI for this crude success rate of overall outcome of treatment evaluated by the AC at Day 42 will be calculated using exact confidence limits. This sensitivity analysis will only be performed if any patient died by Day 42 is considered a success for treatment by the AC.

6.4.1.4 Subgroup Analysis for Primary and Secondary Efficacy Endpoint

Primary and secondary efficacy endpoints will be analyzed as in Section 6.4.1.1 for the following subgroups:

Grouping variable	Subgroups
Age groups	1 to < 12 years of age
	12 to < 18 years of age
Organism	IA
	IM
	Mixed IA/IM
	Other

Site of Infection
Considered ad hoc depending on number of sites.

6.4.2 Analysis of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints will be all-cause mortality through day 84 and EOT. The crude mortality rate will be calculated by dividing the number of deaths by the number of FAS and mFAS subjects, and a 2-sided 95% exact CI will be calculated. All deaths, which occurred on Day 1 (after initial dosing) to days 84 and EOT.

6.4.2.1 Other Analysis of Key Secondary Efficacy Endpoint(s)

Rate of death over time will be estimated using K-M which will generate a survival function from Day 1 through 84 and for Day 1 through EOT. A subject obsevred to endpoint time, and without reported death, will be censored on the subject's last assessment day. The cumulative probabilities of mortality rates (100%-survival rates) by the end of study will be presented. K-M curve for time to death will be generated.

6.4.3 Analysis of Additional Secondary Efficacy Endpoints

Additional secondary efficacy endpoints will be overall, clinical, radiological and mycological response through day 42, day 84 and EOT. AC will assess all endpoints, Investigator's assessment include all endpoints except the overall response.

Each endpoint with the assessment criteria defined below will be summarized descriptively for FAS and mFAS populations through day 42, day 84 and EOT. Frequencies and 95% CI will be reported. All data will be represented in Listings by subject.

6.4.3.1 Investigator-assessed Clinical Response

Category	Outcome
Success	• resolution of all attributable signs and symptoms OR

	• resolution of attributable clinical symptoms and physical findings
Failure	• no resolution of any attributable signs and symptoms OR • no resolution of any attributable signs and symptoms (no change) or worsening of any attributable signs and symptoms
Not Evaluable	• Results not available /subject unevaluable OR • No attributable signs and symptoms

6.4.3.2 Investigator-assessed Mycological Response

Category	**Outcome**
Success	• Eradicated • Presumed Eradication
Failure	• Persistence • Presumed persistence
Not Evaluable	• Indeterminate • No Mycological Follow-up Results Available
No Mycological evidence at screening (up to day 104)	Remains as is
No baseline signs, not applicable for response**.**	Remains as is

6.4.3.3 Investigator-assessed Radiological Response

Category	**Outcome**
Success	• ≥ 90% improvement • ≥ 50% to < 90% improvement • ≥ 25% to 50% improvement (for Day 42 only)
Failure	• < 25% improvement at any time • No Signs o**r** Radiological Images
Not Evaluable	• Results Not Evaluable
	• No Radiological Data Available

6.4.3.4 AC-assessed Clinical Response

Clinical response will be defined as follows:

Summary	**Category**	**Outcome**
Success	Complete	• Resolution of all attributable clinical symptoms and physical findings

	Partial	• Resolution of at Least some of the clinical symptoms and physical findings associated with IFD
Failure	Stable	• Minor of no change in clinical symptoms and physical findings associataed with IFD
	Progression	Worsening or new clinical symptoms and physical findings associated ith IFD, or if alternative systemic antifungal treatment is required
Not Evaluable	Not Assessed	
	No clinical signs or symptoms at baseline	

6.4.3.5 AC-assessed Mycological Response

	Category	**Outcome**
Success	Eradication	No growth of the original (at baseline) causative organism on culture or identified by histology/cytology on post baseline (after day 7) cultures and/or histology/cytology
	Presumed eradication	Missing post baseline documentation of eradication of the original causative organism at baseline PLUS resolution of all or some clinical symptoms/physical finding
Failure	Persistence	Persistence of the original causative organism cultured or identified by histological /cytology at baseline or ??
	Presumed Persistence	Missing post baseline documentation of the persistence of the original causative organism at baseline PLUS no resolution or worsening of any clinical symptoms/physical findings
Not Evaluable	No Mycological Evidence	

6.4.3.6 AC-assessed Radiological Response

Summary	Category	Outcome
Success	Complete:	≥ 90% improvement
	Partial	At least < 25% response at day 42 and at least 50% by Day 84
Failure	Stable	Minor or no change in radiographic abnormalities associated with IFD, but no signs of progression
	Progression	Worsening or new radiological abnormalities associated with IRD
Not Evaluable	No Post baseline Radiology	No post baseline Radiology available with baseline evidence of radiolical disease
	Radiology	Radiology not applicable at baseline

6.4.3.7 AC-assessed Attributable Mortality

Category	Outcome
Directly Due to IFD	Death directly due to consequences of progressive IFD (clear evidence that mortality is due to progressive IFD)
Evidense Death Associated with IFD	Death associated with evidence of residual or ongoing IFD at time of death, but death may be due to IFD or progression of underlying disease
No Evidense Death Associated	Death associated with no evidence of residual or ongoing IFD)
Indeterminant	Indeterminant Cause
No Known Death	No Known Death

6.4.3.8 AC-assessed Overal Response

Category	Outcome
Success	• Complete-Success • Partial-Success
Failure	• Stable-Failure • Progression-Failure
Not Evaluable	• Results Not Evaluable

6.4.4 Other Secondary Endpoints

Population pharmacokinetics and/or pharmacokinetic/pharmacodynamics analyses will be performed by modeling and simulation scientist. All details of the population pharmacokinetic analysis will be

described in a separate analysis plan and a separate population pharmacokinetic modeling report will be written.

6.5 Analysis of Safety

All safety data will be presented for the SAF population. AEs will be coded using MedDRA. Frequency and percentage will be presented for each category.

6.5.1 Adverse Events

TEAE is defined as an AE observed after starting administration of the study drug through 30 days after EOT. The number and percentage of subjects with treatment-emergent AEs, serious adverse events (SAEs), AEs leading to withdrawal of treatment, and AEs related to study drug will be summarized by MedDRA system organ class, MedDRA High Level term, and MedDRA preferred term for overall subjects and by subjects in each age cohort. The number and percentage of AEs by severity will also be summarized. All AEs will be listed.

A study drug-related TEAE is defined as any TEAE with a causal relationship of YES by the investigator. The incidence of treatment emergent AEs will be summarized by relationship to study drug and severity for all subjects and by each age cohort. The protocol defines how Treatment Emergent AEs are determined. Although all AEs are collected, the summary Table will be based on the TEAEs.

Clinically significant out-of-range laboratory findings are to be determined and documented by the investigator/subinvestigator who is a qualified physician. Clinically significant changes will be recorded as AEs.

An overview table will include the following:

- Number of TEAEs,
- Number and percentage of subjects with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of subjects with drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number of TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug, and
- Number of deaths.

The number and percentage of subjects with TEAEs, as classified by SOC, High Level Term (HLT), and PT will be summarized. Summaries will be provided for the following:

- TEAEs

- drug related TEAEs,
- serious TEAEs,
- drug related serious TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- drug related TEAEs leading to permanent discontinuation of study drug,

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by time interval. For each adverse event in a particular interval, a subject will be counted if there is an onset of a treatment-emergent adverse event regardless of onset in other intervals.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by subgroups defined in Section 6.5.7.

6.5.2 Clinical Laboratory Evaluation

Clinical laboratory samples will be collected and reported based on timepoints as listed in the Protocol Table 1 and Table 2 in Section 1 based on lab sample collection visits.

Clinical Laboratory variables will be created for each of the following:

Chemistry:	**Hematology:**
Sodium Potassium Magnesium Calcium Chloride Glucose Creatinine Creatine phosphokinase/Creatine kinase Alkaline phosphatase (ALP)	Red blood cells White blood cells (total leukocytes) Hemoglobin Hematocrit Platelets (thrombocytes) Neutrophils (ANC) Eosinophils Basophils Lymphocytes Monocytes Blast cells
Hepatic Panel:	**Pregnancy Test:**
Albumin Total bilirubin (TBL) Direct Bilirubin Total Protein Alanine aminotransferase (ALT) Aspartate aminotransferase (AST)	Human chorionic gonadotropin (hCG) **Other:** Serum galactomannan (GM) Partial thromboplastin time/international normalized ratio (PTT/INR)

The baseline value will be the last non-missing value taken on or prior to first dose of study drug. Quantitative values evaluated by the central laboratory including hematology and biochemistry will be summarized using mean, standard deviation, minimum, maximum and median at each analysis visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same

way. Clinical Laboratory data will be reported using the SAF population by Clinical Laboratory Tests collected at baseline and days 7, 28, 56 and 84 (or EOT).

Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings. For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline for subjects.

Each laboratory result will be classified as low, normal, or high at each visit according to the laboratory supplied reference ranges as specified in the Protocol.

6.5.3 Liver Safety Assessment

The liver safety assessments will be summarized by the categories below based on the measurement from Alkaline Phasphatase (ALP), Alanine Transaminase (ALT), total bilirubin (TIBILI), Aspartate Transaminase (AST), and their combination. These parameters will be based on measurements from a central laboratory.

The subjects highest value from Day 1 to Day 84 IA or Day 180 IM or EOT will be used. This criterion is without regards to the subjects baseline value.

- ALT > 3xULN, > 5xULN, > 10xULN, > 20xULN
- Total Bilirubin > 2xULN
- (ALT or AST > 3xULN) and Total Bilirubin > 2xULN
- (ALT or AST > 3xULN) and ALP < 2xULN and Total Bilirubin > 2xULN

The last 2 criteria to where 2 or more parameters are evaluated will be with the measurements on the same day or up to 1 day apart. The samples within 1 day to be considered. For example, if ALT is on day 10, ALP in on day 11 and TIBILI in on day 12, this data should be considered. If ALT and ALP is on day 10, and TBILI is on day 11, this data should be considered.

The samples within 1 day apart can be used however the last criterion with 2 parameters, all 3 should be from the same day to be considered. For example, if ALT in on day 10

An eDish display plot of all patients will be created. The step-one eDISH including ALT alanine aminotransferase, TBL total bilirubin, eDISH evaluation of drug-induced serious hepatotoxicity, ULRR upper limit of reference range or normal will be created with all patients plotted.

6.5.4 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for subjects in the SAF by treatment day from day 1 to day 84 (or EOT).

Vital signs data will be displayed in listings.

The baseline visit (screening predose period day -5 to 5) is the last non-missing measurement value taken prior to initial study drug administration. Post baseline visits will include vital signs measured prior to and again approximately 1 hour after the end of each infusion.

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and temperature) will be summarized using mean, standard deviation, minimum, maximum and median by Treatment Visit. Within subject change in vital sign values between visits will be summarized from baseline on.

6.5.5 Routine 12-lead Electrocardiograms

Number and percent of subjects with 12 lead ECG abnormalities as well as number. and percent of subjects whose 12 lead ECG reading changed from normal at baseline to abnormal will be tabulated by Analysis Visit.

The number and percentage of subjects who have treatment emergent changes toward worst category in the ECG interpretations assessed by investigators will be caluculated. The interpretations are the followings: Normal, Abnormal-clinically relevant and Abnormal-not clinically relevant. Subjects who have both baseline and at least one post-baseline value will be included.

6.5.6 Pregnancies

A detailed listing of all pregnancies will be provided.

6.5.7 Other Safety-Related Assessments

None.

6.5.8 Subgroups of Interest for Safety

Safety data will be summarized for for IA, IM and mixed IA/IM groups separately. Selected safety variables (treatment emergent adverse events and vital signs) will be summarized using summary statistics for the subgroups defined on the basis of the categorized variables listed below:

Grouping variable	Subgroup
Age group	< 12 years
	>= 12 years

6.6 Analysis of Pharmacokinetic

6.6.1 Estimation of Pharmacokinetic Parameters

Sampling times along with plasma concentrations of isavuconazonium sulfate levels will be displayed in listings. Descriptive statistics (e.g. n, mean, SD, minimum, median, maximum, coefficient of variation (CV), geometric mean and geometric CV will be provided for plasma concentrations of isavuconazole.

Plasma concentration data from this study will be used to support a population pharmacokinetic (PK) model developed for Isavuconazonium Sulfate. The results and the model development will be described in detail in a separate PPK report. All details of the pharmacokinetic analysis will be described in a separate analysis plan and a separate population pharmacokinetic modeling report will be written.

Existing population pharmacokinetic model will be updated based on isavuconazole plasma concentration data obtained from subjects who have at least 1 pharmacokinetic sample. Population pharmacokinetics and/or pharmacokinetic/pharmacodynamics analyses will be performed by modeling and simulation scientist.

6.7 Other Analyses

None.

6.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

No interim analyses are planned for this study.

6.9 Analysis Windows

AEs and Vital signs will be summarized using Analysis Windows as below:

Analysis Visits	**Analysis Windows**
Baseline	Day(s) <=1 up to initiation of first dose
Day 2	Day 2
Day 3	Day 3
Day 7	Day 5 to 9
Day 14	Day 12 to 16
Day 21	Days 19 to 23
Day 28	Days 26 to 30
Day 35	Days 33 to 37
Day 42	Days 40 to 44
Day 49	Days 47 to 51
Day 56	Days 54 to 58
Day 63	Day 61 to 65
Day 70	Days 68 to 72
Day 77	Days 75 to 79

Cont.

Day 84	Days 80 to 91
Day 110	Days 103 to 117
Day 140	Days 133 to 147
Day 85[1]	Days 81 to 100
Day 115[1]	Days 101 to130
Day 145[1]	Days 143 to 147
Day 210[1]	Days 203 to 217
Day 240[1]	Days 233 to 247

[1]Applies to IM and IA/IM subjects.

See Appendix 1 for details of parameters for visit windows.

6.9.1 Imputation Rules for Incomplete Dates

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs to Treatment Visit and to determine whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

In case of missing partial start and stop dates for AEs and concomitant medications, the following rules will be used:

If the start date is missing or partial:

- if the month is missing, use January
- if the day is missing, use the first day of the month under consideration
- if the year is missing, use year of the informed consent date
- if the entire date is missing, use informed consent date

If the stop date is missing or partial:

- if the month is missing, use December
- if the day is missing, use the last day of the month under consideration
- if the year or the entire date is missing, set the stop date to December 31st, 2019

If the imputed start date is after the stop date, then the imputed start date will be 1 day prior to the stop date.

For AEs, a missing or incomplete onset date will be imputed according to the following conventions.

If an onset date is missing or only the year is known, the imputed onset date will be the date of first dose of study drug.

If only the year is known for the AE onset date, the imputed onset date will be the latest of the following non-missing dates:

- Date of first dose of study drug
- January 1 of the year of AE onset date

If only the month and year is known for the onset date, set the surrogate onset date to the first day of that month and then apply the following rules.

- If the month and year of the onset date is prior to the month and year of the first dose of study drug, then the surrogate onset date will be the imputed onset date.
- If the month and year of the onset date is on or after the month and year of the first dose of study drug, then the imputed onset date will be the **latest** of the following non-missing dates:
  - Date of first dose of study drug
  - Surrogate onset date

    If the imputed onset date is after the adverse event end date, the imputed onset date will be the same as the adverse event end date.

If more than one observation exists within the analysis window, the observation closest to the scheduled visit day will be selected for that visit. If there are two observations that have the same distance from the scheduled day, the value that is after the scheduled day will be selected in the analysis. If more than one observation is made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.

6.9.2 Outliers

Clinically significant out-of-range laboratory findings are to be determined and documented by the investigator/subinvestigator who is a qualified physician. At all scheduled time points during the clinical study, should any of the clinical laboratory test results be outside the normal range, the investigator may decide to repeat tests on new samples.

7 REVISION AND RATIONALE

7.1 List of Changes in SAP Version 2.0 from Version 1.0

The changes from the approved SAP Version 2.0 (Dated dd-Mmm-yyyy) to Version 3.0 that impact analyses are listed with the rationale in the table below.

SAP Sections	Description	Rationale

7.2 List of Changes in SAP Version 3.0 from Version 2.0

The changes from the approved SAP Version 1.0 (Dated dd-Mmm-yyyy) to Version 2.0 that impact analyses are listed with the rationale in the table below.

SAP Sections	Description	Rationale
xxx	yyyy	zzzzz
aaaa	bbbb	cccc

8 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

9 APPENDICES

9.1 Appendix 1 Visit Windows

The value used is that which is closest to the defined assessment day and also within visit day windows. If two values are equally close, the latter is used in the analysis.

All the assessments will be allocated to electronic Case Report Form (eCRF) visit based on the table below.

Visit Windows

Protocol visit	Target day	Visit window	Visit number
Screening and Baseline	≤D1	D-5 to D1	Pre dose period
V1 (Day1)	D1	D1	Visit 1
V2	D2	D2	Visit 2
V3	D3	D3	Visit 3
V4	D7	D5 to D9	Visit 4
V5	D14	D12 to D16	Visit 5
V6	D21	D19 to D23	Visit 6
V7	D28	D26 to D30	Visit 7
V8	D35	D33 to D37	Visit 8
V9	D42	D40 to D44	Visit 9
V10	D49	D47 to D51	Visit 10
V11	D56	D54 to D58	Visit 11
V12	D63	D61 to D65	Visit 12
V13	D70	D68 to D72	Visit 13
V14	D77	D75 to D79	Visit 14
V15	D84	IA D77 to D91 or IM D82 to D86	Visit 15 IA EOT
IA EOS	D110	D103 to D117	IA Follow-up
IA EOS	D140	D133 to D147	IA Follow-up
V16	D115	D113 to D117	IM Visit 16
V17	D145	D143 to D1146	IM Visit 17
V18	D180	D173 to D187	IM Visit 18 EOT

IM EOS	D210 (or 30 day EOS)	D203 to D217	IM Follow-up
IM EOS	D240 (or 60 day EOS)	D233 to D247	IM Follow-up

9.2 Appendix 2 Key Contributors

PPD, Astellas

PPD, Phastar

PPD, Astellas

PPD, Astellas

PPD, Astellas

9.3 Appendix 3 Author and Approver Signatures

<Approve in MAGIC and retain the text indicating that "e-signatures are attached at end of document." If wet signatures are obtained, delete the above statement about e-signature.>

<Create more signature lines as appropriate in each region. Note that MAGIC does not require a box frame around although the older SAP template included.>

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PPD