



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 | v1 |
| This version publication date | 16 June 2023 |
| First version publication date | 16 June 2023 |

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) | EMA-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 (\pm 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 | Capsule, Infusion |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Participants received 10 milligrams/kilograms (mg/kg) dose of isavuconazonium sulfate every 8 hours (\pm 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.

| 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 (\pm 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 | \pm 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 (\pm 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:

Percentage of participants with All - Cause Mortality

FAS population

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to day 84 and end of treatment (EOT) (180 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 | 9.7 (2.04 to 25.75) | | | |
| EOT | 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: $\geq 90\%$ 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 or 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.

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 Success | 0 | | | |
| Day 42 Failure | 0 | | | |
| Day 42 Not Evaluable | 58.1 | | | |
| Day 84 Success | 0 | | | |
| Day 84 Failure | 0 | | | |
| Day 84 Not Evaluable | 35.5 | | | |
| EOT Success | 6.5 | | | |
| EOT Failure | 9.7 | | | |
| EOT Not Evaluable | 83.9 | | | |

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

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 Success | 41.9 | | | |
| Day 42 Failure | 9.7 | | | |
| Day 42 Not Evaluable | 0 | | | |
| Day 84 Success | 32.3 | | | |
| Day 84 Failure | 0 | | | |
| Day 84 Not Evaluable | 0 | | | |
| EOT Success | 61.3 | | | |
| EOT Failure | 29.0 | | | |
| EOT Not Evaluable | 3.2 | | | |

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 $\geq 90\%$ 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 radiological disease Or Radiology not applicable at baseline

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 Success | 29.0 | | | |
| Day 42 Failure | 6.5 | | | |
| Day 42 Not Evaluable | 22.6 | | | |
| Day 84 Success | 25.8 | | | |
| Day 84 Failure | 0 | | | |

| | | | | |
|----------------------|------|--|--|--|
| Day 84 Not Evaluable | 9.7 | | | |
| EOT Success | 51.6 | | | |
| EOT Failure | 16.1 | | | |
| EOT Not Evaluable | 32.3 | | | |

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 $\geq 90\%$ improvement, $\geq 50\%$ to $< 90\%$ improvement, $\geq 25\%$ to 50% improvement (for Day 42 only)
- Failure if $< 25\%$ improvement at any time or no signs or radiological Images
- Not Evaluable if results not evaluable or no radiological data available.

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 Success | 25.8 | | | |
| Day 42 Failure | 3.2 | | | |
| Day 42 Not Evaluable | 12.9 | | | |
| Day 84 Success | 19.4 | | | |
| Day 84 Failure | 0 | | | |
| Day 84 Not Evaluable | 9.7 | | | |
| EOT Success | 48.4 | | | |
| EOT Failure | 16.1 | | | |
| EOT Not Evaluable | 29.0 | | | |

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 was defined as follows:

- Success: Eradicated (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 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 the original causative organism cultured or identified by histological /cytology at baseline); Presumed Persistence (missing post baseline documentation of the persistence of the original causative organism at baseline PLUS no resolution or worsening of any clinical symptoms/physical findings)
- Not Evaluable - no mycological evidence

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 Success | 19.4 | | | |
| Day 42 Failure | 3.2 | | | |
| Day 42 Not Evaluable | 35.5 | | | |
| Day 84 Success | 19.4 | | | |
| Day 84 Failure | 0 | | | |
| Day 84 Not Evaluable | 16.1 | | | |
| EOT Success | 35.5 | | | |
| EOT Failure | 12.9 | | | |
| EOT Not Evaluable | 51.6 | | | |

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 mycological response was defined as follows:

- Success: Eradicated (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 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 the original causative organism cultured or identified by histological /cytology at baseline); Presumed Persistence (missing post baseline documentation of the persistence of the original causative organism at baseline PLUS no resolution or worsening of any clinical symptoms/physical findings)

- Not Evaluable: Indeterminate/no mycological follow-up or results available.

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 Success | 22.6 | | | |
| Day 42 Failure | 6.5 | | | |
| Day 42 Not Evaluable | 22.6 | | | |
| Day 84 Success | 25.8 | | | |
| Day 84 Failure | 0 | | | |
| Day 84 Not Evaluable | 3.2 | | | |
| EOT Success | 45.2 | | | |
| EOT Failure | 12.9 | | | |
| EOT Not Evaluable | 35.5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of Isavuconazonium Sulphate in Plasma: Trough Concentration (C_{trough})

| | |
|-----------------|---|
| End point title | Pharmacokinetics of Isavuconazonium Sulphate in Plasma: Trough Concentration (C _{trough}) |
|-----------------|---|

End point description:

C_{trough} 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 | 31 | | | |
| 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) | 3862.2 (± 1427.1) | | | |
| Age group 12 to <18 Day 14 (n = 6) | 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 | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| 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 | | |
| 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 pruritus | | | |
| 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 occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 31 (3.23%) 1 / 1 0 / 0 | | |
| Immune system disorders Graft versus host disease subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 31 (3.23%) 0 / 1 0 / 0 | | |
| Social circumstances Social problem subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 31 (3.23%) 0 / 1 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders Haemoptysis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 31 (3.23%) 0 / 1 0 / 0 | | |
| Respiratory failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 31 (3.23%) 0 / 1 0 / 0 | | |
| Pleural effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 31 (3.23%) 0 / 1 0 / 0 | | |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 31 (3.23%) 1 / 1 0 / 0 | | |
| Cardiac disorders 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 | | |
| 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 | | |
| 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 | | | |
| 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 | | |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| 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 | | | |
| 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 pseudomonal | | | |
| 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 | | |
| 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 | | |

| | | | | |
|---|----------------|--|--|--|
| 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 | | | |
| 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 | | | |
| 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 | | | |
| Bacteraemia | | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| 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 | | | |
| 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 | | | |
| 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 | 3 / 31 (9.68%) | | |
| occurrences (all) | 3 | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 3 | | |
| Pallor | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 5 / 31 (16.13%) | | |
| occurrences (all) | 5 | | |
| Pain | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 3 | | |
| Pyrexia | | | |
| subjects affected / exposed | 9 / 31 (29.03%) | | |
| occurrences (all) | 13 | | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 3 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| 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 | | |
| 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 | | |
| Tachypnoea | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 3 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 3 | | |
| Respiratory distress | | | |
| 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 occurrences (all) | 3 / 31 (9.68%) 3 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 3 / 31 (9.68%) 3 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) | 3 / 31 (9.68%) 6 3 / 31 (9.68%) 3 2 / 31 (6.45%) 4 3 / 31 (9.68%) 3 | | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 3 | | |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Aphthous ulcer subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea | 3 / 31 (9.68%) 3 3 / 31 (9.68%) 3 4 / 31 (12.90%) 7 3 / 31 (9.68%) 3 | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 8 / 31 (25.81%) | | |
| occurrences (all) | 9 | | |
| Nausea | | | |
| subjects affected / exposed | 4 / 31 (12.90%) | | |
| occurrences (all) | 8 | | |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 31 (16.13%) | | |
| occurrences (all) | 6 | | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 31 (22.58%) | | |
| occurrences (all) | 14 | | |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 3 | | |
| 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 | | |
| Rash | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |
| 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 occurrences (all) | 2 / 31 (6.45%) 2 | | |
| Arthralgia subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 2 | | |
| Infections and infestations COVID-19 subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 2 | | |
| Folliculitis subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 2 | | |
| Oral herpes subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 2 | | |
| Rhinitis subjects affected / exposed occurrences (all) | 3 / 31 (9.68%) 4 | | |
| Metabolism and nutrition disorders Hypophosphataemia subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 2 | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 4 / 31 (12.90%) 7 | | |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 4 / 31 (12.90%) 4 | | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 4 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 12 February 2019 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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 participant 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