Clinical trial results:
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

Summary

EudraCT number	2018-003975-36
Trial protocol	GB BE DE ES Outside EU/EEA
Global end of trial date	14 December 2022

Results information

Result version number	v2 (current)
This version publication date	20 October 2023
First version publication date	16 June 2023
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	9766-CL-0107

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03816176
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
Public contact	Clinical Transparency, Astellas Pharma Global Development, Inc, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Transparency, Astellas Pharma Global Development, Inc, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001301-PIP02-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study was to evaluate the safety and tolerability of isavuconazonium sulfate in pediatric participants. and to assess the efficacy of isavuconazonium sulfate for the treatment of invasive aspergillosis (IA) or invasive mucormycosis (IM) in pediatric subjects. Also to evaluate the pharmacokinetics of isavuconazole by monitoring the plasma concentrations in pediatric subjects during treatment with isavuconazonium sulfate.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	31
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	2

Children (2-11 years)	17
Adolescents (12-17 years)	12
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 31 pediatric participants diagnosed with IA or IM were enrolled and received isavuconazonium sulfate.

Safety Analysis Set (SAF)

Pre-assignment

Screening details:

Male or female participant 1 year to < 18 years of age diagnosed with IA or IM. A positive diagnosis was defined as 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.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Isavuconazonium Sulfate

Arm description:

Participants received 10 milligrams/kilograms (mg/kg) dose of isavuconazonium sulfate every 8 hours (± 2 hours) on days 1 and 2 for a total of 6 doses (via intravenous or oral administration at the investigator's discretion) followed by once-daily maintenance dose of 10 mg/kg for up to 84 days for invasive aspergillosis (IA) or 180 days for invasive mucormycosis (IM) or until the participant had a successful outcome as judged by the investigator, whichever occurred first. The route of administration could have been changed per the investigator’s discretion.

Arm type	Experimental
Investigational medicinal product name	Isavuconazonium Sulfate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Capsule
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Participants received 10 milligrams/killograms (mg/kg) dose of isavuconazonium sulfate every 8 hours (± 2 hours) on days 1 and 2 for a total of 6 doses (via intravenous or oral administration at the investigator's discretion)followed by once-daily maintenance dose of 10 mg/kg for up to 84 days invasive aspergillosis (IA) or 180 days invasive mucormycosis (IM) or until the participant had a successful outcome as judged by the investigator, whichever occured first. The route of administration could have been changed per the investigator’s discretion

Number of subjects in period 1	Isavuconazonium Sulfate
Started	31
Completed	19
Not completed	12
Adverse event, non-fatal	3
Miscellaneous	5
Lack of efficacy	4

Baseline characteristics

Reporting groups	
Reporting group title	Isavuconazonium Sulfate
Reporting group description:	
Participants received 10 milligrams/kilograms (mg/kg) dose of isavuconazonium sulfate every 8 hours (± 2 hours) on days 1 and 2 for a total of 6 doses (via intravenous or oral administration at the investigator's discretion) followed by once-daily maintenance dose of 10 mg/kg for up to 84 days for invasive aspergillosis (IA) or 180 days for invasive mucormycosis (IM) or until the participant had a successful outcome as judged by the investigator, whichever occurred first. The route of administration could have been changed per the investigator's discretion.	

Reporting group values	Isavuconazonium Sulfate	Total	
Number of subjects	31	31	
Age categorical Units: Participants			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	17	17	
Adolescents (12-17 years)	12	12	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Units: years			
arithmetic mean	9.7		
standard deviation	± 5	-	
Sex Units: Participants			
Female	25	25	
Male	6	6	
Analysis Race Units: Subjects			
Asian	5	5	
Black or African American	1	1	
Not specified	2	2	
Other	4	4	
White	19	19	
Ethnicity Units: Subjects			
Hispanic or Latino	10	10	
Not Hispanic or Latino	19	19	
Not specified	2	2	

End points

End points reporting groups

Reporting group title	Isavuconazonium Sulfate

Reporting group description:

Participants received 10 milligrams/kilograms (mg/kg) dose of isavuconazonium sulfate every 8 hours (± 2 hours) on days 1 and 2 for a total of 6 doses (via intravenous or oral administration at the investigator's discretion) followed by once-daily maintenance dose of 10 mg/kg for up to 84 days for invasive aspergillosis (IA) or 180 days for invasive mucormycosis (IM) or until the participant had a successful outcome as judged by the investigator, whichever occurred first. The route of administration could have been changed per the investigator's discretion.

Primary: Percentage of Participants with All - Cause Mortality Through Day 42

End point title	Percentage of Participants with All - Cause Mortality Through Day 42[1]

End point description:

Percentage of participants with All Cause Mortality through Day 42

Full analysis set (FAS) (included all participants who were enrolled and received at least 1 dose of study drug)

End point type	Primary

End point timeframe:

Baseline up to 42 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: statistical analysis were not prespecified for this endpoint

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (confidence interval 95%)	6.5 (0.79 to 21.42)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs)[2]

End point description:

An AE is any untoward medical occurrence in a participant administered a study drug, which does not have to have a causal relationship with this treatment. It can be any unfavorable sign, symptom, or disease temporally associated with the use of a medicinal product. Treatment Emergent Adverse Event defined as an AE observed after starting administration of the study drug through 30 days after the last dose.

The safety analysis set (SAF) consisted of all participant who were enrolled and received at least one dose of study drug.

End point type	Primary

End point timeframe:

From first dose to 30 days after the last dose (maximum 210 Days)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: statistical analysis were not prespecified for this endpoint

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	31[3]			
Units: Participants	29			

Notes:

[3] - SAF (enrolled participants, who received 1 dose of study drug) with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with All - Cause Mortality

End point title	Percentage of Participants with All - Cause Mortality

End point description:

EOT was defined as anytime from "day 1 to a maximum of day 180”. Data reported in the table below for each category, i.e., Day 84 represented data between Day 1 and Day 84 and for EOT, data represented between Day 1 to the EOT day for each individual. Participants who died after EOT assessment but before reaching Day 84 were included in the data for Day 84 category. Only those deaths that occurred after Day 84 would be included in EOT category if the death occurred during the treatment period (i.e. prior to the EOT).
FAS population

End point type	Secondary

End point timeframe:

Baseline up to day 84 and end of treatment (EOT) (up to a maximum of 180 days) (Average duration of treatment: 57.7 days)

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (confidence interval 95%)				
Day 84 EOT	9.7 (2.04 to 25.75) 0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Overall Response: Adjudication Committee (AC) Assessment

End point title	Percentage of Participants with Overall Response: Adjudication Committee (AC) Assessment

End point description:

Overall response was based on a composite of clinical, mycological, and radiological responses with success criteria assessed. Success criteria as assessed by AC in:
Clinical response:
- Complete: Resolution of all attributable clinical symptoms and physical findings
- Partial: Resolution of at Least some of the clinical symptoms and physical findings associated with IFD

Mycological response:
- Eradication: No growth of the original (at baseline) causative organism on culture or identified by histology/cytology on post baseline (after day 7) cultures and/or histology/cytology
- Presumed eradication: Missing post baseline documentation of eradication of the original causative organism at baseline PLUS resolution of all or some clinical symptoms/physical finding

Radiological response:
- Complete: ≥ 90% improvement
- Partial: At least < 25% response at day 42 and at least 50% by Day 84

FAS population

End point type	Secondary

End point timeframe:

Baseline up to days 42, 84 and EOT (180 days)

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (not applicable)				
Day 42	29.0			
Day 84	25.8			
EOT	54.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Clinical Response: AC Assessment

End point title	Percentage of Participants with Clinical Response: AC Assessment

End point description:

AC Assessed Clinical response was defined as follows:
•Success: Complete (if resolution of all attributable clinical symptoms and physical findings occurs); Partial (if resolution of at least some of the clinical symptoms and physical findings associated with IFD)

•Failure: Stable (if minor of no change in clinical symptoms and physical findings associated with IFD); Progression (if worsening or new clinical symptoms and physical findings associated with IFD, or if alternative systemic antifungal treatment is required)

•Not Evaluable: If not assessed or no clinical signs or symptoms at baseline.

•No assessment: Those participants that do not fall under any of the above criteria

FAS population.
If participant did not reach Day 42 or Day 84 of therapy then the AC did not perform these assessments.

End point type	Secondary

End point timeframe:

Baseline up to days 42, 84 and EOT (180 days)

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (not applicable)				
Day 42 Success	0			
Day 42 Failure	0			
Day 42 Not Evaluable	58.06			
Day 42 No Assessment	41.94			
Day 84 Success	0			
Day 84 Failure	0			
Day 84 Not Evaluable	35.48			
Day 84 No Assessment	64.52			
EOT success	6.45			
EOT Failure	9.68			
EOT Not Evaluable	83.87			
EOT No Assessment	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Response: Investigator Assessment

End point title	Percentage of Participants With Clinical Response: Investigator Assessment

End point description:

Investigator-assessed Clinical Response was defined as follows:

- Success: if resolution of all attributable signs and symptoms or resolution of attributable clinical symptoms and physical findings

- Failure: if no resolution of any attributable signs and symptoms or no resolution of any attributable signs and symptoms (no change) or worsening of any attributable signs and symptoms

- Not Evaluable: if results not available /participant unevaluable or if no attributable signs and symptoms

•No assessment: Those participants that do not fall under any of the above criteria

FAS population.
If participant did not reach Day 42 or Day 84 of therapy then the investigator did not perform these assessments.

End point type	Secondary

End point timeframe:

Baseline up to days 42, 84 and EOT (180 days)

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (not applicable)				
Day 42 Success	41.9			
Day 42 Failure	9.7			
Day 42 Not Evaluable	0			
Day 42 No Assessment	48.4			
Day 84 Success	32.3			
Day 84 Failure	0			
Day 84 Not Evaluable	0			
Day 84 No Assessment	67.7			
EOT Success	61.3			
EOT Failure	29.0			
EOT Not Evaluable	3.2			
EOT No Assessment	6.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Radiological Response: AC Assessment

End point title	Percentage of Participants with Radiological Response: AC Assessment

End point description:

AC-assessed Radiological Response was defined as follows:
•Success: Complete (if ≥ 90% improvement); Partial (if at least < 25% response at day 42 and at least 50% response by Day 84)

•Failure: Stable (if minor or no change in radiographic abnormalities associated with IFD, but no signs of progression); Progression (if worsening or new radiological abnormalities associated with IRD)

•Not Evaluable: if no post baseline radiology available with baseline evidence of radiolical disease Or Radiology not applicable at baseline

•No assessment: Those participants that do not fall under any of the above criteria

FAS population.
If participant did not reach Day 42 or Day 84 of therapy then the AC did not perform these assessments.

End point type	Secondary

End point timeframe:

Baseline up to days 42, 84 and EOT (180 days)

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (not applicable)				
Day 42 Success	29.03			
Day 42 Failure	6.45			
Day 42 Not Evaluable	22.58			
Day 42 No Assessment	41.94			
Day 84 Success	25.81			
Day 84 Failure	0			
Day 84 No Evaluable	9.68			
Day 84 No Assessment	64.52			
EOT Success	51.61			
EOT Failure	16.13			
EOT Not Evaluable	32.26			
EOT No Assessment	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Radiological Response: Investigator Assessment

End point title	Percentage of Participants With Radiological Response: Investigator Assessment

End point description:

Investigator’s assessed radiological response was defined as follows:
•Success: if ≥ 90% improvement, ≥ 50% to < 90% improvement, ≥ 25% to 50% improvement (for Day 42 only)

•Failure if < 25% improvement at any time or no signs or radiological Images

•Not Evaluable (NE) if results not evaluable or no radiological data available.

•No assessment: Those participants that do not fall under any of the above criteria

FAS population.
If participant did not reach Day 42 or Day 84 of therapy then the investigator did not perform these assessments.

End point type	Secondary

End point timeframe:

Baseline up to days 42, 84 and EOT (180 days)

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (not applicable)				
Day 42 Success	25.8			
Day 42 Failure	3.2			
Day 42 Not Evaluable	12.9			
Day 42 No Assessment	58.1			
Day 84 Success	19.4			
Day 84 Failure	0			
Day 84 Not Evaluable	9.7			
Day 84 No Assessment	71.0			
EOT Success	48.4			
EOT Failure	16.1			
EOT Not Evaluable	29.0			
EOT No Assessment	6.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Mycological Response: AC Assessment

End point title	Percentage of Participants with Mycological Response: AC Assessment

End point description:

AC assessed mycological response
(MR) was defined as:
Success: Eradicated (no growth of original [at baseline] causative organism on culture or identified by histology/cytology on post baseline [after day 7] cultures and/or histology/cytology); Presumed Eradicated (missing post baseline documentation of eradication of the original causative organism at baseline PLUS resolution of all or some clinical symptoms/physical finding)
Failure: Persistence (persistence of original causative organism cultured or identified by histological /cytology at baseline); Presumed Persistence (missing post baseline documentation of persistence of the original causative organism at baseline PLUS no resolution or worsening of any clinical symptoms/physical findings)
NE - no mycological evidence
No assessment: Those participants that do not fall under any of the above criteria

FAS population. If participant did not reach Day 42 or Day 84 of therapy, then investigator did not perform these assessments

End point type	Secondary

End point timeframe:

Baseline up to days 42, 84 and EOT (180 days)

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (not applicable)				
Day 42 Success	19.35			
Day 42 Failure	3.23			
Day 42 Not Evaluable	35.48			
Day 42 No Assessment	41.94			
Day 84 Success	19.35			
Day 84 Failure	0			
Day 84 Not Evaluable	16.13			
Day 84 No Assessment	64.52			
EOT Success	35.48			
EOT Failure	12.90			
EOT Not Evaluable	51.61			
EOT No Assessment	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Mycological Response: Investigator Assessment

End point title	Percentage of Participants With Mycological Response: Investigator Assessment

End point description:

Investigator’s assessed MR was defined as
Success: Eradicated (no growth of original at baseline causative organism on culture or identified by histology/cytology post baseline after day 7 cultures and/or histology/cytology) Presumed Eradicated (missing post baseline documentation of eradication of original causative organism at baseline PLUS resolution of all or some clinical symptoms/physical finding)

Failure: Persistence (persistence of original causative organism cultured or identified by histological/cytology at baseline) Presumed Persistence (missing post baseline documentation of persistence of original causative organism at baseline PLUS no resolution or worsening of any clinical symptoms/physical findings)
NE: Indeterminate/no mycological follow-up or results available

No assessment: Those participants that do not fall under any of above criteria
FAS population
If participant did not reach Day 42 or Day 84 of therapy, then investigator did not perform these assessments

End point type	Secondary

End point timeframe:

Baseline up to days 42, 84 and EOT (180 days)

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of Participants				
number (not applicable)				
Day 42 Success	22.6			
Day 42 Failure	6.5			
Day 42 Not Evaluable	22.6			
Day 42 No Assessment	48.4			
Day 84 Success	25.8			
Day 84 Failure	0			
Day 84 Not Evaluable	3.2			
Day 84 No Assessment	71.0			
EOT Success	45.2			
EOT Failure	12.9			
EOT Not Evaluable	35.5			
EOT No Assessment	6.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of Isavuconazonium Sulphate in Plasma: Trough Concentration (Ctrough)

End point title	Pharmacokinetics of Isavuconazonium Sulphate in Plasma: Trough Concentration (Ctrough)

End point description:

Ctrough was defined as the predose concentration at the end of dosing interval.

The pharmacokinetic analysis set (PKAS) consisted of all participants who took at least one dose of study drug and who had at least one plasma concentration

End point type	Secondary

End point timeframe:

Predose on days 7, and 14

End point values	Isavuconazonium Sulfate			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Nanograms/milliter (ng/mL)				
arithmetic mean (standard deviation)				
Age group 1 to <6 Day 7 (n = 6)	2965.0 (± 1770.5)			
Age group 1 to <6 Day 14 (n = 6)	2286.7 (± 1991.3)			
Age group 6 to <12 Day 7 (n = 10)	3732.7 (± 1855.0)			
Age group 6 to <12 Day 14 (n = 6)	3623.3 (± 1878.0)			

Age group 12 to <18 Day 7 (n = 9) Age group 12 to <18 Day 14 (n = 6)	3862.2 (± 1427.1) 4380.0 (± 2022.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose to 30 days after the last dose (maximum 210 days)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v23.0

Reporting groups

Reporting group title	Isavuconazonium sulfate

Reporting group description: -

Serious adverse events	Isavuconazonium sulfate		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 31 (58.06%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypertension			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion site pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Infusion site pruritus			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Social problem			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial effusion			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal distension			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Venoocclusive liver disease			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Anuria			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Synovitis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain abscess			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumococcal sepsis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia pseudomonal			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Streptococcal sepsis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Isavuconazonium sulfate		
Total subjects affected by non-serious adverse events subjects affected / exposed	28 / 31 (90.32%)		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3		
Hypertension subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3		
Pallor subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	9 / 31 (29.03%) 13		
Pain subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 3		
Non-cardiac chest pain subjects affected / exposed occurrences (all)	5 / 31 (16.13%) 5		
Chills subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 3		
Respiratory, thoracic and mediastinal disorders Tachypnoea subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3		
Rhinorrhoea			

subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Respiratory distress			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Pulmonary oedema			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Lung opacity			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Hypoxia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Investigations			
QRS axis abnormal			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Transaminases increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Cardiac disorders			
Tachycardia			

subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	6		
Lymphopenia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	7 / 31 (22.58%)		
occurrences (all)	14		
Stomatitis			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	8 / 31 (25.81%)		
occurrences (all)	9		
Constipation			

subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Aphthous ulcer			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	7		
Abdominal pain			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Abdominal distension			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Petechiae			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Muscle spasms			

subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Infections and infestations			
Rhinitis			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		
Oral herpes			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Folliculitis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
COVID-19			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	7		
Hypoalbuminaemia			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Hyperkalaemia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2019	• An additional 24-hour pharmacokinetic sample was added to the pharmacokinetic assessment. This 24-hour sample was obtained between days 21 and 42, while the subject was still receiving study drug. Total Amount of Blood Drawn was updated with the 4 mL of blood required for these new samples. • Added acceptable galactomannan levels for recipients of hematopoietic stem cell transplant who also had clinical and radiologic features consistent with invasive fungal infection.
08 May 2019	• An oral dose of isavuconazonium sulfate in 74.5 mg capsules was added to the study. Oral administration was for participants from 12 to < 18 years of age. Study results for oral isavuconazonium sulfate were added to the dose rationale. • Clarification was added for the intermittently changing administration routes at any time during the loading and/or treatment period. • Times of the 24-hour pharmacokinetic samples were added for oral dosing. • Section 5.1.3 was updated with instructions for participants who were discharged while continuing treatment with either intravenous or oral dosing. • The stopping rule for infusion-related reactions was updated to state that if the infusion-related reactions event was mild and self-limiting, the participants could continue the study at the discretion of the investigator.
05 September 2019	• Additional text was added to specify that no additional vital signs were needed on dosing days for oral administration other than screening and end of treatment. • Additional text was added to footnote 12 (Table 1) to clarify that the pregnancy test may be either urine or serum. • Text was added to specify that the return visit should occur on days when study-related assessments were required. • The lower limit on the age requirement for oral dosing was changed from "12 years of age" to "6 years of age and with a body weight of at least 12 kg." The dose rationale was updated with additional data from Part 2 of Study 9766-CL-0046 (6 to < 11 years of age) to support this change. • A table was added to provide guidance to the investigator defining the elements of a successful outcome. • Inclusion criterion No. 2 was updated to extend the timing of diagnostic tests to confirm invasive fungal disease to 10 calendar days after the first dose of study drug. • Inclusion criterion No. 3 was updated to clarify that the administration would be intravenous and to specify that the sparticipant had to be able to swallow oral capsules. • Inclusion criterion No. 7 was updated to include allergy, hypersensitivity or serious reaction to "any component of the study drug formulation." • Text was added to state that participants who developed serious hypersensitivity adverse reactions without alternative etiology would be discontinued from treatment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported