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

ISN/Protocol 9766-CL-0107

Version 4.0

Incorporating Substantial Amendment 3 [See Section 13]

05 Sep 2019

IND 72593

Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way
Northbrook, IL 60062

Protocol History:
Version 1.0 [24Aug2018]
Version 1.1 [05Sep2018] Incorporating Non-substantial Amendment 1
Version 2.0 [12Feb2019] Incorporating Substantial Amendment 1
Version 3.0 [08May2019] Incorporating Substantial Amendment 2

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 15 Sponsor's Signatures].

2. COORDINATING INVESTIGATOR'S SIGNATURE

The coordinating investigator's signature can be found in [Section 14 Coordinating Investigator's Signature]; located at the end of this document.

3. INVESTIGATOR'S SIGNATURE

A Phase 2, Open-Label, Non-Comparative, Multicenter Study to Evaluate the Safety and Tolerability, 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 have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

Date (DD Mmm YYYY)

Printed Name: ....

<Insert name and qualification of the Investigator>

Address: .....

.....

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24-hour Contact for Serious Adverse Events (SAEs) See [Section 5.5.5 Reporting of Serious Adverse Events] for SAE Fax Number and Email	**Please fax or email the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Pharmacovigilance, US** **Fax number: +1-888-396-3750 or +1-847-317-1241** **Email: Safety-US@astellas.com**
Medical Monitor/Study Physician (US sites):	PPD ICON Clinical Research, US PPD
Medical Monitor/Study Physician (EU sites):	PPD ICON Clinical Research, Latvia PPD
ICON 24/7 Medical Helpdesk (for medical emergency when Medical Monitor unavailable):	Telephone: +1-919-674-5468 International Telephone Details: https://icophone.iconplc.com
Astellas Medical Monitor:	PPD Astellas Pharma Global Development, Inc. PPD
Clinical Research Contacts:	PPD Astellas Pharma Global Development, Inc., US PPD PPD Astellas Pharma Global Development, Inc., US PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AC	Adjudication Committee
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APGD	Astellas Pharma Global Development, Inc.
AST	aspartate aminotransferase
AT	Aminotransferases
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve at 24 hours
AUC_{SS}	area under the concentration-time curve at steady state
AUST	Astellas US Technologies
BAL	bronchoalveolar lavage
CA	Competent Authorities
cEC	concerned Ethics Committee
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CRO	contract research organization
CV	coefficient of variation
CYP3A4	cytochrome P450
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report form
EEA	European Economic Area
EORTC/MSG	European Organisation for Research and Treatment of Cancer/Mycoses Study Group
EOS	end of study
EOT	end of treatment
FAS	full analysis set
GCP	Good Clinical Practice
GI	Gastrointestinal
GM	Galactomannan
GMP	Good Manufacturing Practices
HSCT	hematopoietic stem cell transplant
IA	invasive aspergillosis
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviations	Description of abbreviations
IEC	independent ethics committee
IFI	invasive fungal infection
IM	invasive mucormycosis
IMI	invasive mould infection
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRR	Infusion-related reaction
IRT	interactive response technology
LA-CRF	liver abnormality case report form
LFT	liver function tests
LLOQ	lower limit of quantification
MedDRA	medical dictionary for regulatory activities
mFAS	modified full analysis set
PKAS	pharmacokinetic analysis set
(S)AE	serious adverse event or adverse event
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USM	urgent safety measure
V_d	volume of distribution

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Assessments of subjects as they enter a trial before they receive any treatment.
End of Study (EOS)	End of Study for each subject has occurred when the final protocol – defined assessment has been completed. In this study, the last protocol-defined assessment is approximately 60 days after last study drug dose.
End of Treatment (EOT)	The date the last dose of study drug was taken by the enrolled subject. In this study, the end of treatment is a maximum of 84 days for invasive aspergillosis subjects or 180 days for invasive mucormycosis subjects.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a trial.
Enroll	To register or enter a subject into a clinical trial. **Note:** Once a subject has received the study drug, the clinical trial protocol applies to the subject.
Evaluable Subject	A subject who has received at least one dose of study drug.
Intervention	The drug, device, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent until just before the test drug is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any entity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	05 Sep 2019 / Version 4.0
Sponsor: Astellas Pharma Global Development Inc. (APGD)	**Protocol Number:** 9766-CL-0107
Name of Study Drug: Isavuconazonium sulfate	**Phase of Development:** 2
Title of Study: A Phase 2, Open-Label, Non-Comparative, Multicenter Study to Evaluate the Safety and Tolerability, Efficacy and Pharmacokinetics of Isavuconazonium Sulfate for the Treatment of Invasive Aspergillosis (IA) or Invasive Mucormycosis (IM) in Pediatric Subjects	
Planned Study Period: From 1Q2019 to 1Q2021	
Study Objective(s): <u>Safety Objective</u> To evaluate the safety and tolerability of isavuconazonium sulfate in pediatric subjects <u>Efficacy Objective</u> To assess the efficacy of isavuconazonium sulfate for the treatment of invasive aspergillosis (IA) or invasive mucormycosis (IM) in pediatric subjects <u>Pharmacokinetic Objective</u> To evaluate the pharmacokinetics of isavuconazole by monitoring the plasma concentrations in pediatric subjects during treatment with isavuconazonium sulfate	
Planned Total Number of Study Centers and Location(s): Approximately 30 investigative centers in the US and in Europe	
Study Population: Male and female subjects (1 to < 18 years of age) who have been diagnosed with proven, probable or possible IA or IM	
Number of Subjects to be Enrolled/Randomized: Approximately 30 subjects will be enrolled. 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.	
Study Design Overview: This is a phase 2, open-label, non-comparative, multicenter study to assess the safety and tolerability, efficacy and pharmacokinetics of isavuconazonium sulfate in pediatric subjects for the treatment of IA or IM. An approved informed consent form must be obtained from the subject's parent or legal guardian, and, if required, pediatric assent prior to any study-related procedures being performed. The subjects will enter into screening anytime between days -5 to day 1 (predose). All subjects will be assigned to open-label treatment via intravenous or oral treatment at the discretion of the investigator. The oral formulation can only be given to subjects 6 years to < 18 years of age and with a body weight of at least 12 kg. The route of administration may be changed per the investigator's discretion as needed for treatment purposes as the resulting exposure from the 2 routes of administration is considered equivalent on a mg:mg basis.	

Treatment will begin on day 1, and then subjects will be followed for 60 days post-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. Investigator guidance of a successful outcome is provided in Table 4.

Intravenous and Oral Dosing: Subjects will receive a loading regimen of isavuconazonium sulfate (via intravenous or oral administration at the investigator's discretion), which consists of a 10 mg/kg dose every 8 hours (± 2 hours) on days 1 and 2 (for a total of 6 doses), followed by once daily maintenance 10 mg/kg dosing for up to 84 days (IA) or 180 days (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). Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly for study drug accountability and to receive new oral dosing supplies. Subjects who begin oral administration are to complete the oral dosing acceptability assessment after ingesting their first oral dose. Isavuconazonium sulfate oral capsules can be administered with or without food.

Due to the similarity in exposure (AUC) between intravenous and oral in pediatric subjects, the investigator may change dosing between the 2 routes (intravenous ⇆ oral) throughout the treatment as needed for treatment purposes. If the route of administration is changed after the 2-day loading regimen is completed, there is no need to repeat the loading dose for the new route of administration. The total doses for the loading period should not exceed 6 study drug administrations over the 2-day loading period, even if the route of administration is changed during the 2-day loading period.

Blood sampling for the analysis of isavuconazole trough levels will be obtained from all subjects. The samples should ideally be drawn immediately prior to the next dose of study drug, 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 one day between day 14 and day 42, while the subject is still receiving study drug, for subjects who consent to participation in the 24-hour pharmacokinetic assessment.

Subjects receiving intravenous administration:

The 24-hour pharmacokinetic samples will be obtained for intravenous dosing as follows:

1. within 1 hour prior to the start of the intravenous isavuconazonium sulfate infusion (this sample will be the same as the trough sample prior to dose, if it coincides with scheduled days 14, 21 or 42);
2. immediately after the completion of the intravenous infusion (no more than 5 minutes after);
3. within 4 to 10 hours after the start of the intravenous infusion; and
4. within 16 to 24 hours after the start of the intravenous infusion (must be obtained before the start of the next infusion).

Subjects receiving oral administration:

The 24-hour pharmacokinetic samples will be obtained for oral dosing as follows:

1. within 1 hour of next oral dose (this sample will be the same as the trough sample prior to dose, if it coincides with scheduled days 14, 21 or 42);
2. 1 hour post dose (± 10 minutes);
3. 3 hours post dose (± 10 minutes);
4. 4 hours post dose (± 10 minutes);
5. within 6 to 8 hours (± 30 minutes) of study drug administration; and
6. 24 hours post dose (within 1 hour before next study drug administration) after study drug administration.

No additional samples will be taken from IM subjects after day 84.

Throughout the study, safety and tolerability will be assessed by the recording of adverse events (AEs), vital signs, electrocardiograms (ECGs) and safety laboratory evaluations. This includes assessments at 14 days, 28 days and 56 days. All subjects will complete 2 follow-up visits. At the discretion of the investigator, follow-up visits may be conducted via telephone with the subject, the subject's parent or the subject's legal guardian, 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, 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.

Inclusion/Exclusion Criteria:

Inclusion:

1. Institutional Review Board (IRB)-approved written informed consent and privacy language as required per national regulations (e.g., Health Insurance Portability and Accountability Act authorization) must be obtained from the subject's parent or legal guardian and, if required, subject's assent, prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Male or female subject 1 year to < 18 years of age diagnosed with IA or IM. A positive diagnosis is defined as follows:
   - Proven, probable or possible invasive fungal infection (IFI) per the European Organisation for Research and Treatment of Cancer/Mycoses Study Group [EORTC/MSG], 2008 criteria

     Note: Subjects with "possible" IFI will be eligible for enrollment; however, diagnostic tests to confirm the invasive fungal disease as "probable" or "proven" according to the EORTC/MSG criteria should be completed within 10 calendar days after the first dose of study drug
     - **Note:** In addition to the criteria set for mycological criteria by the EORTC/MSG in 2008, and only for subjects with an underlying hematologic malignancy or recipients of hematopoietic stem cell transplant who also have clinical and radiologic features consistent with invasive fungal infection, the following are acceptable:
       i. Galactomannan (GM) levels (optical density index) meeting the below criteria are acceptable mycological evidence for enrollment or upgrading the diagnosis to probable IA:
          1. A single value for serum or bronchoalveolar lavage (BAL) fluid of ≥ 1.0 or
          2. Two serum GM values of ≥ 0.5 from 2 separate samples
3. Subject has sufficient venous access to permit intravenous administration of study drug or the ability to swallow oral capsules.
4. A female subject is eligible to participate if she is not pregnant and at least one of the following conditions applies:
   a. Not a subject who is of childbearing potential as defined in [Appendix 12.3 Contraception Requirements].
      OR
   b. Subject who is of childbearing potential who agrees to follow the contraceptive guidance as defined in [Appendix 12.3 Contraception Requirements] throughout the treatment period and for at least 30 days after the final study drug administration.
5. Female subject who is of childbearing potential must agree not to breastfeed starting at screening and throughout the study and for 30 days after the final study drug administration.

6. Female subject who is of childbearing potential must not donate ova starting at screening, throughout the study, and for 30 days after the final study drug administration.
7. A male subject with female partner(s) of childbearing potential must agree to use contraception as detailed in [Appendix 12.3 Contraception Requirements] during the treatment period and for at least 30 days after the final study drug administration.
8. Male subject must not donate sperm starting at screening and throughout the study and for 30 days after the final study drug administration.
9. Subject and subject's parent(s) or legal guardian agree that the subject will not participate in another interventional study while on treatment with the exception of oncology trials.

Waivers to the inclusion criteria will **NOT** be allowed.

Exclusion:

1. Subject has familial short QT syndrome, is receiving medications that are known to shorten the QT interval, or has a clinically significant abnormal ECG.
2. Subject has evidence of hepatic dysfunction defined as any of the following:
   - Total bilirubin ≥ 3 times the upper limit of normal (ULN)
   - Alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 5 times the ULN
   - Known cirrhosis or chronic hepatic failure
3. Subject has used strong cytochrome P450 (CYP3A4) inhibitors or inducers such as ketoconazole, high dose ritonavir, rifampin/rifampicin, long acting barbiturates (e.g., phenytoin), carbamazepine and St. John's Wort in the 5 days prior to the first dose of study drug.
4. Subject has another IFI other than possible, probable or proven IA or IM.
5. Subject has chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis.
6. Subject has received mould active systemic antifungal therapy, effective against the primary invasive mould infection, for more than 4 days during the 7 days preceding the first dose.

   Note: Prior use of prophylactic antifungal therapy is acceptable. In case of breakthrough IA while on prophylactic mould-active azole class drugs, additional documentation will be required to be submitted to the sponsor medical monitor or designee to approve subject enrollment.
7. Subject has known history of allergy, hypersensitivity or any serious reaction to any of the azole class antifungals, or any components of the study drug formulation.
8. Subject has any condition, which, in the investigator's opinion, makes the subject unsuitable for study participation.
9. Subject is unlikely to survive 30 days in the investigator's opinion.
10. Subject has received investigational drug, with the exception of oncology drug trials or trials with investigational drugs treating graft versus host disease, within 28 days or 5 half-lives, whichever is longer, prior to screening.

Waivers to the exclusion criteria will **NOT** be allowed.

Investigational Product(s):

Isavuconazonium sulfate, 372 mg, lyophilized powder for injection (200 mg isavuconazole)

Isavuconazonium sulfate 74.5 mg capsules (40 mg isavuconazole)

Dose(s):

The investigator may determine the appropriate route of administration for each subject. The investigator can switch between the 2 routes of administration (intravenous ⇆ oral) throughout the treatment period as needed. Changes to route of administration will be documented.

Intravenous

Subjects weighing ≤ 37 kg:

- Loading regimen of 10.0 mg/kg isavuconazonium sulfate infusions every 8 hours (± 2) for 6 doses (days 1 and 2)
- Maintenance dose of 10.0 mg/kg isavuconazonium sulfate administered once daily starting 12 to 24 hours after the last loading dose

Subjects weighing > 37 kg:

- Loading regimen of 372 mg isavuconazonium sulfate infusions (1 vial) every 8 hours (± 2) for 6 doses (days 1 and 2)
- Maintenance dose of 372 mg isavuconazonium sulfate (1 vial) administered once daily starting 12 to 24 hours after the last loading dose

The maximum loading and daily maintenance doses to be administered to any subject are 372 mg per individual dose.

Oral (only for subjects 6 to < 18 years of age and with a body weight of at least 12 kg)

Subjects will receive an oral loading regimen of isavuconazonium sulfate in a capsule form given every 8 hours (± 2 hours) on days 1 and 2 (a total of 6 doses), followed by once-daily oral maintenance dosing. Isavuconazonium sulfate oral capsules can be administered with or without food. The first maintenance dose should start 12 to 24 hours after the administration of the last loading dose, with subsequent maintenance doses to be administered once daily, 24 hours ± 2 hours from the previous maintenance dose. Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly to receive new oral dosing supplies. Subjects who begin oral administration are to complete the oral dosing acceptability assessment after ingesting their first oral dose.

The daily dose is based on body weight and is intended to deliver a dose approximately equal to 10 mg/kg. The oral and intravenous formulations are equivalent on a mg:mg basis. The lower limit for oral dosing is 6 years of age and a body weight of at least 12 kg.

Body Weight (kg)	Loading (Days 1 and 2)/Total Daily Isavuconazonium Sulfate Dose (mg)	Maintenance (up to 84 days [IA] or 180 days [IM])/Total Daily Isavuconazonium Sulfate Dose (mg)
12 to < 18	3 × 2 capsules/447 mg	1 × 2 capsules/149 mg
18 to < 25	3 × 3 capsules/670.5 mg	1 × 3 capsules/223.5 mg
25 to < 32	3 × 4 capsules /894 mg	1 × 4 capsules/298 mg
≥ 32	3 × 5 capsules/1117.5 mg	1 × 5 capsules/372.5 mg

Route of Administration:

Either intravenous or oral as shown below:

Intravenous: 1-hour (± 10 minutes) intravenous infusion of isavuconazonium sulfate through an in-line filter.

Oral: Isavuconazonium sulfate will be administered orally.

Comparative Drug(s):
Not applicable.

Concomitant Medication Restrictions or Requirements:
Treatments with concomitant drugs that are strong inhibitors or inducers of CYP3A4 are prohibited, including ketoconazole, high dose ritonavir, rifampin/rifampicin, carbamazepine and St. John's Wort or long acting barbiturates (e.g., phenytoin). Concomitant use of sirolimus, atorvastatin, cyclosporine, tacrolimus, midazolam, bupropion, mycophenolate mofetil and digoxin should be made with caution.

Treatments with concurrent drugs that are CYP3A4 substrates and have a narrow therapeutic range (e.g., vincristine) should be used with caution, and if clinically warranted, consider reduction of substrate dose.

Use of other systemic antifungals is prohibited during study drug administration.

Duration of Treatment
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. Investigator guidance of a successful outcome is provided in Table 4.

Formal Stopping Rules
Individual subject(s) must be discontinued from treatment for any of the following:

- Subject requests to stop treatment.
- Any clinical AE, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject.
- Parent(s) or legal guardian withdraws consent.
- Subject experiences a systemic infusion-related reaction (IRR) such as hypotension, dyspnea, chills, dizziness, paresthesia and hypoesthesia attributable to study drug during or shortly after the intravenous administration; however, in case of an infusion-related reaction, the infusion must be stopped immediately and the subject must be discontinued from treatment.
  Note: If the IRR signs and symptoms are mild and self-limiting, the subject may continue in the study at the discretion of the investigator.
- Serious hypersensitivity or severe skin reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azoles. If subject develops a severe hypersensitivity adverse reaction without alternative etiology, the subject must be discontinued from treatment.
- Investigator's decision that further treatment is not in the best interest of the subject.
- Female subject becomes pregnant.
- Subject is lost to follow-up despite diligent efforts to contact.

Discontinuation of the subject from treatment should also be considered if a subject experiences an increase in liver enzymes as follows:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and (TBL > 2 x or International Normalized Ratio [INR] > 1.5) (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Endpoints for Evaluation:

Safety Endpoints:

Safety outcomes will include AEs, vital signs, ECGs and laboratory parameters.

Efficacy Endpoints:

The primary efficacy endpoint will be all-cause mortality through day 42.

The key secondary efficacy endpoint will be all-cause mortality through day 84 and EOT.

Additional secondary efficacy endpoints will be overall, clinical, radiological and mycological response through day 42, day 84 and at EOT.

Other Endpoints:

Plasma trough (pre-dose) levels will be measured on days 7, 14, 21, 42 and 84 or EOT.

In addition to the above, 24-hour pharmacokinetic samples will be obtained on any one day between day 14 and day 42, while the subject is still receiving study drug.

After receiving their first dose of oral capsules, subjects will be asked to assess their initial experience with the new oral formulation (i.e., Acceptability Assessment).

Statistical Methods:

This study is not designed to make statistical inferences. Data will be summarized using appropriate summary statistics. Categorical data will be described using absolute and relative frequencies (n and %). Continuous data will be presented using descriptive statistics (n, mean, standard deviation, minimum, median and maximum).

All variables will be listed in individual subject listings.

Sample Size Justification

A formal statistical justification of the sample size is not made. The sample size of approximately 30 subjects is planned. 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.

Safety

All AEs will be listed by subject and by age cohort. The incidence of the following AEs will be summarized by system organ class and preferred term for overall subjects and by subjects in each age cohort: overall, serious, related to study drug and leading to the permanent discontinuation of study drug.

Vital signs will be listed and summarized. Laboratory test values will be presented in shift tables and by individual listings with flagging of values outside the normal reference ranges. ECG findings will be presented by listings and frequency tables, as appropriate.

The incidence of treatment emergent AEs will also be summarized by relationship to study drug and severity for all subjects and by subjects in each age cohort.

Efficacy

Per each diagnosis (IA or IM) accrued, the crude all-cause mortality rates will be calculated by dividing the number of deaths by the number of subjects in the full analysis set (FAS) (i.e., all enrolled subjects who received at least one dose of study drug), and a 2-sided exact 95% CI will be calculated. Each subject will be classified as either death or alive. Subjects who died on or before day 42/day 84/EOT, as well as subjects who are lost to follow-up before day 42/day 84/EOT will be counted as deaths.

Efficacy *(continued)*

Crude success rates and 2-sided exact 95% CIs will be calculated for the overall, clinical, radiological and mycological response at day 42, day 84 and EOT in the FAS.

For each efficacy endpoint, a summary will be presented for overall subjects and by subjects in each age cohort.

Pharmacokinetics

Observed plasma concentration data for isavuconazole will be presented in listings.

In addition, pharmacokinetic plasma concentrations will be analyzed using population pharmacokinetic model. Details of the model and modeling procedure will be provided in separate modeling report.

Pharmacodynamics

Not applicable.

Interim Analyses

Not applicable.

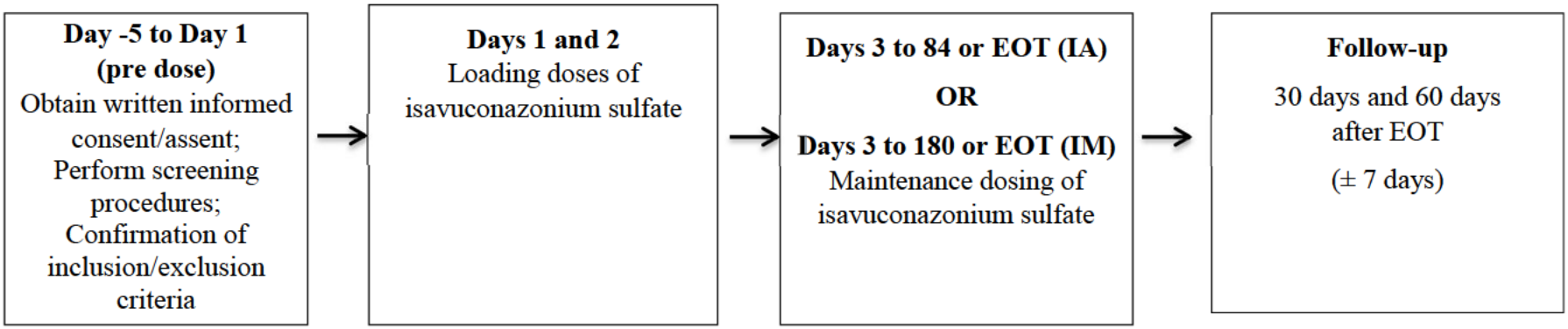
Data and Safety Monitoring Board and Adjudication Committees

A Data and Safety Monitoring Board will be utilized to monitor subject safety throughout the study.

An Adjudication Committee will be utilized to confirm the diagnosis and overall, clinical, radiological and mycological response of IA or IM.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Figure 1 Flow Chart



EOT: end of treatment; IA: invasive aspergillosis; IM: invasive mucormycosis

Table 1 Schedule of Assessments (IA and IM Subjects) – Screening through Day 84 and IA Follow-up (30 and 60 Days Post-Day 84 or EOT [Last Dose of Study Drug])

Period	Screening		Treatment														IA Follow-up[2]	
Day	-5 to 1 (predose)	1	2	3	7	14	21	28	35	42	49	56	63	70	77	84 or IA EOT[1]	110 (30 Day) IA or EOS	Day 140 (60 Day) IA or EOS
Visit window (days)	none	none	none	none	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 7	± 7	± 7
ASSESSMENTS																		
Informed consent/assent	X																	
Verify eligibility criteria	X	X																
Demographics	X																	
Medical/surgical history	←	―	―	―	―	―	―	―	―	―	―	―	―	―	―	→	→	→
EORTC/MSG diagnosis[3]	←	―	―	―	→													
Physical examination	X															X		
Height and weight[4]	X															X		
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Routine 12-lead ECG[6]	X	X			X	X		X				X				X		
Serum or BAL galactomannan	X																	
Efficacy response assessment[7]	←	―	―	―	―	―	―	―	―	―	―	―	―	―	―	→	→	→
Pharmacokinetic trough sampling[8]					X	X	X			X						X		
Pharmacokinetic 24-hour sampling[9]						X												
Clinical laboratory tests (chemistry, INR, hematology)[10]	X				X			X				X				X		
Hepatic panel[11]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy test[12]	X							X		X						X		
Prior and concomitant medications[13]	←	―	―	―	―	―	―	―	―	―	―	―	―	―	―	→	→	→
AE[14]	←	―	―	―	―	―	―	―	―	―	―	―	―	―	―	→	→	→
Isavuconazonium sulfate dosing[15]		q8h	q8h	X	X	X	X	X	X	X	X	X	X	X	X	X		
Oral dosing acceptability assessment		X[16]																
Mortality Status[17]										X						X		

AE: adverse event; BAL: bronchoalveolar lavage; ECG: electrocardiogram; EORTC/MSG: European Organisation for Research and Treatment of Cancer/Mycoses Study Group; EOS: end of study; EOT: end of treatment; IA: invasive aspergillosis; IM: invasive mucormycosis; INR: international normalized ratio; q8h: once every 8 hours.

Footnotes continued on next page

1. If subject discontinues study drug prior to day 84 for IA subjects, all EOT procedures must be completed. If subject continues to allow consent, EOS information to be collected on follow-up.
2. Follow-up is to be completed 30 (± 7) and 60 days (± 7) post-last dose from day 84 or EOT for IA subjects, and may be performed via telephone at the discretion of the investigator.
3. Diagnosis must be completed within 10 days of first dose.
4. Height is to be collected at baseline only. Weight is to be taken at baseline and day 84 or EOT.
5. Vital signs are to be measured within 1 hour prior to and approximately 1 hour after the end of each infusion. No additional vital signs are needed on dosing days for oral administration.
6. 12-lead ECG will be performed prior to study drug administration on each scheduled day.
7. Record assessments that are performed during the study to document response to antifungal therapy (e.g., serum galactomannan, radiology, mycological tests, changes in clinical signs and symptoms and any surgical procedure).
8. Pharmacokinetic trough samples should ideally be drawn immediately prior to the next dose of study drug, but must be taken no earlier than 1 hour prior to the next dose on days 7, 14, 21, 42 and 84 or EOT.
9. For both intravenous and oral dosing: 24-hour pharmacokinetic samples will be obtained on any one day between day 14 and day 42, while the subject is still receiving study drug, for subjects who consent to participation in the 24-hour pharmacokinetic assessment. The intravenous pharmacokinetic samples will be collected as follows: within 1 hour prior to the start of the intravenous isavuconazonium sulfate infusion. This sample will be the same as the trough sample prior to dose, if it coincides with scheduled days 14, 21 or 42, and immediately after the completion of the intravenous infusion (no more than 5 minutes after); and within 4 to 10 hours after the start of the intravenous infusion and within 16 to 24 hours after the start of the intravenous infusion (must be obtained before the start of the next infusion).

   The oral pharmacokinetic samples will be collected as follows: within 1 hour of the next oral dose (this sample will be the same as the trough sample prior to dose, if it coincides with scheduled days 14, 21 or 42); 1 hour post dose (± 10 minutes); 3 hours post dose (± 10 minutes); 4 hours post dose (± 10 minutes); within 6 to 8 hours (± 30 minutes) of study drug administration; and 24 hours (within 1 hour before next study drug administration) after study drug administration.
10. Clinical (safety) laboratory samples will be assessed by the local laboratory.
11. Hepatic panels will be collected at baseline, day 3, day 7 and then weekly thereafter while subjects are receiving study drug.
12. Pregnancy testing not applicable for male subjects. Not necessary for female subjects who are of non-childbearing potential (e.g., premenarchal in the judgment of the investigator on day 1 and throughout the study treatment, or documented surgically sterile). Pregnancy testing may be urine or serum, dependent upon institutional standard of care.
13. Concomitant medications are to be captured during the study and only related to AE's during the 30- and 60-day follow-up period.
14. All AEs must be monitored until symptom resolution or until the condition stabilizes.
15. For both intravenous and oral dosing: Loading doses on days 1 and 2 will be administered every 8 (± 2) hours. 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 ± 2 hours from the previous maintenance dose). Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly to receive new oral dosing supplies. Return visits should coincide with days when study-related assessments are required. Oral dosing is allowed for subjects 6 to < 18 years of age and with a body weight of at least 12 kg.

Footnotes continued on next page

16. Subjects who begin oral administration are to complete the oral dosing acceptability assessment after ingesting their first oral dose.
17. All-cause Mortality will be assessed on days 42 and 84 or EOT.

Table 2 Extended Schedule of Assessments (IM Subjects) – Day 85 through Day 180 and IM Follow-up (30 and 60 days Post-Day 180 [Last Dose of Study Drug])

Period		**Treatment**			**Follow-up[2]**	
Day	85	115	145	180/IM or EOT[1]	210 (30 Day) IM or EOS	240 (60 Day) IM or EOS
Visit window (days)	± 2	± 2	± 2	± 7	± 7	± 7
ASSESSMENTS						
Physical examination				X		
Weight				X		
Vital signs[3]	X	X	X	X		
Routine 12-lead ECG[4]	X	X	X	X		
Efficacy response assessment[5]	←	—	—	—	—	→
Clinical laboratory tests (chemistry, hematology, hepatic panel, INR)[6]		X	X	X		
Pregnancy test[7]				X		
Prior and concomitant medications[8]	←	—	—	—	—	→
AE[9]	←	—	—	—	—	→
Isavuconazonium sulfate dosing[10]	X	X	X	X		
Oral dosing acceptability assessment	X[11]					
Mortality Status[12]				X		

AE: adverse event; EOS: end of study (30 days post-last dose); EOT: end of treatment (60 days post-last dose); IA: invasive aspergillosis; IM: invasive mucormycosis; INR: international normalized ratio

1. If subject discontinues study drug prior to day 180 for IM subjects, all EOT procedures must be completed. If subject continues to allow consent, EOS information to be collected on Follow-up.
2. Follow-up is to be completed 30 days (± 7) and 60 days (± 7) post-last dose from day 180/EOT for IM subjects; may be performed via telephone at the discretion of the investigator.
3. Vital signs are to be measured within 1 hour prior to and approximately 1 hour after the end of each infusion. No additional vital signs are needed on dosing days for oral administration.
4. 12-lead ECG will be performed prior to study drug administration on each scheduled day.
5. Record assessments that are performed during the study to document response to antifungal therapy (e.g., serum galactomannan, radiology, mycological tests, changes in clinical signs and symptoms and any surgical procedures).
6. Clinical (safety) laboratory samples will be assessed by the local laboratory. Clinical laboratory tests (chemistry, hematology, hepatic panel and INR) to be drawn monthly.

Footnotes continued on next page

7. Pregnancy testing not applicable for male subjects. Not necessary for female subjects who are of non-childbearing potential (e.g., premenarchal in the judgment of the investigator on day 1 and throughout the study treatment, or documented surgically sterile).
8. Concomitant medications are to be captured during the study and only related to AE's during the 30- and 60-day follow-up period.
9. All AEs must be monitored until symptom resolution or until the condition stabilizes.
10. For both intravenous and oral dosing: Subsequent maintenance doses will be administered once daily (24 ± 2 hours from the previous maintenance dose). Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly to receive new oral dosing supplies. Return visits should coincide with days when study-related assessments are required. Oral dosing is allowed for subjects 6 to < 18 years of age and with a body weight of at least 12 kg.
11. Subjects who begin oral administration are to complete the oral dosing acceptability assessment after ingesting their first oral dose.
12. All-cause Mortality will be assessed at day 180 or EOT.

1 INTRODUCTION

Isavuconazonium sulfate is a new azole antifungal agent that was approved for use in adults for the treatment of invasive aspergillosis (IA) and invasive mucormycosis (IM) in the US and in Europe for treatment of IA; and for the treatment of IM in subjects for whom amphotericin B is inappropriate. These same invasive fungal pathogens are also important hospital-acquired pathogens in critically-ill pediatric subjects, especially those with underlying conditions compromising the immune system and there are currently very limited approved treatment options for pediatric subjects.

Therefore, establishing an efficacious and safe dosage regimen for isavuconazole for use in pediatric subjects will provide important information for physicians treating these subjects.

1.1 Background

As in adults, fungal infections remain an important cause of morbidity and mortality in pediatric subjects. In immunocompromised pediatric subjects, invasive mould infections (IMIs) are a leading cause of mortality [Georgiadou et al, 2012; Al-Rezqi et al, 2009; Burgos et al, 2008; Walsh et al, 2008; Sung & Johnston, 2007; Zaoutis et al, 2006]. In a large prospective multinational study to evaluate the epidemiology and spectrum of IMIs in children, which enrolled 131 pediatric subjects with proven or probable IMIs, the most common diagnosis was IA (75%), followed by other IMIs (17%) and IM (13%) [Wattier et al, 2015]. A large proportion of these subjects had some underlying immunosuppression. Overall mortality was 30% at 12 weeks [Wattier et al, 2015]. Another study identified 48 pediatric subjects with proven or probable IMIs from a retrospective single-center in the US [Georgiadou et al, 2012] and found similar trends with *Aspergillus* species being the most common organism and the majority of subjects being immunocompromised with hematologic malignancy and/or neutropenia. Overall mortality in this study was 31% at 12 weeks; in all subjects, death was attributed to both IMI and the underlying disease.

Invasive Aspergillosis: Risk factors and underlying disease characteristics for IA are comparable between adults and children with the most common being malignancy, such as acute myeloid leukemia (AML) and allogeneic hematopoietic stem cell transplant (HSCT). Chronic granulomatous disease, which is typically diagnosed in children, is also a risk factor [Dornbusch et al, 2009]. The Infectious Diseases Society of America guidelines for the treatment of IA do not distinguish between the disease characteristics in adults and children [Walsh et al, 2008]. Therefore, aside from systemic dosing differences, the treatment guidelines for these 2 populations do not differ.

Invasive Mucormycosis: IM is extremely rare and can occur not only in subjects with a severely compromised immune system, but also occasionally in subjects with traumatic injuries or in subjects with uncontrolled diabetes mellitus. IM is one of the most life-threatening mould infections in subjects with hematologic malignancies and in HSCT recipients [Skiada et al, 2011; Chamilos et al, 2008; Roden et al, 2005]. In a 10-year (1997 to 2006) retrospective study in France, the incidence of IM annually increased with age, from 0.3 per million in children less than 9 years to 3.9 per million subjects > 89 years; overall the

annual incidence was 0.9 per million subjects [Bitar et al, 2009]. The incidence is reportedly 1/10 of the incidence of IA on average [Abidi et al, 2014].

Presentation and pathogenesis of the disease are similar between children and adults. Therefore, diagnosis and treatment recommendations are the same in both populations at risk.

Given the similarity of the pathogenesis and features of invasive fungal infection (IFI) between adults and pediatric subjects for both IA and IM, this IA and IM treatment study in children is designed to assess the safety of the proposed clinical dosage regimen. The proposed clinical dosage regimen is supported by a prior clinical pharmacokinetic and safety study in children. The dosage regimen generates exposures in the pediatric population that are consistent with the exposures achieved in adults receiving the recommended clinical dose for adults. The current pediatric study is intended to evaluate the safety and tolerability of isavuconazonium sulfate in the pediatric population from 1 to < 18 years of age.

1.2 Nonclinical and Clinical Data

An overview of the nonclinical and adult clinical data of isavuconazole can be found in the latest version of the investigator's brochure (IB).

Isavuconazole has been investigated in a phase 1 pharmacokinetic, safety and tolerability study in pediatric subjects following intravenous administration. In this study, a total of 27 pediatric subjects received at least 1 dose of study drug (Protocol 9766-CL-0046). Nine subjects were between 1 and < 6 years of age, 8 subjects were between 6 and < 12 years of age and 10 subjects were between 12 and < 18 years of age. A majority of subjects were white and male. Most subjects had an underlying malignancy. Subjects weighing ≤ 40 kg received 10 mg/kg of isavuconazonium sulfate, and subjects > 40 kg received 372 of isavuconazonium sulfate intravenously daily, after a loading regimen.

The vast majority of subjects experienced at least 1 adverse event (AE), and serious adverse events (SAEs) were experienced by about half of all subjects, which is expected given the medical history of the subjects enrolled. About a third of subjects experienced drug-related AEs. Important drug-related events included gastrointestinal (GI) disorders and infusion-related reactions. Two subjects were withdrawn from the study due to an AE. The events leading to withdrawal were increased liver enzymes and QT prolongation, and both events were considered related to study drug. No differences were observed in the AE experience between the 3 age cohorts.

1.3 Summary of Key Safety Information for Study Drugs

In the isavuconazole juvenile toxicity study, the no-observed-adverse-effect-level in rats was determined to be 10 mg/kg per day. In this study, no toxicities were observed in pediatric sensitive organs. A summary of the juvenile toxicity study, as well as an overview of the key isavuconazole safety data collected in adult subjects during the clinical development program can be found in the latest version of the IB.

In addition, isavuconazonium sulfate has been investigated in one pediatric clinical study [Study 9766- CL-0046]. In this small study, important adverse reactions were GI disorders, rash, increased liver enzymes and infusion-related reactions.

1.4 Risk Benefit Assessment

The safety of isavuconazonium sulfate in pediatric subjects has been investigated in a study with a total of 27 subjects. In this small study, isavuconazonium sulfate appeared to be generally well-tolerated with a safety profile similar to that observed in adults. The efficacy of isavuconazonium sulfate in pediatric subjects has not yet been studied. It is expected that the dosage regimen used in the study will result in efficacious exposures in pediatric subjects and therefore subjects will likely benefit from participating in this study.

Subjects enrolled in this study may experience AEs, including previously unknown AEs related to study drug or may experience procedural complications (e.g., bruising from blood draws and slight skin irritation from the adhesive on the electrocardiogram [ECG] electrodes). While the proposed dosage regimen was established to minimize the number of subjects reaching exposures associated with increased toxicity in adults, some pediatric subjects could reach exposures that resulted in central nervous system and GI-type adverse effects in adults. Subjects with familial short QT syndrome are excluded from participation in this study. Pediatric subjects enrolled in this study will be closely monitored for AEs, especially for liver toxicity. Overall, based on the target population selected for this study, the exclusion criteria and the proposed dosage regimen, which matches adult efficacious exposures, the benefit and risk assessment associated with the participation of pediatric subjects in this clinical study is favorable.

2 STUDY OBJECTIVE(S), DESIGN AND ENDPOINTS

2.1 Study Objective(s)

2.1.1 Safety Objective

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

2.1.2 Efficacy Objective

To assess the efficacy of isavuconazonium sulfate for the treatment of IA or IM in pediatric subjects.

2.1.3 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 and Dose Rationale

2.2.1 Study Design

This is a phase 2, open-label, non-comparative, multicenter study to assess the safety and tolerability, 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, pediatric assent prior to any study-related procedures being performed.

Approximately 30 centers in the US and EU are planned to enroll approximately 30 subjects 1 to < 18 years of age with at least 25 subjects evaluable. Every effort will be made to achieve at least 5 evaluable subjects per age cohort below:

- Cohort 1: 1 to < 12 years of age
- Cohort 2: 12 to < 18 years of age

The sponsor reserves the right to stop enrollment if the cohort requirements are not achieved.

The subjects will enter into screening anytime between days -5 to day 1 (predose). All subjects will be assigned to open-label treatment via intravenous or oral treatment at the discretion of the investigator. The oral formulation can only be given to subjects 6 years to < 18 years of age and with a body weight of at least 12 kg. The route of administration may be changed per the investigator's discretion as needed for treatment purposes as the resulting exposure from the 2 routes of administration is considered equivalent on a mg:mg basis. Treatment will begin on day 1, and then subjects will be followed for 60 days post-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. Investigator guidance of a successful outcome is provided in Table 4.

Intravenous and Oral Dosing: Subjects will receive a loading regimen of isavuconazonium sulfate (via intravenous or oral administration at the investigator's discretion), which consists of a 10 mg/kg dose every 8 hours (± 2 hours) on days 1 and 2 (for a total of 6 doses), followed by once daily maintenance 10 mg/kg dose for up to 84 days (IA) or 180 days (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). Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly for study drug accountability and to receive new oral dosing supplies. Return visits should coincide with days when study-related assessments are required. Subjects who begin oral administration are to complete the oral dosing acceptability assessment after ingesting their first oral dose.

Due to the similarity in exposure (AUC) between intravenous and oral in pediatric subjects, the investigator may change dosing between the 2 routes (intravenous ⇆ oral) throughout the treatment as needed for treatment purposes. If the route of administration is changed after the 2-day loading regimen is completed, there is no need to repeat the loading dose for the new route of administration. The total doses for the loading period should not exceed 6 study drug

administrations over the 2-day loading period, even if the route of administration is changed during the 2-day loading period.

Blood sampling for the analysis of isavuconazole trough levels will be obtained from all subjects. The samples should ideally be drawn immediately prior to the next dose of study drug, 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 one day between day 14 and day 42, while the subject is still receiving study drug, for subjects who consent to participation in the 24-hour pharmacokinetic assessment.

Subjects receiving intravenous administration:

The 24-hour pharmacokinetic samples will be obtained for intravenous dosing as follows:

1. within 1 hour prior to the start of the intravenous isavuconazonium sulfate infusion (this sample will be the same as the trough sample prior to dose, if it coincides with scheduled days 14, 21 or 42);
2. immediately after the completion of the intravenous infusion (no more than 5 minutes after);
3. within 4 to 10 hours after the start of the intravenous infusion; and
4. within 16 to 24 hours after the start of the intravenous infusion (must be obtained before the start of the next infusion).

Subjects receiving oral administration:

The 24-hour pharmacokinetic samples will be obtained for oral dosing as follows:

1. within 1 hour of next oral dose (this sample will be the same as the trough sample prior to dose, if it coincides with scheduled days 14, 21 or 42);
2. 1 hour post dose (± 10 minutes);
3. 3 hours post dose (± 10 minutes);
4. 4 hours post dose (± 10 minutes);
5. within 6 to 8 hours (± 30 minutes) of study drug administration; and
6. 24 hours post dose (within 1 hour before next study drug administration) after study drug administration.

No additional samples will be taken from IM subjects after day 84.

Throughout the study, safety and tolerability will be assessed by the recording of AEs, vital signs, ECGs and safety laboratory evaluations. This includes assessments at 14 days, 28 days and 56 days. All subjects will complete 2 follow-up visits. At the discretion of the investigator, follow-up visits may be conducted via telephone with the subject, the subject's parent or the subject's legal guardian, 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, 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.

2.2.2 Dose Rationale

The safety and efficacy of isavuconazonium sulfate in adults has been demonstrated for the treatment of IA and IM. The clinical dosage regimen used to establish the safety and efficacy was 372 mg isavuconazonium sulfate (equivalent to 200 mg isavuconazole) every 8 hours for the first 2 days followed by 372 mg once daily thereafter. While dosing is reflected as milligrams of the administered prodrug (isavuconazonium sulfate), exposure is represented as milligrams of the active moiety (isavuconazole), which is immediately present in the systemic circulation.

An exposure-response analysis was conducted using data from adult subjects receiving isavuconazonium sulfate for the treatment of IA in the phase 3 SECURE clinical study [Study 9766-CL-0104] and the population pharmacokinetic model [Company Report 9766-PK-0005; Desai et al, 2017]. The objective was to determine if there was a threshold of exposure or plasma concentration that was optimal for successful outcome in the adult subjects receiving isavuconazonium sulfate for the treatment of IA. For this analysis, plasma concentrations at day 7 (C_7), day 14 (C_{14}) and at steady-state (C_{ss}) and steady-state area under the concentration-time curve at 24 hours (AUC_{24}) estimates simulated from the population pharmacokinetic model in adults were used. No specific exposure parameter or threshold of exposure or concentration showed a significant relationship with any measure of response (i.e., all-cause mortality through day 42, all-cause mortality through day 84, overall response at end of therapy and overall response at day 42) observed in subjects from [Study 9766-CL-0104].

These results suggested that the exposures achieved by the clinical dosage regimen were adequate to treat the infecting organisms in subjects treated in the study.

In addition, the probability of target attainment analysis, which assessed the ability of the clinical dosage regimen to achieve the pharmacodynamic target defined by the experimental IA model, suggested that the clinical dosage regimen was adequate to cover the wild-type population of *Aspergillus* species according to the defined epidemiological cutoff values for isavuconazole [Espinel-Ingroff et al, 2013].

The efficacy described for IM was established based on exposure to the same clinical dosing regimen in adults; therefore, the expectation would be that the exposure required (median AUC_{ss} of 89.6 mg·h/L) for this disease in children would be similar.

In order to establish the upper exposure target for the proposed pediatric dosing regimen for the proposed pediatric study, the safety information from 2 clinical studies in which doses higher than the clinical adult dose of isavuconazonium sulfate were administered were reviewed:

- [Study 9766-CL-0102]: dose-ranging study in adult subjects with AML receiving doses up to 744 mg isavuconazonium sulfate and
- [Study 9766-CL-0017]: thorough QT study with healthy adult subjects receiving doses up to 1116 mg isavuconazonium sulfate.

The mean AUC_{24} for subjects in the 1116 mg isavuconazonium sulfate group was 353 mg*h/L, and the minimum AUC_{24} in this dose group was 233 mg*h/L [Study 9766-CL-0017].

Population Pharmacokinetic Model for Pediatric Data

A pediatric population pharmacokinetic model was developed utilizing plasma concentration data from 27 subjects administered intravenous isavuconazonium sulfate from Part 1 of Study 9766-CL-0046, 10 subjects administered oral dose from Part 2 of Study 9766-CL-0046 (12 to < 18 years of age) and 24 subjects from the 9766-CL-0018 study, an intravenous study in which subjects were administered single dose of 372 mg of isavuconazonium sulfate. The model was updated to include plasma concentration data from an additional 9 subjects from Part 2 of Study 9766-CL-0046 (6 to < 12 years of age), who were administered oral isavuconazonium sulfate.

Data was modeled using a nonlinear relationship with the following equation:

$$P_{child} = P_{adults} \cdot \left(\frac{WT}{70}\right)^{x}$$

where P is the parameter of interest (clearance [CL] or volume of distribution [V_d]),

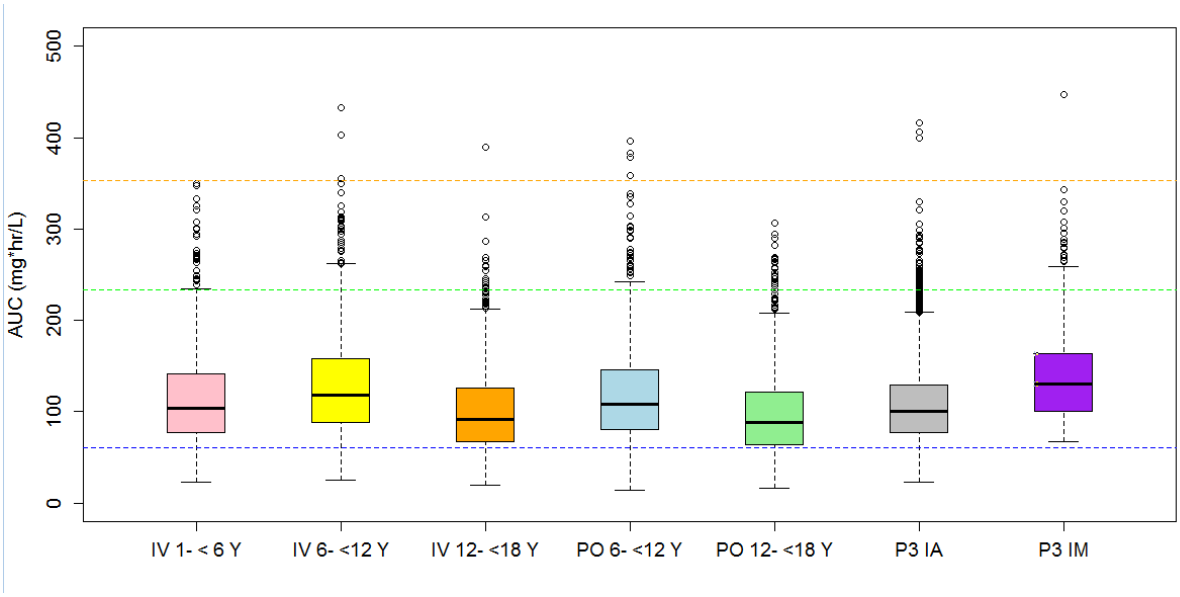
WT is the weight in kg for the individual subject and x for the relevant allometric component, which was fixed to 0.75 for CL related parameters and one for V_d related parameters

A 3-compartment model with combined zero order absorption, first order absorption and linear elimination described the data adequately. Inter-individual variability was observed on clearance, volume of distribution of central and peripheral compartment and inter-compartmental clearance.

Monte Carlo simulations were performed for 1000 randomly chosen subjects for each age group in pediatrics and 1000 to 5000 randomly chosen subjects for adult data. Area under the isavuconazole concentration-time curve at steady-state (AUC_{ss}) was calculated for each simulated subject. The dosing schedule for the simulation was similar to that for subjects in Study 9766-CL-0046, with subjects weighing ≤ 37 kg administered 10 mg/kg dose and subjects > 37 kg receiving the adult dose of 372 mg.

Figure 2 compares pediatric exposures against exposures from Study 9766-CL-0104 (SECURE), a successful phase 3 study in adults with IA, in which subjects received isavuconazonium sulfate via both intravenous and oral routes of administration and against data from Study 9766-CL-0103 (VITAL), a successful phase 3 adult study in subjects with IM and other rare invasive fungal infections, in which subjects received isavuconazonium sulfate via oral route of administration. The dosage regimen in both adult studies was similar.

Figure 2 Box Plot of Isavuconazole Exposure Across Age Groups Including Adults in Phase 3 Program



Boxes represent the median and 25th and 75th percentiles, whiskers represent the range of maximum and minimum values within 1.5 × the interquartile range, and outliers are shown as circles. Dashed blue line is the lowest targeted value (25th percentile, with AUC_{ss} of 60 mg*hr/L) based on exposures from SECURE study. Dashed green and orange lines are the minimum (233 mg*hr/L) and mean (353 mg*hr/L) AUC_{ss} values in a high dose adult study (1116 mg) with increased toxicity.

From the figure, it can be seen that exposures predicted for pediatric subjects across all age ranges for intravenous and for subjects 6 to < 18 years of age for the oral route of administration are within the efficacious range that was observed in adult studies.

An isavuconazonium sulfate dose of 10 mg/kg for all age groups weighing ≤ 37 kg and the adult dose for pediatric subjects weighing > 37 kg provide mean exposures that were similar to and/or above the 372 mg adult dose and significantly below the 1116 mg dose group, where toxicities were observed. For intravenous, across all age groups, > 99% of the predicted AUC_{ss} values were below the mean AUC values for the adult population administered 1116 mg isavuconazonium sulfate dose and > 94% of the predicted AUC_{ss} values were below the minimum adult AUC_{ss} values for the adult subject population administered the supra therapeutic dose clinical (1116 mg) dose [Study 9766-CL-0017]. For oral (12 to < 18 years of age), > 99% of the predicted AUC_{ss} values and > 98% of the predicted AUC_{ss} values were below the mean and minimum adult AUC_{ss} values from the 9766-CL-0017 study. For oral (6 to < 12 years of age), > 99% of the predicted AUC_{ss} values and > 96% of the predicted AUC_{ss} values were below the mean and minimum adult AUC_{ss} values from Study 9766-CL-0017.

Also, > 88% and approximately 80% of the predicted AUC_{ss} values for the intravenous and oral routes of administration were above the 25th percentile of exposure values from the

SECURE study in subjects who received 372 mg dose of isavuconazonium sulfate. Table 3 is updated based on simulations from the most recent population pharmacokinetic model that included oral data from subjects 6 to < 12years of age.

Table 3 Percentage of Pediatric Patients with Predicted AUC_{ss} Values of Isavuconazole Below or Above the Specified Adult AUC Values

Route	Age Group	% of Subjects Below Mean Adult AUC_{24} 1116 mg Dose	% of Subjects Below Minimum Adult AUC_{24} 1116 mg Dose	% of Subjects Above the 25th Percentile Adults AUC_{ss} 372 mg Dose
Intravenous	1 to < 6 years	100%	97.0%	88.6%
	6 to < 12 years	99.7%	94.0%	92.7%
	12 to < 18 years	99.9%	98.2%	82.1%
Oral	6 to < 12 years	99.6%	96.4%	90.7%
	12 to < 18 years	100%	98.2%	78.8%

Source: Data on file

AUC_{24}: area under the concentration-time curve at 24 hours; AUC_{SS}: area under the concentration-time curve at steady state

Based on modeling and simulation results, the proposed daily dose administered either as intravenous (across all age groups) or oral (6 years to < 18 years of age and with a body weight of at least 12 kg) for the clinical study in pediatric subjects is:

- 10 mg/kg isavuconazonium sulfate for subjects weighing ≤ 37 kg (the maximum loading and daily maintenance doses to be administered to any subject are 372 mg)

  OR

- 372 mg isavuconazonium sulfate for subjects weighing > 37 kg.

NOTE: The oral administration is only available for pediatric subjects 6 years and older due to the difficulty in swallowing the oral capsule.

Due to similarity in exposures between intravenous and oral in pediatric subjects, the route of administration can be switched from intravenous to oral and oral to intravenous, as needed. Currently, interchangeability of administration is permitted in adults in approved product labeling (US Package Insert). Isavuconazonium sulfate oral capsules can be administered with or without food.

2.3 Endpoints

2.3.1 Safety Endpoints

Safety outcomes will include AEs, vital signs, ECGs and laboratory parameters.

2.3.2 Efficacy Endpoints

The primary efficacy endpoint will be all-cause mortality through day 42.

The key secondary efficacy endpoint will be all-cause mortality through day 84 and EOT.

Additional secondary efficacy endpoints will be overall, clinical, radiological and mycological response through day 42, day 84 and EOT.

2.3.3 Other Endpoints

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

In addition to the above, 24-hour pharmacokinetic samples will be obtained on any one day between day 14 and day 42, while the subject is still receiving study drug.

After receiving their first dose of oral capsules, subjects will be asked to assess their initial experience with the new oral formulation (i.e., Acceptability Assessment [Appendix 12.7]). The assessment is being conducted to assess the acceptability of the new oral formulation in a pediatric population. Refer to [Section 5.3.3 Oral Dosing Acceptability Assessment] for details regarding this assessment.

3 STUDY POPULATION

3.1 Selection of Study Population

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization) must be obtained from the subject's parent or legal guardian and, if required, subject's assent, prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Male or female subject 1 year to < 18 years of age diagnosed with IA or IM. A positive diagnosis is defined as follows:
    - Proven, probable or possible IFI per the European Organisation for Research and Treatment of Cancer/Mycoses Study Group [EORTC/MSG], 2008 criteria.

      Note: Subjects with "possible" IFI will be eligible for enrollment; however, diagnostic tests to confirm the invasive fungal disease as "probable" or "proven" according to the EORTC/MSG criteria should be completed within 10 calendar days after the first dose of study drug.

        - Note: In addition to the criteria set for mycological criteria by the EORTC/MSG in 2008, and only for subjects with an underlying hematologic malignancy or recipients of HSCT who also have clinical and radiologic features consistent with invasive fungal infection, the following are acceptable:
            i. Galactomannan (GM) levels (optical density index) meeting the below criteria are acceptable mycological evidence for enrollment or upgrading the diagnosis to probable IA:

1. A single value for serum or bronchoalveolar lavage (BAL) fluid of ≥ 1.0 or
2. Two serum GM values of ≥ 0.5 from 2 separate samples

3. Subject has sufficient venous access to permit intravenous administration of study drug or the ability to swallow oral capsules.
4. A female subject is eligible to participate if she is not pregnant and at least one of the following conditions applies:
    a. Not a subject who is of childbearing potential as defined in [Appendix 12.3 Contraception Requirements].

    OR

    b. Subject who is of childbearing potential who agrees to follow the contraceptive guidance as defined in [Appendix 12.3 Contraception Requirements] throughout the treatment period and for at least 30 days after the final study drug administration.
5. Female subject who is of childbearing potential must agree not to breastfeed starting at screening and throughout the study, and for 30 days after the final study drug administration.
6. Female subject who is of childbearing potential must not donate ova starting at screening and throughout the study, and for 30 days after the final study drug administration.
7. A male subject with female partner(s) of childbearing potential must agree to use contraception as detailed in [Appendix 12.3 Contraception Requirements] during the treatment period and for at least 30 days after the final study drug administration.
8. Male subject must not donate sperm starting at screening and throughout the study and for 30 days after the final study drug administration.
9. Subject and subject's parent(s) or legal guardian agree that the subject will not participate in another interventional study while on treatment with the exception of oncology trials.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Subject has familial short QT syndrome, is receiving medications that are known to shorten the QT interval, or has a clinically significant abnormal ECG.
2. Subject has evidence of hepatic dysfunction defined as any of the following:
    - Total bilirubin (TBL) ≥ 3 times the upper limit of normal (ULN)
    - Alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 5 times the ULN
    - Known cirrhosis or chronic hepatic failure

3. Subject has used strong cytochrome P450 (CYP3A4) inhibitors or inducers such as ketoconazole, high dose ritonavir, rifampin/rifampicin, long acting barbiturates (e.g., phenytoin), carbamazepine and St. John's Wort in the 5 days prior to the first dose of study drug.
4. Subject has another IFI other than possible, probably or proven IA or IM.
5. Subject has chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis.
6. Subject has received mould active systemic antifungal therapy, effective against the primary IMI, for more than 4 days during the 7 days preceding the first dose.

   Note: Prior use of prophylactic antifungal therapy is acceptable. In case of breakthrough IA while on prophylactic mould-active azole class drugs, additional documentation will be required to be submitted to the sponsor medical monitor or designee to approve subject enrollment.
7. Subject has known history of allergy, hypersensitivity or any serious reaction to any of the azole class antifungals, or any components of the study drug formulation.
8. Subject has any condition, which, in the investigator's opinion, makes the subject unsuitable for study participation.
9. Subject is unlikely to survive 30 days in the investigator's opinion.
10. Subject has received investigational drug, with the exception of oncology drug trials, or trials with investigational drugs treating graft versus host disease, within 28 days or 5 half-lives, whichever is longer, prior to screening.

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Study Drug(s)

The test drugs for this study are 372 mg isavuconazole sulfate for injection or 74.5 mg isavuconazonium sulfate oral capsules.

Intravenous Dosing:

Isavuconazonium sulfate for injection is supplied in a single-dose vial as a sterile lyophilized white to yellow powder containing 372 mg of isavuconazonium sulfate, which is equivalent to 200 mg of isavuconazole.

Store isavuconazonium sulfate for injection vials at 2°C to 8°C (36°F to 46°F) in a refrigerator.

For additional information regarding dosage preparation, refer to the product package insert or pharmacy manual.

Oral Dosing:

Isavuconazonium sulfate will be supplied as oral capsules packaged in aluminum blisters with desiccants in secondary child-resistant cards. Each capsule contains 74.5 mg isavuconazonium sulfate (40 mg isavuconazole). The capsule is a Swedish orange color.

Store isavuconazonium sulfate capsules at 20°C to 25°C (68°F to 77°F) in the original packaging to protect from moisture.

Excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. For additional information, refer to the protocol-specific pharmacy manual.

4.1.2 Comparative Drug(s)

Not applicable.

4.2 Packaging and Labeling

The study drug used in this study is the marketed commercial product, Cresemba® for injection or investigational study drug for oral dosing. The study drug is prepared, packaged and labeled under the responsibility of qualified staff at Astellas Pharma Global Development (APGD)-Astellas US Technologies (AUST) or sponsor's designee in accordance with APGD-AUST or sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

In addition to the commercial labeling, the intravenous study drug will bear a protocol label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug. The oral study drug will only bear a protocol label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by the investigator/or designee and that:

- Such deliveries are recorded,
- Study drug is handled and stored according to labeled storage conditions,
- Study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- Any unused study drug is returned to the sponsor.

Study drug inventory and accountability records will be kept by the investigator designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator designee agrees not to supply study drugs to any persons, except the eligible subjects in this study, in accordance with the protocol.

- The investigator designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- A study drug inventory will be maintained by investigator designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned study drug. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site staff must return study drug to the sponsor or designee at the end of the study or upon expiration unless otherwise approved by the sponsor.

4.4 Blinding

This section is not applicable as this is an open-label study.

4.5 Assignment and Allocation

All subject numbers will be assigned using the Interactive Response Technology (IRT) starting at screening. All subjects will have a unique, 10-digit subject number. The first 5 digits of this number will be the investigator's research number. The second 5 digits assigned will represent the subject's accession number. This will be the number that identifies a subject during the course of the study.

Only subjects who meet all inclusion criteria and exhibit none of the exclusion criteria will be enrolled into the study through IRT. Specific procedures related to the IRT are contained in the study procedures manual.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

The isavuconazonium sulfate will be administered as an intravenous infusion or as oral capsule(s) per the investigator's discretion. The 1-hour (± 10 minutes) intravenous infusion will be administered through an in-line filter. The start and stop times of the infusion must be clearly documented. Oral administration is only for subjects 6 to < 18 years of age and with a body weight of at least 12 kg. The investigator may determine the appropriate route of administration for the subject in the context of the relevant age range. The route of administration can be interchangeable from intravenous to oral (6 to < 18 years of age with a body weight of at least 12 kg) or oral (6 to < 18 years of age and with a body weight of at least 12 kg) to intravenous during the loading dose period and throughout the treatment

period, the mg:mg is equivalent in both routes. The details of dose and route of administration will be captured in the electronic case report form (eCRF).

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. Table 4 provides guidance to the investigator outlining the elements collectively informing a successful outcome. The investigator is encouraged to have clinical resolution of symptoms and associated mycological and/or radiologic data supporting the assessment of successful outcome.

Table 4 Investigator Guidance for Successful Outcome

	Clinical Response	**Mycological Response**	**Radiological Response**
Success	• Resolution of all attributable clinical symptoms and physical findings • Partial resolution of attributable clinical symptoms and physical findings	• Eradication • Presumed Eradication	• Improvement from screening • No signs on radiological images at screening (only for proven IFI based on other investigations)

IFI: invasive fungal infection

Intravenous Dosing:

Subjects weighing ≤ 37 kg:

- Loading regimen of 10.0 mg/kg isavuconazonium sulfate infusions every 8 hours (± 2) for 6 doses (days 1 and 2)
- Maintenance dose of 10.0 mg/kg isavuconazonium sulfate administered once daily starting 12 to 24 hours after the last loading dose

The maximum loading and daily maintenance doses to be administered to any subject are 372 mg per individual dose.

Subjects weighing > 37 kg:

- Loading regimen of 372 mg isavuconazonium sulfate infusions (1 vial) every 8 hours (± 2) for 6 doses (days 1 and 2)
- Maintenance dose of 372 mg isavuconazonium sulfate (1 vial) administered once daily starting 12 to 24 hours after the last loading dose

The maximum loading and daily maintenance doses to be administered to any subject are 372 mg per individual dose.

The maximum treatment is 84 days for IA subjects and 180 days for IM subjects, whichever occurs first.

Subjects will receive isavuconazonium sulfate as an intravenous infusion. 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).

Oral Dosing (for subjects 6 to < 18 years of age with a body weight of at least 12 kg):

Subjects will receive an oral loading regimen of isavuconazonium sulfate in a capsule form given every 8 hours (± 2 hours) on days 1 and 2 (a total of 6 doses), followed by once-daily oral maintenance dosing. The first maintenance dose should start 12 to 24 hours after the administration of the last loading dose, with subsequent maintenance doses to be administered once daily, 24 hours (± 2 hours) from the previous maintenance dose. Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly to receive new oral dosing supplies. Return visits should coincide with days when study-related assessments are required. Subjects who begin oral administration are to complete the oral dosing acceptability assessment after ingesting their first oral dose.

The daily dose is based on body weight and is intended to deliver a dose approximately equal to 10 mg/kg. The oral and intravenous formulations are equivalent on a mg:mg basis. The lower limit for oral dosing is 6 years of age and with a body weight of at least 12 kg.

Subjects will receive isavuconazonium sulfate as an oral capsule (the number of capsules will correspond to their weight; see Table 5).

Table 5 Oral Dosing Regimen by Body Weight

Body weight (kg)	Loading (Day 1 and Day 2)/Total Daily Isavuconazonium Sulfate Dose (mg)	Maintenance (up to 84 days [IA] or 180 days [IM])/Total Daily Isavuconazonium Sulfate Dose (mg)
12 to < 18	3 × 2 capsules/447 mg	1 × 2 capsules/149 mg
18 to < 25	3 × 3 capsules/670.5 mg	1 × 3 capsules/223.5 mg
25 to < 32	3 × 4 capsules/894 mg	1 × 4 capsules/298 mg
≥ 32	3 × 5 capsules/1117.5 mg	1 × 5 capsules/372.5 mg

Increase or Reduction in Dose of the Study Drug(s)

The mg/kg dose is to be consistent throughout study conduct. Dose increase or reductions to the study drug on a mg/kg basis are not allowed. However, if a subject has substantial weight changes, the number of capsules for oral dosing should be reassessed per Table 5.

5.1.2 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

Systemic antifungal medications taken for IM or IA or suspected mycoses and other medication taken within 28 days prior to the screening visit and up to the first dose of study

drug (investigational period) will be documented as prior antimycotic medications or other prior medication, respectively.

Medications taken after the first dose of study drug and up to EOS will be documented as concomitant medications.

Prior and concomitant medications and nonmedications to be documented include, but are not limited to, the following: vitamins, herbal remedies (e.g., St. John's Wort, valerian) and over-the-counter and prescription medications. Any medications taken for treatment of pain symptoms will be documented as such.

Subjects are instructed not to take any concomitant medication without first consulting the investigator or study coordinator throughout the duration of the study.

Prohibited Therapies:

Treatments with concomitant drugs that are strong inhibitors or inducers of CYP3A4 are prohibited, including ketoconazole, high dose ritonavir, rifampin/rifampicin, carbamazepine and St. John's Wort or long acting barbiturates (e.g., phenytoin). Concomitant use of sirolimus, atorvastatin, cyclosporine, tacrolimus, midazolam, bupropion, mycophenolate mofetil and digoxin should be made with caution.

Treatments with concurrent drugs that are CYP3A4 substrates and have a narrow therapeutic range (e.g., vincristine) should be used with caution, and if clinically warranted, consider reduction of substrate dose.

Use of other systemic antifungals is prohibited during study drug administration.

Subjects taking prohibited medications who are willing to discontinue these medications, as clinically indicated and based upon the investigator's recommendation, may washout over a period of 5 half-lives on a schedule determined by the investigator.

5.1.3 Treatment Compliance

Study drug is administered at the research facility under the supervision of study personnel while the subject remains as an inpatient.

If the subject is discharged while continuing treatment with intravenous dosing, the subject must return to the research facility or other approved location every day to receive the daily intravenous dose. Vital signs will be taken pre and post dose. Infusion reaction and other safety monitoring will be conducted.

Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly for study drug accountability and to receive new oral dosing supplies. Subjects will be provided with approximately 1-week worth of study medication, dosing instructions and a daily dosing log for documentation of ingestion of the oral study medication.

The subject or parent/legal guardian must record the date and time of oral dosing once the first capsule is ingested. The subject should ingest the entire dose within 5 minutes. If the entire dose is not ingested within 5 minutes, record the reason for dosing delay in the source

documentation. If the subject should vomit any of the medication, this is to be recorded as well. The dose is NOT to be repeated. Compliance of the study drug will be monitored by review of the oral dosing log and the accounting of unused medication returned by the subject at each scheduled visit after day 7 and/or at the EOT visit.

When study drug is administered at the research facility, it will be administered under the supervision of study personnel. A subject daily dosing log will be collected to record date/time and completeness of dosing for each day.

Study subjects and their parents/legal guardians should be counseled on the need to meet 100% compliance with study drug dosing. The investigator or designee should ensure that study subjects adhere to this goal throughout the study.

If compliance is less than 80%, the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic characteristics will be recorded at the screening visit. This will include age, sex, race, ethnicity (if known), height and body weight. Height and weight are to be measured while the subject is clothed, but not wearing shoes.

5.2.2 Medical History

The medical history of diseases other than the underlying diseases or conditions or infectious diseases will be identified at screening, by means of diagnosis and duration of the disease.

The medical history will include information related to the duration (i.e., the number of months or years). Subject's relevant medical and surgical history must be documented.

5.2.2.1 Underlying Diseases or Conditions

At screening, all underlying diseases or other conditions that predispose the subject to IFIs will be recorded.

5.2.2.2 Infectious Disease History

History of all fungal, viral and bacterial infections within 14 days prior to screening will be recorded.

5.3 Efficacy and Pharmacokinetic Assessments

5.3.1 Efficacy Assessment

All clinical, mycological, radiological assessments and diagnostic tests performed to document the baseline mould infection must be recorded. Criteria for possible, probable and proven disease based on the EORTC/MSG criteria require evidence including host factors (neutropenia, hematological malignancy, etc.), mycological criteria (positive culture from normally sterile site, BAL fluid, serum or BAL GM and histology of tissue demonstrating the

presence of fungal elements), and clinical signs and symptoms (radiological evidence of fungal disease at the infected body site). These data will be recorded in the eCRF.

During treatment with study drug, record any tests performed to demonstrate changes from baseline or evaluate the status of the fungal infection, such as mycological evidence of fungal culture or histology results (positive and negative) from the relevant site of infection or any new site, new fungal infection, changes in clinical signs and symptoms, including radiological findings relevant to the baseline fungal infection under treatment, and any serological markers performed (serum GM) and any surgical procedures. Record any procedures conducted to further assess or treat the fungal infection such as surgical debridement, amputation, etc. and the results of such procedures. Negative results of tests demonstrating resolution of infection should also be documented and recorded in the eCRF. Mortality status will be assessed per [Table 1 and Table 2 Schedule of Assessments].

Every effort should be made to speciate and characterize any fungal organisms grown in cultures. Results of susceptibility testing done locally will be collected. Fungal isolates from all positive fungal cultures should be stored and a reference laboratory will be made available by the sponsor. The reference laboratory will provide confirmation of the fungal genus and species, as well as in vitro susceptibility to isavuconazole, as well as relevant mould-active antifungal drugs. The reference laboratory results will not be available until after the end of the study.

5.3.2 Pharmacokinetic Assessment

Blood samples will be collected for pharmacokinetic analysis of isavuconazole as depicted in [Table 1 and Table 2 Schedule of Assessments]. Blood sample collection, handling and storage will be described in the laboratory manual.

Blood sampling for the analysis of trough levels will be obtained from all subjects. The samples should ideally be drawn immediately prior to the dose of study drug, but must be taken no earlier than 1 hour prior to the dose on days 7, 14, 21, 42 and 84 or EOT.

In addition to the above, 24-hour pharmacokinetic samples for intravenous or oral dosing will be obtained on any one day between day 14 and day 42, while the subject is still receiving study drug, for subjects who consent to participation in the 24-hour pharmacokinetic assessment. The goal is to achieve approximately 6 subjects in each age cohort by the time enrollment is completed for the study.

The 24-hour **intravenous** pharmacokinetic samples will be obtained as follows:

1. within 1 hour prior to the start of the intravenous isavuconazonium sulfate infusion (this sample will be the same as the trough sample prior to dose if it coincides with scheduled days 14, 21 or 42);
2. immediately after the completion of the intravenous infusion (no more than 5 minutes after);
3. within 4 to 10 hours after the start of the intravenous infusion; and
4. within 16 to 24 hours after the start of the intravenous infusion (must be obtained before the start of the next infusion).

The 24-hour **oral** pharmacokinetic samples will be obtained as follows:

1. within 1 hour of next oral dose (this sample will be the same as the trough sample prior to dose, if it coincides with scheduled days 14, 21 or 42);
2. 1 hour post dose (± 10 minutes);
3. 3 hours post does (± 10 minutes);
4. 4 hours post dose (± 10 minutes);
5. within 6 to 8 hours (± 30 minutes) of study drug administration; and
6. 24 hours (within 1 hour before next study drug administration) after study drug administration.

5.3.3 Oral Dosing Acceptability Assessment

This assessment will be conducted to assess the acceptability of the new oral formulation in this subject population. Subjects who begin oral administration of the study drug will complete an assessment shortly after taking their first oral dose. A 5-point hedonic scale rating the oral dosing is included on the assessment. There are 5 faces with descriptions from really bad to really good that rank the response to the following questions:

- How was the TASTE of the medication?
- How was it to SWALLOW the medication?
- How would you FEEL if you took this medication again?

Refer to [Appendix 12.7 Oral Dosing Acceptability Assessment].

5.4 Safety Assessment

5.4.1 Vital Signs

Vital signs (temperature, pulse rate and blood pressure) are to be measured within 1 hour before the start and approximately 1 hour after the end of each infusion on dosing days. No additional vital signs are needed on dosing days for oral administration. Temperature to be taken as per institution's policy based on age of subject. Vital signs will be collected as shown in the schedule of assessments [Table 1 and Table 2]. When vital signs are scheduled for the same time as a blood sample, the vital signs will be taken before the blood sample.

5.4.2 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study and assessed by the local laboratory. In the event the protocol-specified clinical laboratory has already been collected and results available, these data are sufficient for monitoring safety as per the protocol and must be recorded in the eCRF. In order to minimize blood draws, it is not necessary to draw an additional sample for the sole purposes of the clinical trial.

Clinical laboratory samples should be collected at the same time as other blood samples such as pharmacokinetic whenever possible to minimize the need for unnecessary blood sampling for the subject. See [Table 1 and Table 2 Schedule of Assessment] for study visit days and allowed windows for lab sample collection.

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

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. 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. A urine or serum pregnancy test will be performed for female subjects of childbearing potential prior to dosing, day 28, day 42 and day 84 (IA) or EOT, day 180 (IM) or EOT.

5.4.3 Physical Examination

Subjects will be examined by a medically qualified person at the times specified in [Table 1 and Table 2 Schedule of Assessments].

A complete physical examination consisting of an examination of general appearance, eyes, nose, throat, neck (including thyroid), lymph nodes, chest, lungs, cardiovascular, abdomen, skin, extremities, musculoskeletal and neurological system including mental status is to be conducted. A symptom-directed physical exam may be performed during subsequent visits, if necessary.

Height will be measured at screening only. Weight will be measured at screening, day 84 or EOT (IA and IM subjects) and/or day 180/EOT (IM subjects).

The screening physical examination also includes significant, ongoing medical conditions. Any changes between screening and day 1 are to be captured in the medical history.

Any abnormal finding(s) at screening must not be exclusionary per the eligibility criteria if a subject is to be enrolled in the study. Post initial study drug dosing, new abnormal findings or a worsening of an ongoing abnormal condition must be recorded as an AE.

5.4.4 Electrocardiogram

Standard 12-lead ECG recordings will be used for the purposes of safety assessment by the investigator.

A 12-lead, resting ECG is to be recorded, as indicated in [Table 1 and Table 2 Schedule of Assessments]. Subjects should remain supine for at least 5 minutes prior to all ECGs being performed. Dates and times may be generated by the machine's internal clock and are considered source data. The results are to be interpreted by qualified personnel in real time. The principal investigator/ designee will initial and date and provide his/her clinical interpretation on each report. The results (normal, abnormal not clinically significant, abnormal clinically significant) are to be recorded.

The ECG recorded during screening will be used to determine eligibility for study participation. Subjects who have familial short QT syndrome, or a clinically significant abnormal ECG, will not be eligible for the study. The interpretation of the ECG from screening will be the baseline to which post study drug dosing ECGs will be compared.

ECGs will be performed at screening and prior to study drug administration on each scheduled day as indicated in [Table 1 and Table 2 Schedule of Assessments].

Unscheduled ECGs will be performed if clinically indicated.

The original printout and an electronic copy of all scheduled and unscheduled ECG tracings should be maintained on site as source data.

5.4.5 Order of Assessments

The following sequence order will be in effect when more than one assessment is required at a time point with blood sampling for pharmacokinetics being collected nearest to the scheduled time point:

1. Vital signs
2. ECG
3. Laboratory assessments (hematology, chemistry and hepatic panel) blood draw
4. Pharmacokinetic blood draw

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered a study drug, and which does not necessarily have to 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 (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received study drug treatment. AE collection begins after the signing of the ICF and will be collected until 60 days after the last dose of study drug or the subject is determined to be a screen failure.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

5.5.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, clinical chemistry, hepatic panel or INR) or other safety assessment (e.g., ECGs, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an SAE or AE ((S)AE).

Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

5.5.1.2 Potential Cases of Drug-Induced Liver Injury

Refer to [Appendix 12.5 Liver Safety Monitoring and Assessment] for detailed instructions on drug induced liver injury. Abnormal values in AST and/or ALT concurrent or with abnormal elevations in TBL that meet the criteria outlined in [Appendix 12.5 Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (including potential Hy's Law cases) and are always to be considered important medical events and reported per [Section 5.5.5 Reporting of Serious Adverse Events].

5.5.1.3 Disease Progression and Study Endpoints

Under this protocol, the following event(s) will not be considered as an (S)AE:

- Pre-planned and elective hospitalizations or procedures for diagnostic, therapeutic or surgical procedures for a pre-existing condition that did not worsen during the course of the clinical trial. These procedures are collected per the eCRFs Completion Guidelines.

5.5.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life-threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect
- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE). Hospitalization for treatment/observation/examination caused by AE is to be considered as serious.
- Other medically important events (defined in paragraph below)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical 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 in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

5.5.2.1 Always Serious Adverse Events

The sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered by the sponsor to be an SAE per this classification as "always serious", additional information on the event (e.g., investigator confirmation of seriousness, causality) will be requested.

5.5.3 Criteria for Causal Relationship to Study Drug

A medically qualified investigator is obligated to assess the relationship between the study drug and each occurrence of each (S)AE. This medically qualified investigator will use medical judgment, as well as the Reference Safety Information (refer to the IB) to determine the relationship. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The medically qualified investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

Following a review of the relevant data, the causal relationship between the study drug and each (S)AE will be assessed by answering '**yes**' or '**no**' to the question "**Do you consider that there is a reasonable possibility that the event may have been caused by the study drug**".

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a 'reasonable possibility' that an (S)AE may have been caused by the study drug (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study drug and (S)AE onset and/or resolution. Has the subject actually received the study drug? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study drug?
- Plausibility; i.e., could the event been caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the (S)AE and the study drug (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study drug exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the medically qualified investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor. With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of 'no' is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

5.5.4 Criteria for Defining the Severity of an Adverse Event

The investigator will use the following definitions to rate the severity of each AE:

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

5.5.5 Reporting of Serious Adverse Events (SAEs)

The collection of AEs and the expedited reporting of SAEs will start following receipt of the ICF and will continue until 60 days after last administration of study drug or the subject is determined to be a screen failure.

In the case of a SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator must complete and submit an SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by email or fax immediately (within 24 hours of awareness).

The SAE worksheet must be signed by a medically qualified investigator (as identified on Delegation of Authority Log). Signature confirms accuracy and completeness of the SAE data, as well as the investigator causality assessment including the explanation for the causality assessment.

For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE/Special Situations worksheet to:

Astellas Pharma Global Development – US
Pharmacovigilance
Fax number +1-888-396-3750 or +1-847-317-1241
Email: Safety-US@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor/study physician or his/her designee [Section II Contact Details of Key Sponsor's Personnel].

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records, SAE/Special Situation Worksheet and on the eCRF.

The following minimum information is required:

- International study number/study number,
- subject number, sex and age,
- the date of report,
- a description of the SAE (event, seriousness criteria),
- causal relationship to the study drug (including reason), and
- the drug provided (if any).

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality and expectedness of the events (e.g., Suspected Unexpected Serious Adverse Reaction [SUSAR] reporting) according to current local/regional regulatory requirements in participating countries. The sponsor or sponsor's designee will submit expedited safety reports (e.g., IND

Safety Reports, SUSAR, Council for International Organizations of Medical Sciences [CIOMS] Form I) to Competent Authorities (CA) and concerned Ethics Committee (cEC) per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/local Independent Ethics Committee (IEC) within timelines set by regional regulations (e.g., EMA, FDA) where required. Documentation of the submission to and receipt by the IRB/local IEC of expedited safety reports should be retained by the site.

The sponsor will notify all investigators responsible for ongoing clinical studies with the study drug of all SUSARs, which require submission per local requirements.

The investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

The investigator may contact the sponsor's medical monitor/study physician for any other problem related to the safety, welfare or rights of the subject.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

If after the protocol defined AE collection period [see Section 5.5.1 Definition of Adverse Event], an AE progresses to a SAE, or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the study drug treatment or study participation, the investigator must promptly notify the sponsor.

5.5.7 Monitoring of Common Serious Adverse Events

Not applicable for this study.

5.5.8 Special Situations

Certain special situations observed in association with the study drug, such as incorrect administration (e.g., wrong dose of study drug) are collected in the eCRF, as protocol deviation per [Section 8.3 Major Protocol Deviations] or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a special situation is associated with, or results in, an AE, the AE is to be assessed separately from the special situation and captured as an AE in the eCRF. If the AE meets the definition of a SAE, the SAE is to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] and the details of the associated special situation are to be included in the clinical description on the SAE worksheet.

The special situations are:

- Pregnancy
- Medication error, overdose and "off-label use"
- Misuse/abuse
- Occupational exposure
- Suspected drug-drug or other (e.g., food) interaction
- (Suspicion of) Transmission of infectious agent

Table 6 provides a list of special situations along with how each should be reported.

Table 6 Special Situations

Special Situation	Collected		
	SAE/Special Situations Worksheet	eCRF	Protocol Deviation [Section 8.3]
Overdose of the medicinal product(s) [Section 5.5.8.2]			X
Suspected misuse/abuse of the investigational medicinal product	X		X
Occupational exposure	X		
Suspected drug-drug or other interaction		X	
Off-label use of study drug	X		
Pregnancy	X	X	
Medication error		X	

eCRF: electronic case report form; SAE: serious adverse event

5.5.8.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in **[**Section 5.5.5 Reporting of Serious Adverse Events] using the Pregnancy Reporting Form and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing and report the information to the sponsor according to the timelines in [Section 5.5.5 Reporting of Serious Adverse Event**s**] using the Pregnancy Reporting Form.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female study subject as an AE in the eCRF or SAE per [Section 5.5.5 Reporting of Serious Adverse

Events]. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the Pregnancy Reporting Form.

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- ″Spontaneous abortion″ includes miscarriage, abortion and missed abortion.
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator.
- Congenital anomaly (including anomaly in miscarried fetus)

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination. (S)AEs experienced by the newborn/infant should be reported via the Pregnancy Reporting Form. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

5.5.8.2 Medication Error, Overdose and “Off-label Use”

If a medication error, overdose or “off-label use” (i.e., use outside of what is stated in the protocol) is suspected, refer to [Section 8.3 Major Protocol Deviations]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with the details of the medication error, overdose and/or “off-label use”.

In the event of suspected isavuconazonium sulfate overdose, the subject should receive supportive care and monitoring. At supratherapeutic doses (equivalent to isavuconazole 600 mg/day maintenance dose) evaluated in a thorough QT study in adults, there were proportionally more treatment-emergent adverse events (TEAEs) than in the therapeutic dose group (equivalent to isavuconazole 200 mg/day maintenance dose) for the following: headache, dizziness, paraesthesia, somnolence, disturbance in attention, dysgeusia, dry mouth, diarrhoea, oral hypoesthesia, vomiting, hot flush, anxiety, restlessness, palpitations, tachycardia, photophobia and arthralgia. Isavuconazole is not removed by hemodialysis.

There is no specific antidote for isavuconazole.

The medical monitor should be contacted as applicable.

5.5.8.3 Misuse/Abuse

If misuse or abuse of the study drug(s) is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with details of the misuse or abuse of the study drug(s).

5.5.8.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the study drug of site staff while preparing it for administration to the subject) to the study drug occurs, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the Special Situation are to be reported on the Special Situations worksheet.

5.5.9 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the sponsor will inform all investigators involved in the clinical study, as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the subjects, who will be required to sign an updated ICF in order to continue in the clinical study.

5.5.10 Urgent Safety Measures

An urgent safety measure (USM) is an intervention, which is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant CA, IRB/IEC, where applicable, in order to protect study participants from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate an USM. The cause of an USM can be safety, product or procedure related.

5.5.11 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the Astellas study physician (within 24 hours of awareness). Full details of the potential USM are to be recorded in the subject's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be an USM the sponsor will take appropriate action to ensure the safety and welfare of the subjects. These actions may include, but are not limited to, a change in study procedures or study treatment, halting further enrollment in the trial, or stopping the study in its entirety. The sponsor or sponsor's designee will notify CA and cEC within the timelines required per current local regulations, and will inform the investigators as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

5.6 Test Drug Concentration

Plasma concentrations of isavuconazole will be analyzed to monitor the levels of isavuconazole in the subject population during treatment. For the purpose of this study, serial blood samples (approximately 1 mL) will be collected in 1-mL potassium ethylenediaminetetraacetic acid. Vacutainer tubes for each scheduled nominal time point on days 7, 14, 21, 42 and day 84 or EOT. The samples should ideally be drawn immediately prior to the dose of study drug, must be taken no earlier than 1 hour prior.

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 who consent to participation in the 24-hour pharmacokinetic assessment. The goal is to achieve approximately 6 subjects in each age cohort by the time enrollment is completed for the study.

The intravenous pharmacokinetic samples will be obtained as follows:

1. within 1 hour prior to the start of the intravenous isavuconazonium sulfate infusion (this sample will be the same as the trough sample prior to dose if it coincides with scheduled days 14, 21 or 42);
2. immediately after the completion of the intravenous infusion (no more than 5 minutes after);
3. within 4 to 10 hours after the start of the intravenous infusion; and
4. within 16 to 24 hours after the start of the intravenous infusion (must be obtained before the start of the next infusion).

The oral pharmacokinetic samples will be obtained as follows:

1. within 1 hour prior to the next oral dose (this sample will be the same as the trough sample prior to dose if it coincides with scheduled days 14, 21 or 42);
2. 1 hour post dose (± 10 minutes);
3. 3 hours post dose (± 10 minutes);
4. 4 hours post dose (± 10 minutes);
5. within 6 to 8 hours (± 30 minutes) of study drug administration; and
6. 24 hours (within 1 hour before next study drug administration) after study drug administration.

No additional pharmacokinetic samples will be taken from IM subjects during days 85 to 180.

Immediately after each sample collection, gently invert the blood sample 8 to 10 times and place in an ice water bath. Within 1 hour of sample collection, centrifuge the blood sample(s) at 1200 g for 10 minutes at approximately 4°C in order to obtain plasma.

Plasma will be harvested and divided equally into 2 (primary and back-up) appropriately labeled storage tubes.

Store the plasma samples in a freezer set to maintain -20°C ± 10°C or lower immediately following centrifugation and separation.

Primary and back-up samples will be shipped separately to the bioanalytical laboratory.

5.7 Other Measurements, Assessments or Methods

Not applicable.

5.8 Total Amount of Blood

The total blood volume to be collected on subjects 1 to < 18 years of age for the study through day 84 or EOT should not be more than 45 mL. Table 7 provides the amount of blood drawn for each laboratory parameters and study visit for these subjects.

Table 7 Total Amount of Blood Drawn

Parameter	Study Visit						Total Volume
	Screening	Labs: Days 7, 28, 56 and 84 or EOT	Pharmaco-kinetics: Days 7, 14, 21, 42 and 84 or EOT	Days 3, 14, 21, 35, 42, 49, 63, 70 and 77	IV Pharmaco-kinetics: 24-hour Sampling Day Anytime Between Days 14 and 42	Oral Pharmaco-kinetics: 24-hour Sampling Day Anytime Between Days 14 and 42	
Hematology	2 mL	2 mL/visit (8 mL)	N/A	N/A	N/A	N/A	10 mL
Chemistry	2 mL	2 mL/visit (8 mL)	N/A	N/A	N/A	N/A	10 mL
Hepatic Panel	*	*	N/A	1 mL/visit (9 mL)	N/A	N/A	9 mL
Serum GM	2 mL	N/A	N/A	N/A	N/A	N/A	2 mL
Pharmacokinetics	N/A	N/A	1 mL/visit (5 mL)	N/A	1 mL/time point (4 mL)	1 mL/time point (7 mL)	9 mL or 12 mL
PT/INR	1 mL	1 mL/visit (4 mL)	N/A	N/A	N/A	N/A	5 mL
TOTAL	**7 mL**	**20 mL**	**5 mL**	**9 mL**	**4 mL**	**7 mL**	**45 mL (IV 24-hr PK) -OR- 48 mL (Oral 24-hr PK)**

EOT: end of treatment; GM: galactomannan; INR: international normalized ratio; IV: intravenous; N/A: not applicable; PK: pharmacokinetics; PT: prothrombin time

* Included with chemistry

The total blood volume to be collected on IM subjects 1 to < 18 years of age during the IM follow-up period should not be more than 15 mL. Table 8 provides the amount of blood drawn for each laboratory parameters for these subjects.

Table 8 Blood Drawn During IM Follow-up

Parameter	Study Visits Days 115, 145 and 180 or EOT	Approximate Total Volume
Hematology	2 mL/visit (6 mL)	6 mL
Chemistry	2 mL/visit (6 mL)	6 mL
Hepatic Panel	*	N/A
PT/INR	1 mL/visit (3 mL)	3 mL
TOTAL	**15 mL**	**15 mL**

*Hepatic panel to be drawn with chemistry panel.

INR: international normalized ratio; PT: prothrombin time

Regarding the protocol-specified clinical laboratory, if clinical safety laboratory results are already available, these data are sufficient for monitoring safety as per the protocol and must be recorded in the eCRF. In order to minimize blood draws, it is not necessary to draw an additional sample for the sole purposes of the clinical trial.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s) From Study Treatment

A discontinuation from treatment is a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason. The reason for discontinuation from study treatment must be documented in the subject's medical records.

A subject must discontinue study treatment for any of the following reasons:

- Subject requests to stop treatment.
- Any clinical AE, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject.
- Parent(s) or legal guardian withdraws consent.
- Subject experiences a systemic infusion-related reaction (IRR) such as hypotension, dyspnea, chills, dizziness, paresthesia and hypoesthesia attributable to study drug during or shortly after the intravenous administration; however, in case of an infusion-related reaction, the infusion must be stopped immediately and the subject must be discontinued from treatment.
  Note: If the IRR signs and symptoms are mild and self-limiting, the subject may continue in the study at the discretion of the investigator.
- Serious hypersensitivity or severe skin reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azoles. If subject develops a severe hypersensitivity adverse reaction without alternative etiology, the subject must be discontinued from treatment.
- Investigator's decision that further treatment is not in the best interest of the subject.
- Female subject becomes pregnant.
- Subject is lost to follow-up despite diligent efforts to contact.

Discontinuation of the subject from treatment should be considered if a subject experiences an increase in liver enzymes. For specific liver abnormalities, refer to [Appendix 12.5].

All subjects who discontinue study treatment will remain in the study and should continue to be followed for protocol specific follow-up procedures as outlined in [Table 1 Schedule of Assessments]. The only exception to this is when the subject specifically withdraws consent for any further contact, with him/her or persons previously authorized by the participant to provide this information.

6.1.1 Lost to Follow-up

Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments and record outstanding data.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

6.3 Discontinuation of the Study

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be justified in the clinical study report.

In general, continuous data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) and frequency and percentage for categorical data.

7.1 Sample Size

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

Evaluable subjects are subjects who 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.

7.2 Analysis Sets

Detailed criteria for analysis sets will be laid out in classification specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set (FAS)

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.

7.2.2 Modified Full Analysis Set (mFAS)

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. The mFAS will be a secondary analysis set for efficacy analyses. Select demographic and baseline characteristics may also be summarized for the mFAS.

7.2.3 Safety Analysis Set (SAF)

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

7.2.4 Pharmacokinetic Analysis Set (PKAS)

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.

7.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, ethnicity, weight, height and body mass index) will be summarized for each analysis set.

7.3.1 Subject Disposition

The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all enrolled subjects and for subjects in the SAF by age cohort and overall. Similar tables for screening disposition, investigational period disposition and follow-up disposition will also be presented for all enrolled subjects by age cohort and overall. All disposition details and dates of first and last evaluations for each subject will be listed.

7.3.2 Previous and Concomitant Medications

All previous and concomitant medications will be summarized for subjects in FAS and SAF analysis sets and will also be presented in listings.

7.3.3 Medical History

Medical history for each subject will be presented in a listing.

7.4 Analysis of Efficacy

This is an open-label trial without a comparator group, and its analysis will be descriptive. No formal inferential analyses will be performed. Appropriate confidence intervals (CI) will be part of the description/summary of the data. Efficacy variables will be summarized with frequencies and percentages for the FAS and mFAS sets unless otherwise specified. For each efficacy endpoint, a summary will be presented for overall subjects and by subjects in each age cohort.

7.4.1 Analysis of Primary Efficacy Endpoint

7.4.1.1 Primary Efficacy Analysis

The primary efficacy endpoint of crude rate in all-cause mortality through day 42 will be analyzed on FAS population as a primary analysis. Any death that occurred after first dose of study drug through day 42 will be included.

Each subject will be classified as either a death 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.

7.4.1.2 Secondary Efficacy Analysis

The same analysis of the primary endpoint as described in [Section 7.4.1 Primary Analysis] will be conducted using the mFAS.

7.4.2 Analysis of Secondary Efficacy Endpoints

7.4.2.1 Analysis of Key Secondary Endpoints

Crude rate in all-cause mortality through day 84/EOT is considered as key secondary efficacy endpoint, which will be analyzed as described in [Section 7.4.1 Primary Analysis] for FAS and mFAS analysis sets. Any death that occurred after first dose of study drug through day 84/EOT will be included.

Subjects who die on or before day 84/EOT, as well as subjects who are lost to follow-up before day 84/EOT, will be counted as deaths.

7.4.2.2 Analysis of Additional Secondary Endpoints

Additional secondary efficacy endpoints include the overall, clinical, radiological and mycological response through day 42, day 84 and EOT. An Adjudication Committee (AC) will be utilized to confirm the diagnosis and overall, clinical, radiological and mycological response of IA or IM at each time point.

Crude success rates and 2-sided exact 95% CIs will be calculated and summarized for FAS and mFAS analysis sets.

7.5 Analysis of Safety

7.5.1 Adverse Events

AEs will be coded using MedDRA.

TEAE is defined as an AE observed after starting administration of the study drug through 30 days after the last dose. The number and percentage of subjects with treatment-emergent AEs, SAEs, AEs leading to withdrawal of treatment and AEs related to study drug will be summarized by MedDRA system organ class, MedDRA preferred term for overall subjects and by subjects in each 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.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline for subjects in the SAF by treatment visit.

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.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for subjects in the SAF by treatment visit.

Vital signs data will be displayed in listings.

7.5.4 Physical Examination

Physical examination will be listed.

7.5.5 Routine 12-lead Electrocardiograms

All 12-lead ECG results will be summarized by time point.

7.6 Analysis of Pharmacokinetics

Descriptive statistics (e.g., n, mean, standard deviation, minimum, median, maximum, coefficient of variation [CV], geometric mean and geometric CV) will be provided for plasma concentrations of isavuconazole.

7.6.1 Analytical Method

Isavuconazole plasma concentration will be determined by a validated LC-MS/MS method with a lower limit of quantitation (LLOQ) of 100 ng/mL.

7.6.2 Estimation of Pharmacokinetic Parameters

Plasma trough levels will be measured (pre-dose) on days 7, 14, 21, 42 and 84 or EOT.

24-hour pharmacokinetic samples will be measured on any day between days 14 and 42, while the subject is still receiving intravenous or oral study drug, for subjects who consent to participation in the 24-hour pharmacokinetic assessment.

Plasma concentrations will be analyzed using population pharmacokinetic model.

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.

7.7 Major Protocol Deviations and Other Analyses

Major protocol deviations as defined in [Section 8.3 Major Protocol Deviations] will be summarized for all enrolled subjects by site. A data listing will be provided by site and subject.

The major protocol deviation criteria will be uniquely identified in the summary table and listing.

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

No formal interim analysis is planned.

7.9 Handling of Missing Data, Outliers, Visit Windows and Other Information

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 a treatment group, in addition to determining 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.

See the SAP for details of the definition for windows to be used for analyses by visit.

Plasma concentration values below the LLOQ will be set to 0 for calculation of summary statistics. If one or more values are less than the LLOQ, the geometric mean will not be calculated.

8 OPERATIONAL CONSIDERATIONS

8.1 Data Collection

The investigator or site designee will enter data collected using an electronic data capture system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 5 days after the subject visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Concomitant medications will be collected during the study and related only to AE's/SAE's during the 30- and 60-day follow-up period.

Pharmacokinetic samples will be analyzed at the bioanalytical laboratory. The pharmacokinetic data will be transferred electronically to the sponsor or designee at predefined intervals during the study.

All procedures conducted under the protocol must be documented. For screen failures, the minimum demographic data (sex, birth date, race and ICF/assent date), outcome of eligibility assessment (inclusion and exclusion criteria), reason for screen failure and AEs details must be documented.

The investigator or designee will be responsible for eCRF completion and that all data and queries are accurate, complete and are verifiable with the source. The source should be appropriately maintained by the clinical unit.

Electronic data sources and any supporting documents should be available for review/retrieval by the sponsor/designee at any given time.

8.1.1 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated IC/assent forms
- Visit dates
- Medical history and physical examination details
- Key pharmacokinetic and safety data, if applicable (as specified in the protocol)
- AEs and concomitant medication
- Results of relevant examinations (e.g., ECG charts, etc.)
- Laboratory printouts (if applicable)
- Details of dispensing of study drug
- Reason for premature discontinuation (if applicable)
- Subject number (if applicable)
- Pharmacokinetic sample processing and storage history, including date/time each sample is transferred to the freezer, freezer identification and the temperature log for the freezer (if applicable)

8.1.2 Clinical Study Monitoring

The sponsor or delegated contract research organization (CRO) is responsible for monitoring the clinical study to ensure that subject's human rights, safety and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP and study data reported by the investigator/subinvestigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.3 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO, as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents [Section 8.1.2] when they are requested by the sponsor monitors and auditors, the IRB/IEC or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.4 Data Management

Data management will be coordinated by Astellas Data Science or designee in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Astellas Data Management. Completion of eCRFs will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and WHO Drug Dictionary, respectively.

8.2 Screen Failures

For screen failures, the demographic data, reason for failing, ICF, inclusion and exclusion criteria and AEs will be collected in the eCRF.

8.3 Major Protocol Deviations

A major protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The major protocol deviation criteria are 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.

When a major deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy OR pharmacokinetic parameters of the subject to determine subject continuation in the study.

If a major deviation impacts the safety of a subject, the investigator must contact the sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the sponsor and maintained within the trial master file.

9 END OF TRIAL

The end of the study is defined as the last visit or scheduled procedure shown in the schedule of assessments [Table 1 and Table 2] for the last study participant in the study.

10 STUDY ORGANIZATION

10.1 Data and Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board's (DSMB) primary responsibilities will be safeguarding the interests of study subjects and assessing the safety of the study treatment(s) and study procedures. Safety monitoring by the DSMB will be ongoing during the course of the study and provide medical input for activities such as SAE reviews and recommendations to Astellas. The organization and operating procedures for the DSMB will be described in a separate DSMB Charter. The DSMB members will not be employees of Astellas nor otherwise involved with the study conduct; however, members of the DSMB could be members of the AC.

The DSMB Charter will mandate that all relevant data be carefully reviewed and recommendations will be made whether the study should continue without protocol modification, continue with protocol modification, suspend enrollment, continue dose escalation or reduction, increase sample size and/or stop study due to safety concerns.

10.2 Adjudication Committee (AC)

The AC's primary responsibilities will be to confirm the diagnosis and overall, clinical, radiological and mycological response of IA or IM.

The organization and operating procedures for the AC will be described in a separate AC Charter. The AC members will not be employees of Astellas nor otherwise involved with the study conduct; however, members of the AC could be members of the DSMB.

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12 APPENDICES

12.1 Ethical, Regulatory and Study Oversight Considerations

12.1.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

12.1.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the IB, the ICF and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, ICF and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IRB/IEC approval before implementation, except for changes necessary to eliminate an immediate hazard to subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable) and all other applicable local regulations

12.1.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC, CA approval or notification may be required. The changes will become effective only after the approval of the sponsor, the investigator, the regulatory authority and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the ICF, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new ICF must also be forwarded to the sponsor.

12.1.4 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.1.5 Informed Consent of Subjects

12.1.5.1 Subject Information and Consent/Assent

If there are study related procedures that require a separate consent (i.e., pharmacogenetics sample, tumor biopsy) the consent process for the procedure should be described here.

The investigator or his/her representative will explain the nature of the study to the subject and/or parent or legal guardian and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF/assent will be reviewed and signed and dated by the subject and/or parent(s) or legal guardian, the person who administered the ICF/assent and any other signatories according to local requirements. A copy of the signed ICF/assent will be given to the subject and/or parent(s) or legal guardian and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent/assent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent/assent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

12.1.5.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's

medical record. An entry must be made in the subject's records documenting the re-consent process.

12.1.6 Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electric devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol related assessments, AE tracking and/or drug accountability.

Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments and audit trail information), if applicable. All printed records must be kept in the subject file and available for archive.

12.1.7 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data, CRFs and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the NDA or discontinuation of the IND). The sponsor will notify the site/investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPD/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subject's medical records and/or study progress notes.

12.1.8 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless otherwise the subject provides written consent or approval. Additional medical information may be given only after approval of the subject to the investigator or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and Privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then sponsor shall serve as the controller of such data, as defined by the European Union (EU) Data Protection Directive, and Investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. If sponsor is not based in the EEA, sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the Directive.

12.1.9 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the IB and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the clinical study agreement.

12.1.10 Insurance of Subjects and Others

The sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the investigator's file.

12.1.11 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report, which forms part of a marketing authorization application, be signed by the

representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator (s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

12.2 Procedure for Clinical Study Quality Control

12.2.1 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/subinvestigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

12.2.2 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO, as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records including source documents when they are requested by the sponsor monitors and auditors, the IRB/IEC or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

12.2.3 Data Management

Data Management will be coordinated by the Data Science department of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and WHO Drug Dictionary, respectively.

12.2.4 Quality Assurance

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the quality assurance and quality control systems and written SOPs of the CRO will be applied.

The sponsor or sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms and source documents. Direct access to these documents will be required by the auditors.

12.3 Contraception Requirements

Subjects who are of childbearing potential participants who choose complete abstinence must continue to have pregnancy tests, as specified in schedule of assessments [Table 1 and Table 2].

SUBJECTS WHO ARE OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

A female subjects is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.

Female subjects in the following category are not considered subjects who are of childbearing potential

- Premenarchal

Documentation of any of this category can come from the site personnel's review of the female subject's medical records, medical examination or medical history interview.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required at the time of informed consent and until the end of relevant systemic exposure, defined as 30 days after the final study drug administration.*****

Highly Effective Contraceptive Methods (Failure rate of < 1% per year when used consistently and correctly)[a]

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

- oral
- intravaginal
- transdermal

Progestogen-only hormonal contraception associated with inhibition of ovulation

- oral
- injectable
- implantable

Hormonal methods of contraception containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system

- intrauterine device
- bilateral tubal occlusion

Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the subject who is of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*

Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. It is not necessary to use any other method of contraception when complete abstinence is elected.*

[*] Local laws and regulations may require use of alternative and/or additional contraception methods.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during treatment and until the end of relevant systemic exposure defined as 30 days after final drug administration.*****

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom during treatment and until end of relevant systemic exposure defined as 30 days after final drug administration.
- Female partners of male participants who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 30 days after final drug administration.

12.4 List of Excluded Concomitant Medications

Treatments with concomitant drugs that are strong inhibitors or inducers of CYP3A4 are prohibited, including ketoconazole, high dose ritonavir, rifampin/rifampicin, carbamazepine and St. John's Wort or long acting barbiturates (e.g., phenytoin). Concomitant use of sirolimus, atorvastatin, cyclosporine, tacrolimus, midazolam, bupropion, mycophenolate mofetil and digoxin should be made with caution.

Treatments with concurrent drugs that are CYP3A4 substrates and have a narrow therapeutic range (e.g., vincristine) should be used with caution, and if clinically warranted, consider reduction of substrate dose. Use of other systemic antifungals is prohibited during study drug administration.

12.5 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least ALT, AST, alkaline phosphatase [ALP] and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**TBL**
Moderate	> 3 × ULN	or	> 2 × ULN
Severe	> 3 × ULN	and	> 2 × ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and International Normalized Ratio (INR) > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site staff is to complete the liver abnormality case report form (LA-CRF). Subjects with confirmed abnormal liver function tests (LFTs) should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases is to be recorded as "AEs" within the eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic subjects, and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, is to be entered in the eCRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents),
    - Ultrasound or other imaging to assess biliary tract disease,
    - Other laboratory tests including INR, direct bilirubin.
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Treatment Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, preexisting or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Discontinuation of study treatment should be considered if:

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

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, study treatment should be discontinued.

*Hy's Law Definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10 to 50% mortality (or transplant).

The 2 “requirements” for Hy’s Law are:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 × ULN (2 × ULN elevations are too common in treated and untreated subjects to be discriminating).
2. Cases of increased bilirubin (at least 2 × ULN) with concurrent transaminase elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert’s syndrome [Temple, 2006].

FDA Guidance for Industry titled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” issued on July 2009:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3 x ULN, one or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B or C; preexisting or acute liver disease; or another drug capable of causing the observed injury. [Guidance for Industry titled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” issued by FDA on July 2009]

References

Temple R. Hy’s law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006;15(Suppl 4):241-3.

Guidance for Industry titled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” issued by FDA on July 2009.

12.6 Common Serious Adverse Events

For this protocol, there is no list of common SAEs anticipated for the study population for the purposes of IND safety reporting.

12.7 Oral Dosing Acceptability Assessment

SITE NUMBER: _____ DATE:_____/_____/_____ (DD/MMM/YYYY)
SUBJECT NUMBER: _____

General Instructions

The questionnaire will be completed for all subjects who received oral study medication:

- By the patient him/herself (when the patient is able to do so), or
- By the parent/legal guardian/study nurse (based on input from the patient).

The questionnaire will be completed:

- Following the first oral dose (shortly after taking the study medication).

Subject Instructions

You have just taken the oral study medication.

- Please answer the three questions below.
- Put a cross in the box below the best answer.
- If you make a mistake, cross it out with a single line and cross the correct answer. The original entry should still be legible.

Questions

1. How was the TASTE of the medication?

0	1	2	3	4
				
Really bad	Bad	Not bad, not good	Good	Really good
☐	☐	☐	☐	☐

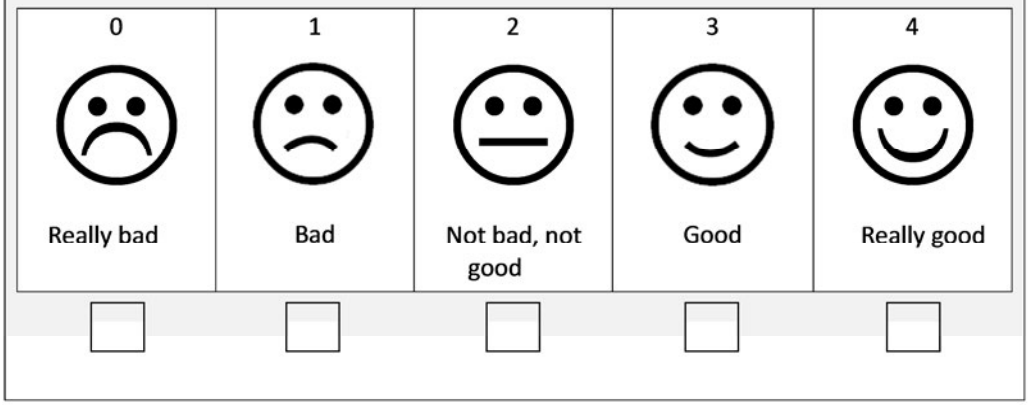
2. How was it to SWALLOW the medication?

0	1	2	3	4
				
Really bad	Bad	Not bad, not good	Good	Really good
☐	☐	☐	☐	☐

SITE NUMBER: _____ DATE: _____ (DD/MMM/YYYY)

SUBJECT NUMBER: _____

3. How would you FEEL if you took the medication again?



13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 3

I. The purpose of this amendment is:

Substantial Changes
1. Clarify Vital Signs for Subjects who Receive Oral Dosing
DESCRIPTION OF CHANGE:
Additional text is added to specify that no additional vital signs are needed on dosing days for oral administration other than screening and end of treatment.
RATIONALE:
This change is made to clarify that no additional vital signs are required for subjects who receive oral dosing as the additional vital signs are only required for monitoring of the intravenous dosing.
2. Clarify Pregnancy Testing in the Schedule of Assessments
DESCRIPTION OF CHANGE:
Additional text is added to footnote 12 (Table 1) to clarify that the pregnancy test may be either urine or serum.
RATIONALE:
Added text to clarify the type of pregnancy test that is acceptable.
3. Update Timing of the Return Visit
DESCRIPTION OF CHANGE:
Text is added to specify that the return visit should occur on days when study-related assessments are required.
RATIONALE:
Added text to clarify the timing of return study visits to minimize the burden to subjects for unnecessary return visits.
4. Change Age Requirement for Oral Formulation
DESCRIPTION OF CHANGE:
The lower limit on the age requirement for oral dosing is changed from “12 years of age” to “6 years of age and with a body weight of at least 12 kg.” The dose rationale is updated with additional data from Part 2 of Study 9766-CL-0046 (6 to < 11 years of age) to support this change.
RATIONALE:
Added lower age range and minimum body weight for oral dosing as supported by additional

pharmacokinetic modeling data provided.
5. Add Investigator Guidance for Successful Outcome
DESCRIPTION OF CHANGE:
A table is added to provide guidance to the investigator defining the elements of a successful outcome.
RATIONALE:
Added guidance for the investigator regarding the definition of a successful outcome to aid in their decision making regarding end of treatment.
6. Update Inclusion Criterion #2
DESCRIPTION OF CHANGE:
This criterion is updated to extend the timing of diagnostic tests to confirm invasive fungal disease to 10 calendar days after the first dose of study drug.
RATIONALE:
Revised the timeframe allowed to confirm invasive fungal infection diagnosis to align with time estimated per site's institutional practice.
7. Update Inclusion Criterion #3
DESCRIPTION OF CHANGE:
This criterion is updated to clarify that the administration will be intravenous and to specify that the subject must be able to swallow oral capsules.
RATIONALE:
Added clarification that subject must either have venous access for intravenous infusion or the ability to swallow oral capsules to be eligible for the study.
8. Update Exclusion Criterion #7
DESCRIPTION OF CHANGE:
This criterion is updated to include allergy, hypersensitivity or serious reaction to "any component of the study drug formulation."
RATIONALE:
Updated the exclusion criterion to include allergy or hypersensitivity to ensure subject safety.
9. Add Discontinuation Due to Serious Hypersensitivity Adverse Reactions
DESCRIPTION OF CHANGE:

Text is added to state that subjects who develop serious hypersensitivity adverse reactions without alternative etiology will be discontinued from treatment.
RATIONALE:
Added discontinuation criterion for serious hypersensitivity adverse reactions as an additional safety precaution.

Nonsubstantial Changes
1. Update Contact Details of Key Sponsor's Personnel
DESCRIPTION OF CHANGE:
The Astellas medical monitor is replaced.
RATIONALE:
Sponsor personnel details are updated based on changes to study team members.
2. Update Inclusion Criterion #8
DESCRIPTION OF CHANGE:
The phrase "of childbearing potential" is removed from this criterion.
RATIONALE:
This change is made to correct an error.
3. Add Appendix with Acceptability Assessment
DESCRIPTION OF CHANGE:
The Acceptability Assessment is added to the protocol as Appendix 12.7. Cross references to this appendix are added as appropriate.
RATIONALE:
This change is made to include the details of the Acceptability Assessment to be used for this study.
4. Update Packaging of Oral Capsules
DESCRIPTION OF CHANGE:
The packaging information for oral capsules is updated to specify that aluminum blisters with desiccants will be used, and then placed in secondary child-resistant cards.
RATIONALE:
Added additional details related to the packaging of oral capsule for packaging identification purposes.

5. Update Treatment Compliance
DESCRIPTION OF CHANGE:
Additional details are added to the treatment compliance section.
RATIONALE:
Provided additional details regarding treatment compliance for oral dosing to ensure appropriate subject compliance and re-education throughout the study.
6. Clarify that Members of the Data and Safety Monitoring Board (DSMB) could be Members of the Adjudication Committee (AC), and Vice Versa
DESCRIPTION OF CHANGE:
Section 10.1 is updated to clarify that members of the DSMB could be members of the AC, and Section 10.2 is updated to clarify that members of the AC could be members of the DSMB.
RATIONALE:
This change is made to clarify that members may belong to both groups.
7. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes (e.g., typos, format, numbering and consistency throughout the protocol).
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.

II. Amendment Summary of Changes:

IIA. Substantial Changes

IV Synopsis, Dose(s)
WAS:
The investigator may determine the appropriate route of administration for each subject. They can change dosing between the 2 routes of administration (intravenous ⇆ oral) throughout the treatment period as needed.
IS AMENDED TO:
The investigator may determine the appropriate route of administration for each subject. **The investigator can switch**~~They can change dosing~~ between the 2 routes of administration (intravenous ⇆ oral) throughout the treatment period as needed. **Changes to route of administration will be documented.**

V Flow Chart and Schedule of Assessments *Table 1 Schedule of Assessments (IA and IM Subjects) – Screening through Day 84 and IA Follow-up (30 and 60 Days Post-Day 84 or EOT [Last Dose of Study Drug])*
WAS:
3. Diagnosis must be completed within 7 days of first dose. 5. Vital signs are to be measured within 1 hour prior to and approximately 1 hour after the end of each infusion. 9. For both intravenous and oral dosing: 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 who consent to participation in the 24-hour pharmacokinetic assessment. 12. Pregnancy testing not applicable for male subjects. Not necessary for female subjects who are of non-childbearing potential (e.g., premenarchal in the judgment of the investigator on day 1 and throughout the study treatment, or documented surgically sterile). 15. For both intravenous and oral dosing: Loading doses on days 1 and 2 will be administered every 8 (± 2) hours. 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 ± 2 hours from the previous maintenance dose). Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly to receive new oral dosing supplies.
IS AMENDED TO:
3. Diagnosis must be completed within **10**~~7~~ days of first dose. 5. Vital signs are to be measured within 1 hour prior to and approximately 1 hour after the end of each infusion. **No additional vital signs are needed on dosing days for oral administration.** 9. For both intravenous and oral dosing: 24-hour pharmacokinetic samples will be

obtained on any **one** day between day 14 and day 42, while the subject is still receiving study drug, for subjects who consent to participation in the 24-hour pharmacokinetic assessment.

12. Pregnancy testing not applicable for male subjects. Not necessary for female subjects who are of non-childbearing potential (e.g., premenarchal in the judgment of the investigator on day 1 and throughout the study treatment, or documented surgically sterile). **Pregnancy testing may be urine or serum, dependent upon institutional standard of care.**
15. For both intravenous and oral dosing: Loading doses on days 1 and 2 will be administered every 8 (± 2) hours. 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 ± 2 hours from the previous maintenance dose). Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly to receive new oral dosing supplies. **Return visits should coincide with days when study-related assessments are required. Oral dosing is allowed for 6 to < 18 years of age and with a body weight of at least 12 kg.**

V Flow Chart and Schedule of Assessments

Table 2 Extended Schedule of Assessments (IM Subjects) – Day 85 through Day 180 and IM Follow-up (30 and 60 days Post-Day 180 [Last Dose of Study Drug])

WAS:

Period	
Day	85
Visit window (days)	

3. Vital signs are to be measured within 1 hour prior to and approximately 1 hour after the end of each infusion.
10. For both intravenous and oral dosing: Subsequent maintenance doses will be administered once daily (24 ± 2 hours from the previous maintenance dose). Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly to receive new oral dosing supplies.

IS AMENDED TO:

Period	
Day	85
Visit window (days)	**± 2**

3. Vital signs are to be measured within 1 hour prior to and approximately 1 hour after the end of each infusion. **No additional vital signs are needed on dosing days for oral administration.**
10. For both intravenous and oral dosing: Subsequent maintenance doses will be administered once daily (24 ± 2 hours from the previous maintenance dose). Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly to receive new oral dosing supplies. **Return visits should coincide with days when study-related assessments are required. Oral dosing is allowed for subjects 6 to < 18 years of age and with a body weight of at least 12 kg.**

IV Synopsis, Study Design Overview and 2 Study Objective(s), Design and Endpoints *2.2.1 Study Design*
WAS:
The subjects will enter into screening anytime between days -5 to day 1 (predose). All subjects will be assigned to open-label treatment via intravenous or oral treatment at the discretion of the investigator. The oral formulation can only be given to subjects 12 years to < 18 years of age. Subjects who begin oral administration are to complete the oral dosing acceptability assessment after ingesting their first oral dose. 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 who consent to participation in the 24-hour pharmacokinetic assessment.
IS AMENDED TO:
The subjects will enter into screening anytime between days -5 to day 1 (predose). All subjects will be assigned to open-label treatment via intravenous or oral treatment at the discretion of the investigator. The oral formulation can only be given to subjects ~~12~~ **6** years to < 18 years of age **and with a body weight of at least 12 kg**. Subjects who begin oral administration are to complete the oral dosing acceptability assessment after ingesting their first oral dose. **Isavuconazonium sulfate oral capsules can be administered with or without food.** In addition to the above, 24-hour pharmacokinetic samples will be obtained on any **one** day between day 14 and day 42, while the subject is still receiving study drug, for subjects who consent to participation in the 24-hour pharmacokinetic assessment.

2 Study Objective(s), Design and Endpoints *2.2.1 Study Design*
WAS:
Visits should occur on days when study related assessments are required.
IS AMENDED TO:
Investigator guidance of a successful outcome is provided in Table 4. **Return visits should coincide with days when study-related assessments are required.**~~Visits should occur on days when study related assessments are required.~~

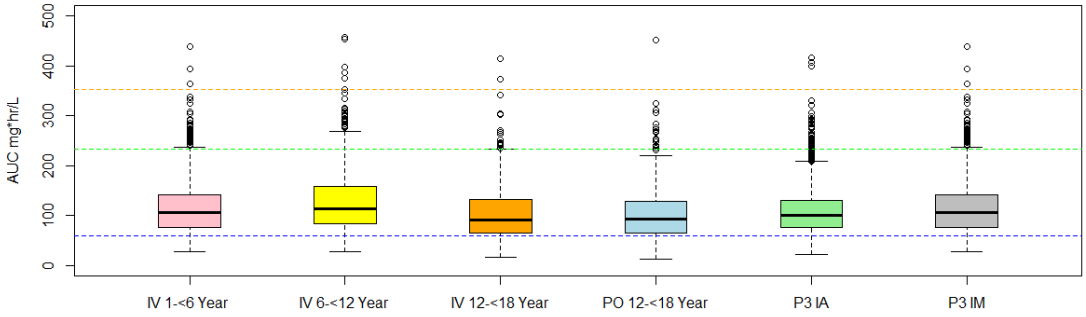
2 Study Objective(s), Design and Endpoints *2.2.2 Dose Rationale*
WAS:
Population Pharmacokinetic Model for Pediatric Data An initial pediatric population pharmacokinetic model was developed utilizing plasma concentration data from 27 subjects administered intravenous isavuconazonium sulfate from

Part 1 of Study 9766-CL-0046 and 24 subjects from the 9766-CL-0018 study, an intravenous study in which subjects were administered single dose of 372 mg of isavuconazonium sulfate. The initial model was updated with 10 subjects from Part 2 of Study 9766-CL-0046, who were administered oral isavuconazonium sulfate.

A 3-compartment model with combined zero order absorption, first order absorption and linear elimination described the data adequately.

Monte Carlo simulations were performed for 1000 to 5000 randomly chosen subjects for each age group in pediatrics and adult data. Area under the isavuconazole concentration-time curve at steady-state (AUCss) was calculated for each simulated subject. The dosing schedule for the simulation was similar to that for subjects in Study 9766-CL-0046, with subjects weighing < 40 mg administered 10 mg/kg dose and subjects > 40 kg getting adult dose of 372 mg.

The figure shown below compares pediatric exposures against exposures from Study 9766-CL-0104 (SECURE), a successful phase 3 study in adults with IA, in which subjects received isavuconazonium sulfate via both intravenous and oral routes of administration and against data from Study 9766-CL-0103 (VITAL), a successful phase 3 adult study in subjects with IM and other rare invasive fungal infections, in which subjects received isavuconazonium sulfate via oral route of administration. The dosage regimen in both adult studies was similar.



Red dots are the means. Dashed orange line is the lowest targeted value (25th percentile, with AUC_{ss} of 60 mg*hr/L) based on exposures from SECURE study.

From the figure, it can be seen that exposure predicted for pediatric subjects across all ranges for intravenous and for 12 to < 18 years of age for oral route of administration are within the efficacious range that was observed in adult studies.

An isavuconazonium sulfate dose of 10 mg/kg for all age groups weighing > 37 kg and the adult dose for pediatric subjects weighing > 40 kg provide mean exposures that were similar to and/or above the 372 mg adult dose and significantly below the 1116 mg dose group, where toxicities were observed. For intravenous, across all age groups, > 97% of the predicted AUC_{ss} values were below the AUC values for the adult population administered 1116 mg isavuconazonium sulfate dose and > 86% of the predicted AUC_{ss} values were below the minimum adult AUC_{ss} values for the adult subject population administered the supra therapeutic dose clinical (1116 mg) dose [Study 9766-CL-0017]. For oral (12 to < 18 years of age), > 99% of the predicted AUC_{ss} values and > 97% of the predicted AUC_{ss} values were below the mean and minimum adult AUC_{ss} values from the 9766-CL-0017 study.

Also, > 86% and > 80% of the predicted AUC_{ss} values for the intravenous and oral routes of administration were above the 25th percentile of exposure values from the SECURE study in subjects who received 372 mg dose of isavuconazonium sulfate.

Route	Age Group	% of Subjects Below Mean Adult AUC_{24} 1116 mg Dose	% of Subjects Below Minimum Adult AUC_{24} 1116 mg Dose	% of Subjects Above the 25th Percentile Adults AUC_{ss} 372 mg Dose
Intravenous	1 to < 6 years	98.8%	91.9%	87.2%
	6 to < 12 years	97.9%	88.3%	91.5%
	12 to <18 years	97.1%	86.1%	92.0%
Oral	12 to < 18 years	99.8%	97.5%	80.4%

Based on modeling and simulation results, the proposed daily dose administered either as intravenous (across all age groups) or oral (12 to < 18 years of age) for the clinical study in pediatric subjects is:

Details of modeling and simulation are presented in the modeling report [Study 9766-PK-0007].

IS AMENDED TO:

Population Pharmacokinetic Model for Pediatric Data

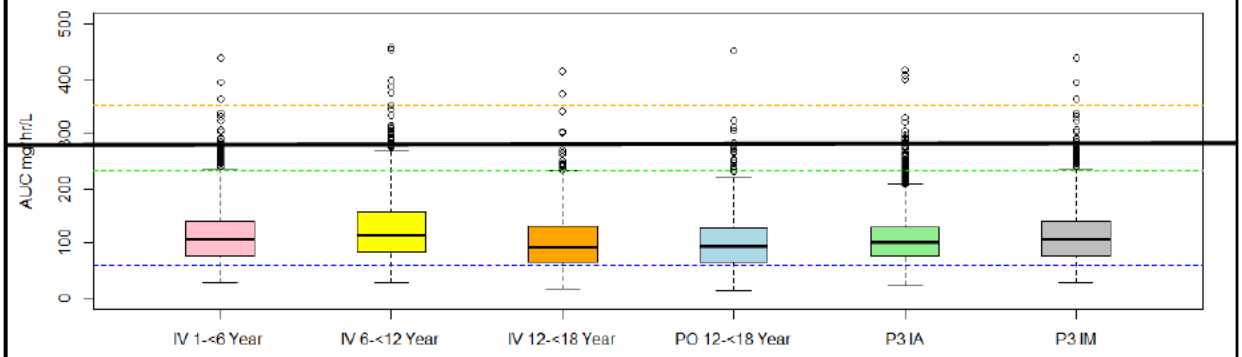
A~~n initial~~ pediatric population pharmacokinetic model was developed utilizing plasma concentration data from 27 subjects administered intravenous isavuconazonium sulfate from Part 1 of Study 9766-CL-0046**, 10 subjects administered oral dose from Part 2 of Study 9766-CL-0046 (12 to < 18 years of age)** and 24 subjects from the 9766-CL-0018 study, an intravenous study in which subjects were administered single dose of 372 mg of isavuconazonium sulfate. The ~~initial~~ model was updated ~~with~~**to include plasma concentration data from an additional 9**~~10~~ subjects from Part 2 of Study 9766-CL-0046 **(6 to < 12 years of age)**, who were administered oral isavuconazonium sulfate.

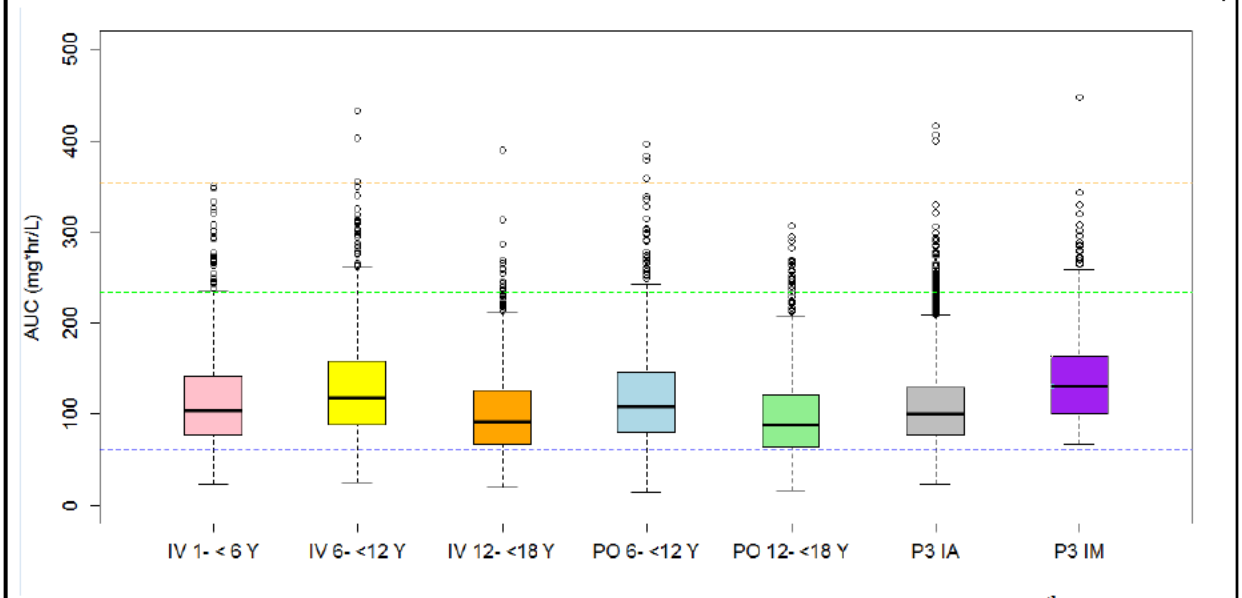
A 3-compartment model with combined zero order absorption, first order absorption and linear elimination described the data adequately**. Inter-individual variability was observed on clearance, volume of distribution of central and peripheral compartment and inter-compartmental clearance.**

Monte Carlo simulations were performed for 1000 ~~to 5000~~ randomly chosen subjects for each age group in pediatrics and **1000 to 5000 randomly chosen subjects for** adult data. Area under the isavuconazole concentration-time curve at steady-state (AUCss) was calculated for each simulated subject. The dosing schedule for the simulation was similar to that for subjects in Study 9766-CL-0046, with subjects weighing **≤ 37 kg** ~~< 40 mg~~ administered 10 mg/kg dose and subjects > **37**~~40~~ kg **receiving**~~getting~~ **the** adult dose of 372 mg.

~~The figure shown below~~ **Figure 2** compares pediatric exposures against exposures from Study 9766 CL-0104 (SECURE), a successful phase 3 study in adults with IA, in which subjects received isavuconazonium sulfate via both intravenous and oral routes of administration and against data from Study 9766-CL-0103 (VITAL), a successful phase 3 adult study in subjects with IM and other rare invasive fungal infections, in which subjects received isavuconazonium sulfate via oral route of administration. The dosage regimen in both adult studies was similar.

Figure 2 Box Plot of Isavuconazole Exposure Across Age Groups Including Adults in Phase 3 Program





~~Red dots are the means.~~ Dashed **blue**~~orange~~ line is the lowest targeted value (25th percentile, with AUC_{ss} of 60 mg*hr/L) based on exposures from SECURE study.

From the figure, it can be seen that exposures predicted for pediatric subjects across all **age** ranges for intravenous and for **subjects** ~~6~~12 to < 18 years of age for **the** oral route of administration are within the efficacious range that was observed in adult studies.

An isavuconazonium sulfate dose of 10 mg/kg for all age groups weighing ~~<~~ 37 kg and the adult dose for pediatric subjects weighing > **37**~~40~~ kg provide mean exposures that were similar to and/or above the 372 mg adult dose and significantly below the 1116 mg dose group, where toxicities were observed. For intravenous, across all age groups, > **99**~~97~~% of the predicted AUC_{ss} values were below the **mean** AUC values for the adult population administered 1116 mg isavuconazonium sulfate dose and > **94**~~86~~% of the predicted AUC_{ss} values were below the minimum adult AUC_{ss} values for the adult subject population administered the supra therapeutic dose clinical (1116 mg) dose [Study 9766-CL-0017]. For oral (12 to < 18 years of age), > 99% of the predicted AUC_{ss} values and > **98**~~97~~% of the predicted AUC_{ss} values were below the mean and minimum adult AUC_{ss} values from the 9766-CL-0017 study. **For oral (6 to < 12 years of age), > 99% of the predicted AUC_{ss}**

values and > 96% of the predicted AUC_{ss} values were below the mean and minimum adult AUC_{ss} values from Study 9766-CL-0017.

Also, > **88**~~86~~% and ~~>~~**approximately** 80% of the predicted AUC_{ss} values for the intravenous and oral routes of administration were above the 25th percentile of exposure values from the SECURE study in subjects who received 372 mg dose of isavuconazonium sulfate. **This table is updated based on simulations from the most recent population pharmacokinetic model that included oral data from subjects 6 to < 12 years of age.**

Table 3 Percentage of Pediatric Patients with Predicted AUC_{ss} Values of Isavuconazole Below or Above the Specified Adult AUC Values

Route	Age Group	% of Subjects Below Mean Adult AUC_{24} 1116 mg Dose	% of Subjects Below Minimum Adult AUC_{24} 1116 mg Dose	% of Subjects Above the 25th Percentile Adults AUC_{ss} 372 mg Dose
Intravenous	1 to < 6 years	**100**~~98.8~~%	**97.0**~~91.9~~%	**88.6**~~87.2~~%
	6 to < 12 years	**99.7**~~97.9~~%	**94.0**~~88.3~~%	**92.7**~~91.5~~%
	12 to <18 years	**99.9**~~97.1~~%	**98.2**~~86.1~~%	**82.1**~~92.0~~%
Oral	**6**~~12~~ to < **12**~~18~~ years	**99.6**~~99.8~~%	**96.4**~~97.5~~%	**90.7**~~80.4~~%
	12 to < 18 years	**100%**	**98.2%**	**78.8%**

Based on modeling and simulation results, the proposed daily dose administered either as intravenous (across all age groups) or oral (**6**~~12~~ **years** to < 18 years of age **and with a body weight of at least 12 kg**) for the clinical study in pediatric subjects is:

NOTE: The oral administration is only available for pediatric subjects 6 years and older due to the difficulty in swallowing the oral capsule.

~~Details of modeling and simulation are presented in the modeling report [Study 9766 PK 0007].~~

Isavuconazonium sulfate oral capsules can be administered with or without food.

IV Synopsis, Inclusion/Exclusion Criteria and 3 Study Population
3.2 Inclusion Criterion #2

WAS:

Male or female subject 1 year to < 18 years of age diagnosed with IA or IM. A positive diagnosis is defined as follows:

- Proven, probable or possible IFI per the European Organisation for Research and Treatment of Cancer/Mycoses Study Group [EORTC/MSG], 2008 criteria.

  Note: Subjects with "possible" IFI will be eligible for enrollment; however, diagnostic tests to confirm the invasive fungal disease as "probable" or "proven" according to the EORTC/MSG criteria must be completed within 7 days after the first dose of study drug.

IS AMENDED TO:
Male or female subject 1 year to < 18 years of age diagnosed with IA or IM. A positive diagnosis is defined as follows: ● Proven, probable or possible IFI per the European Organisation for Research and Treatment of Cancer/Mycoses Study Group [EORTC/MSG], 2008 criteria. **Note:** Subjects with "possible" IFI will be eligible for enrollment; however, diagnostic tests to confirm the invasive fungal disease as "probable" or "proven" according to the EORTC/MSG criteria ~~must~~ **should** be completed within ~~7~~ **10 calendar** days after the first dose of study drug.

IV Synopsis, Inclusion/Exclusion Criteria and 3 Study Population *3.2 Inclusion Criterion #3*
WAS:
Subject has sufficient venous access to permit administration of study drug and monitoring of safety laboratories.
IS AMENDED TO:
Subject has sufficient venous access to permit **intravenous** administration of study drug **or the ability to swallow oral capsules** ~~and monitoring of safety laboratories~~.

IV Synopsis, Inclusion/Exclusion Criteria and 3 Study Population *3.3 Exclusion Criterion #7*
WAS:
Subject has known history of allergy, hypersensitivity or any serious reaction to any of the azole class antifungals.
IS AMENDED TO:
Subject has known history of allergy, hypersensitivity or any serious reaction to any of the azole class antifungals**, or any components of the study drug formulation**.

IV Synopsis, Dose(s) and 5 Treatments and Evaluation *5.1.1 Dose/Dose Regimen and Administration Period*
WAS:
Oral (only for subjects 12 to < 18 years of age) Subjects will receive an oral loading regimen of isavuconazonium sulfate in a capsule form given every 8 hours (± 2 hours) on days 1 and 2 (a total of 6 doses), followed by once-daily oral maintenance dosing. The daily dose is based on body weight and is intended to deliver a dose approximately equal to 10 mg/kg. The oral and intravenous formulations are equivalent on a mg:mg basis. The lower limit for oral dosing is 12 years of age and body weight of 18 kg.

Body Weight (kg)	Loading (Days 1 and 2)/Total Daily Isavuconazonium Sulfate Dose (mg)	Maintenance (up to 84 days [IA] or 180 days [IM])/Total Daily Isavuconazonium

		Sulfate Dose (mg)
18 to 24	3 × 3 capsules/670.5 mg	1 × 3 capsules/223.5 mg
25 to 31	3 × 4 capsules /894 mg	1 × 4 capsules/298 mg
≥ 32	3 × 5 capsules/1117.5 mg	1 × 5 capsules/372.5 mg

IS AMENDED TO:

Oral (only for subjects **6~~12~~** *to < 18 years of age* ***and with a body weight of at least 12 kg)***

Subjects will receive an oral loading regimen of isavuconazonium sulfate in a capsule form given every 8 hours (± 2 hours) on days 1 and 2 (a total of 6 doses), followed by once-daily oral maintenance dosing. **Isavuconazonium sulfate oral capsules can be administered with or without food.**

The daily dose is based on body weight and is intended to deliver a dose approximately equal to 10 mg/kg. The oral and intravenous formulations are equivalent on a mg:mg basis. The lower limit for oral dosing is **6~~12~~** years of age and **a** body weight of **at least 12~~18~~** kg.

Body Weight (kg)	Loading (Days 1 and 2)/Total Daily Isavuconazonium Sulfate Dose (mg)	Maintenance (up to 84 days [IA] or 180 days [IM])/Total Daily Isavuconazonium Sulfate Dose (mg)
12 to < 18	**3 × 2 capsules/447 mg**	**1 × 2 capsules/149 mg**
18 to **< 25~~24~~**	3 × 3 capsules/670.5 mg	1 × 3 capsules/223.5 mg
25 to **< 32~~31~~**	3 × 4 capsules /894 mg	1 × 4 capsules/298 mg
≥ 32	3 × 5 capsules/1117.5 mg	1 × 5 capsules/372.5 mg

5 Treatments and Evaluation

5.1.1 Dose/Dose Regimen and Administration Period

WAS:

The isavuconazonium sulfate will be administered as an intravenous infusion or as oral capsule(s) per the investigator's discretion. The1-hour (± 10 minutes) intravenous infusion will be administered through an in-line filter. The start and stop times of the infusion must be clearly documented. Oral administration is only for subjects 12 to < 18 years of age. The investigator may determine the appropriate route of administration for the subject. The mode of administration can be interchangeable from intravenous to oral (12 to < 18 years of age) or oral (12 to < 18 years of age) to intravenous during the loading dose period and throughout the treatment period, the mg:mg is equivalent in both routes.

The maximum treatment is 84 days for IA subjects and 180 days for IM subjects, whichever occurs first.

Mode of Intravenous Administration:

Oral Dosing (only for subjects 12 to < 18 years of age):

Visits should occur on days when study related assessments are required.

The daily dose is based on body weight and is intended to deliver a dose approximately equal to 10 mg/kg. The oral and intravenous formulations are equivalent on a mg:mg basis. The lower limit for oral dosing is 12 years of age and body weight of 18 kg.

Body weight (kg)	Loading (Day 1 and Day 2)/Total Daily Isavuconazonium Sulfate Dose (mg)	Maintenance (up to 84 days [IA] or 180 days [IM])/Total Daily Isavuconazonium Sulfate Dose (mg)
18 to 24	3 × 3 capsules/670.5 mg	1 × 3 capsules/223.5 mg
25 to 31	3 × 4 capsules/894 mg	1 × 4 capsules/298 mg
≥ 32	3 × 5 capsules/1117.5 mg	1 × 5 capsules/372.5 mg

Mode of Oral Administration:

Subjects will receive isavuconazonium sulfate as an oral capsule (the number of capsules will correspond to their weight; see table above).

Increase or Reduction in Dose of the Study Drug(s)

Dose increases and reductions to study drug for a given individual subject are prohibited.

IS AMENDED TO:

The isavuconazonium sulfate will be administered as an intravenous infusion or as oral capsule(s) per the investigator's discretion. The 1-hour (± 10 minutes) intravenous infusion will be administered through an in-line filter. The start and stop times of the infusion must be clearly documented. Oral administration is only for subjects **6~~12~~** to < 18 years of age **and with a body weight of at least 12 kg**. The investigator may determine the appropriate route of administration for the subject **in the context of the relevant age range**. The **route~~mode~~** of administration can be interchangeable from intravenous to oral (**6~~12~~** to < 18 years of age **with a body weight of at least 12 kg**) or oral (**6~~12~~** to < 18 years of age **with a body weight of at least 12 kg**) to intravenous during the loading dose period and throughout the treatment period, the mg:mg is equivalent in both routes.~~.~~ **The details of dose and route of administration will be captured in the electronic case report form (eCRF).**

~~The maximum treatment is 84 days for IA subjects and 180 days for IM subjects, whichever occurs first.~~

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. Table 4 provides guidance to the investigator outlining the elements collectively informing a successful outcome. The investigator is encouraged to have clinical resolution of symptoms and associated mycological and/or radiologic data supporting the assessment of successful outcome.

Table 4 Investigator Guidance for Successful Outcome

	Clinical Response	**Mycological Response**	**Radiological Response**

Success	• **Resolution of all attributable clinical symptoms and physical findings** • **Partial resolution of attributable clinical symptoms and physical findings**	• **Eradication** • **Presumed Eradication**	• **Improvement from screening** • **No signs on radiological images at screening (only for proven IFI based on other investigations)**

IFI: invasive fungal infection

~~Mode of Intravenous Administration:~~

*Oral Dosing (~~only~~ for subjects ~~12~~**6** to < 18 years of age **with a body weight of at least 12 kg**)*:

Return visits should coincide with days when study- related assessments are required.~~Visits should occur on days when study related assessments are required.~~

The daily dose is based on body weight and is intended to deliver a dose approximately equal to 10 mg/kg. The oral and intravenous formulations are equivalent on a mg:mg basis. The lower limit for oral dosing is ~~12~~ **6** years of age and **with a** body weight of **at least 12**~~18~~ kg.

Subjects will receive isavuconazonium sulfate as an oral capsule (the number of capsules will correspond to their weight; see Table 5).

Table 5 Oral Dosing Regimen by Body Weight

Body weight (kg)	Loading (Day 1 and Day 2)/Total Daily Isavuconazonium Sulfate Dose (mg)	Maintenance (up to 84 days [IA] or 180 days [IM])/Total Daily Isavuconazonium Sulfate Dose (mg)
12 to< 18	**3 × 2 capsules/447 mg**	**1 × 2 capsules/149 mg**
18 to **< 25**~~24~~	3 × 3 capsules/670.5 mg	1 × 3 capsules/223.5 mg
25 to **< 32**~~31~~	3 × 4 capsules/894 mg	1 × 4 capsules/298 mg
≥ 32	3 × 5 capsules/1117.5 mg	1 × 5 capsules/372.5 mg

~~*Mode of Oral Administration:*~~

~~Subjects will receive isavuconazonium sulfate as an oral capsule (the number of capsules will correspond to their weight; see table above).~~

Increase or Reduction in Dose of the Study Drug(s)

~~Dose increases and reductions to study drug for a given individual subject are prohibited.~~

The mg/kg dose is to be consistent throughout study conduct. Dose increase or reductions to the study drug on a mg/kg basis are not allowed. However, if a subject has substantial weight changes, the number of capsules for oral dosing should be reassessed per Table 5.

5 Treatments and Evaluation *5.4.1 Vital Signs*
ADDED:
No additional vital signs are needed on dosing days for oral administration.

IV Synopsis, Formal Stopping Rules and 6 Discontinuation *6.1 Discontinuation of Individual Subject(s) From Study Treatment*
WAS:
All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol specific follow-up procedures as outlined in [Table 1 Schedule of Assessments].
IS AMENDED TO:
• **Serious hypersensitivity or severe skin reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azoles. If subject develops a severe hypersensitivity adverse reaction without alternative etiology, the subject must be discontinued from treatment.** All subjects who discontinue study treatment will remain in the study and ~~must~~**should** continue to be followed for protocol specific follow-up procedures as outlined in [Table 1 Schedule of Assessments].

7 Statistical Methodology *7.2.2 Modified Full Analysis Set (mFAS)*
WAS:
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 1 week after first dose.
IS AMENDED TO:
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**~~**1 week**~~ after first dose.

IIB. Nonsubstantial Changes

II Contact Details of Key Sponsor's Personnel	
WAS:	
Astellas Medical Monitor:	PPD Astellas Pharma Global Development, Inc., US PPD

IS AMENDED TO:

Astellas Medical Monitor:	PPD Astellas Pharma Global Development, Inc.~~, US~~ PPD

IV Synopsis, Study Design Overview
WAS:
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.
IS AMENDED TO:
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. **Investigator guidance of a successful outcome is provided in Table 4.**

IV Synopsis, Mode of Administration
WAS:
Mode of Administration:
IS AMENDED TO:
Route~~**Mode**~~ of Administration:

IV Synopsis, Duration of Treatment
WAS:
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.
IS AMENDED TO:
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. **Investigator guidance of a successful outcome is provided in Table 4.**

IV Synopsis, Statistical Methods
WAS:
Pharmacokinetics Observed plasma trough concentration data for isavuconazole will be presented in listings. Spaghetti plots by age cohort will be produced.
IS AMENDED TO:
Pharmacokinetics Observed plasma ~~trough~~ concentration data for isavuconazole will be presented in listings. ~~Spaghetti plots by age cohort will be produced.~~

V Flow Chart and Schedule of Assessments *Flow Chart*
WAS:
Flow Chart
IS AMENDED TO:
Figure 1 Flow Chart

2 Study Objective(s), Design and Endpoints *2.3.3 Other Endpoints*
WAS:
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. After receiving their first dose of oral capsules, subjects will be asked to assess their initial experience with the new oral formulation (i.e., Acceptability Assessment).
IS AMENDED TO:
In addition to the above, 24-hour pharmacokinetic samples will be obtained on any **one** day between day 14 and day 42, while the subject is still receiving study drug. After receiving their first dose of oral capsules, subjects will be asked to assess their initial experience with the new oral formulation (i.e., Acceptability Assessment **[Appendix 12.7]**).

IV Synopsis, Inclusion/Exclusion Criteria and 3 Study Population *3.2 Inclusion Criterion #8*
WAS:
Male subject who is of childbearing potential must not donate sperm starting at screening and throughout the study and for 30 days after the final study drug administration.
IS AMENDED TO:
Male subject ~~who is of childbearing potential~~ must not donate sperm starting at screening and throughout the study and for 30 days after the final study drug administration.

4 Treatment(s)
4.1.1 Study Drug(s)

WAS:

The test drugs for this study are 372 mg isavuconazole sulfate for injection or 74.5 mg isavuconazonium oral capsules.

Oral Dosing:

Isavuconazonium sulfate will be supplied as oral capsules per blister card. Each capsule contains 74.5 mg isavuconazonium sulfate (40 mg isavuconazole). The capsule is a Swedish orange color.

IS AMENDED TO:

The test drugs for this study are 372 mg isavuconazole sulfate for injection or 74.5 mg isavuconazonium **sulfate** oral capsules.

Oral Dosing:

Isavuconazonium sulfate will be supplied as oral capsules ~~per blister card~~**packaged in aluminum blisters with desiccants in secondary child-resistant cards**. Each capsule contains 74.5 mg isavuconazonium sulfate (40 mg isavuconazole). The capsule is a Swedish orange color.

5 Treatments and Evaluation
5.1.3 Treatment Compliance

WAS:

If the subject is discharged while continuing treatment with intravenous dosing, the subject must return to the research facility or other approved facility every day to receive the daily dose. Vital signs will be taken pre and post dose. Infusion reaction and other safety monitoring will be conducted.

Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly for study drug accountability and to receive new oral dosing supplies. Subjects will be provided with 1 week worth of study medication, instructions and a daily dosing log for documentation of ingestion of the oral study medication.

Study subjects and their parents/legal guardians should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study period.

The date and time of dosing will be recorded once the first capsule is ingested. The subject should ingest the entire dose within 5 minutes. If the entire dose is not ingested within 5 minutes, record the reason for dosing delay in the source documentation. If the subject should vomit any of the medication, this is to be recorded as well. The dose is NOT to be repeated. Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject at visits. Compliance will be verified by the accounting of study drug at the weekly visits after day 7 and/or at the EOT visit.

When study drug is administered at the research facility, it will be administered under the supervision of study personnel. A subject daily dosing log will be collected to record date/time and completeness of dosing for each day.

IS AMENDED TO:

If the subject is discharged while continuing treatment with intravenous dosing, the subject must return to the research facility or other approved **location**~~facility~~ every day to receive the daily **intravenous** dose. Vital signs will be taken pre and post dose. Infusion reaction and other safety monitoring will be conducted.

Subjects who are discharged from the hospital with oral capsules for at-home administration must return weekly for study drug accountability and to receive new oral dosing supplies. Subjects will be provided with **approximately** 1-week worth of study medication, **dosing** instructions and a daily dosing log for documentation of ingestion of the oral study medication.

~~Study subjects and their parents/legal guardians should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study period.~~

The **subject or parent/legal guardian must record the** date and time of **oral** dosing ~~will be recorded~~ once the first capsule is ingested. The subject should ingest the entire dose within 5 minutes. If the entire dose is not ingested within 5 minutes, record the reason for dosing delay in the source documentation. If the subject should vomit any of the medication, this is to be recorded as well. The dose is NOT to be repeated. Compliance of the study drug will be monitored by **review of the oral dosing log and** the accounting of unused medication returned by the subject at each scheduled visit~~s. Compliance will be verified by the accounting of study drug at the weekly visits~~ after day 7 and/or at the EOT visit.

When study drug is administered at the research facility, it will be administered under the supervision of study personnel. A subject daily dosing log will be collected to record date/time and completeness of dosing for each day.

Study subjects and their parents/legal guardians should be counseled on the need to meet 100% compliance with study drug dosing. The investigator or designee should ensure that study subjects adhere to this goal throughout the study.

5 Treatments and Evaluation
5.3.2 Pharmacokinetic Assessment

WAS:

In addition to the above, 24-hour pharmacokinetic samples for intravenous or oral dosing will be obtained on any day between day 14 and day 42, while the subject is still receiving study drug, for subjects who consent to participation in the 24-hour pharmacokinetic assessment.

IS AMENDED TO:

In addition to the above, 24-hour pharmacokinetic samples for intravenous or oral dosing will be obtained on any **one** day between day 14 and day 42, while the subject is still receiving study drug, for subjects who consent to participation in the 24-hour

pharmacokinetic assessment.

5 Treatments and Evaluation *5.3.3 Oral Dosing Acceptability Assessment*
ADDED:
Refer to [Appendix 12.7 Oral Dosing Acceptability Assessment].

5 Treatments and Evaluation *Table 4 Total Amount of Blood Drawn*
WAS:
Table 4 Total Amount of Blood Drawn
IS AMENDED TO:
Table **7**-4 Total Amount of Blood Drawn **IV: intravenous;**

10 Study Organization *10.1 Data and Safety Monitoring Board (DSMB)*
WAS:
The DSMB members will not be employees of Astellas nor otherwise involved with the study conduct.
IS AMENDED TO:
The DSMB members will not be employees of Astellas nor otherwise involved with the study conduct**; however, members of the DSMB could be members of the AC**.

10 Study Organization *10.2 Adjudication Committee (AC)*
WAS:
The AC members will not be employees of Astellas nor otherwise involved with the study conduct.
IS AMENDED TO:
The AC members will not be employees of Astellas nor otherwise involved with the study conduct**; however, members of the AC could be members of the DSMB**.

12 Appendices

ADDED:

12.7 Oral Dosing Acceptability Assessment

SITE NUMBER: _____ DATE:_____/_____/_____ (DD/MMM/YYYY)
SUBJECT NUMBER: _____

General Instructions

The questionnaire will be completed for all subjects who received oral study medication:

- By the patient him/herself (when the patient is able to do so), or
- By the parent/legal guardian/study nurse (based on input from the patient).

The questionnaire will be completed:

- Following the first oral dose (shortly after taking the study medication).

Subject Instructions

You have just taken the oral study medication.

- Please answer the three questions below.
- Put a cross in the box below the best answer.
- If you make a mistake, cross it out with a single line and cross the correct answer. The original entry should still be legible.

Questions

1. How was the TASTE of the medication?

0	1	2	3	4
				
Really bad	Bad	Not bad, not good	Good	Really good
☐	☐	☐	☐	☐

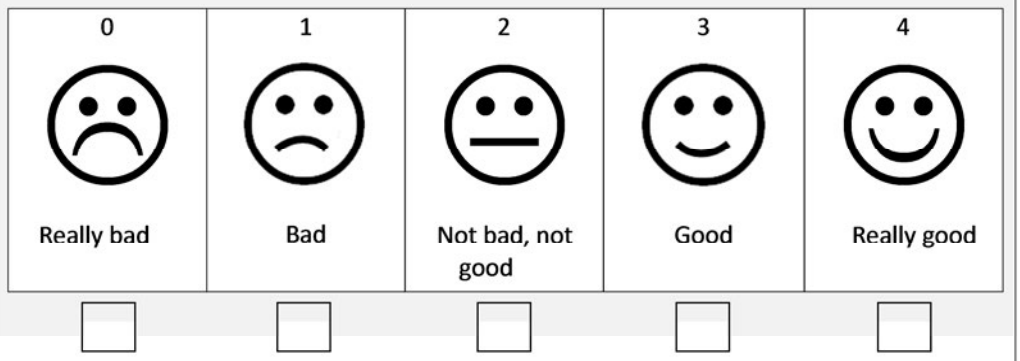
2. How was it to SWALLOW the medication?

0	1	2	3	4
				
Really bad	Bad	Not bad, not good	Good	Really good
☐	☐	☐	☐	☐

SITE NUMBER: _____ DATE: _____ (DD/MMM/YYYY)

SUBJECT NUMBER: _____

3. How would you FEEL if you took the medication again?



14 COORDINATING INVESTIGATOR'S SIGNATURE

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

ISN/Revised Protocol 9766-CL-0107

Version 4.0 Incorporating Substantial Amendment 3

05 Sep 2019

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: ..... Date (DD Mmm YYYY)

<Insert name, department/affiliation, name of institution>

Printed Name: .....

Address: .....

.....

15 SPONSOR SIGNATURES