



Clinical trial results:

Open label study of isavuconazole in the treatment of patients with invasive Aspergillosis with renal impairment (RI) or of patients with invasive fungal disease (IFD) caused by rare moulds, yeasts or dimorphic fungi.

Summary

EudraCT number	2006-005003-33
Trial protocol	GB BE HU CZ DE ES
Global end of trial date	05 May 2016

Results information

Result version number	v3 (current)
This version publication date	22 April 2017
First version publication date	05 June 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	9766-CL-0103
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00634049
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Global Pharma Development, Inc
Sponsor organisation address	1 Astellas Way, Northbrook, United States,
Public contact	Medical Head ID/IM/TX, Astellas Pharma Global Development, Astellas.resultsdisclosure@astellas.com
Scientific contact	Medical Head ID/IM/TX, Astellas Pharma Global Development, Astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 January 2014
Global end of trial reached?	Yes
Global end of trial date	05 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial was to describe the safety and efficacy of isavuconazole in the treatment of invasive Aspergillosis in patients with renal impairment (RI) or in patients with invasive fungal disease (IFD) caused by rare moulds, yeasts or dimorphic fungi.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH 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:

Participants eligible for the study were primarily, but not limited to, those with underlying hematologic malignancies. Treatments for participants underlying disease were not standardized.

Evidence for comparator:

This study did not have a comparator arm. The choice of a uniform comparator for all patients included in this study was not feasible due to the allowance of patients with IFD caused by many different rare pathogens.

Actual start date of recruitment	21 April 2008
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	Lebanon: 1
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	United States: 57
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Brazil: 20
Country: Number of subjects enrolled	Thailand: 15
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 3
Country: Number of subjects enrolled	India: 5
Worldwide total number of subjects	149
EEA total number of subjects	17

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	119
From 65 to 84 years	29
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Consenting participants with proven, probable or possible invasive Aspergillosis and RI or IFD caused by rare molds, yeasts or dimorphic fungi meeting the inclusion and none of the exclusion criteria were enrolled at multicenter study at 34 centers globally, including centers in the US, European Union, South America, Asia and the Middle East.

Pre-assignment

Screening details:

Candidates for screening were male and female participants aged ≥ 18 years of age, at high risk for developing IFD caused by Aspergillus species, rare molds, yeasts, or other dimorphic fungi. Excluded participants had hepatic dysfunction, chronic aspergillosis, aspergilloma, allergic aspergillosis, advanced HIV or AIDS or were unlikely to survive 30 days.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Isavuconazole
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Arm description:

Isavuconazole (BAL4815) is a broad spectrum triazole. It inhibits sterol 14 α -demethylase, a microsomal P450 enzyme (P45014DM) essential for ergosterol biosynthesis in fungi.

Arm type	Experimental
Investigational medicinal product name	isavuconazole/CRESEMBA
Investigational medicinal product code	BAL8557
Other name	isavuconazonium sulfate, (CRESEMBA) as a pro drug of isavuconazole
Pharmaceutical forms	Capsule, Injection
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

The IV and oral formulations are 98% bioequivalent and therefore interchangeable. A loading regimen of isavuconazole (IV or PO) was used over 2 days, followed by a maintenance regimen from Day 3 to EOT. During Days 1 and 2, three doses of 200 mg isavuconazole were administered every 8 hours for a total of six doses and from Day 3 to End of Treatment (EOT), maintenance dose of 200 mg isavuconazole was administered once daily up to 180 days; with an option for extended treatment under specified criteria.

Number of subjects in period 1	Isavuconazole
Started	149
Completed	146
Not completed	3
Screening failure	1
Patient died prior to receiving any study drug	1
Patient never received study drug	1

Baseline characteristics

Reporting groups

Reporting group title	Isavuconazole
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Reporting group description:

Isavuconazole (BAL4815) is a broad spectrum triazole. It inhibits sterol 14 α -demethylase, a microsomal P450 enzyme (P45014DM) essential for ergosterol biosynthesis in fungi.

Reporting group values	Isavuconazole	Total	
Number of subjects	149	149	
Age categorical			
Units: Subjects			
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)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	116	116	
From 65-84 years	29	29	
85 years and over	1	1	
Not Recorded	3	3	
Age continuous			
Units: years			
arithmetic mean	49.9	-	
standard deviation	± 16.78	-	
Gender categorical			
Units: Subjects			
Female	46	46	
Male	100	100	
Not Recorded	3	3	
Race			
Race			
Units: Subjects			
White	108	108	
Black or African American	10	10	
Asian	24	24	
Other	4	4	
Not Recorded	3	3	
Ethnicity			
Units: Subjects			
Hispanic or Latino	22	22	
Not Hispanic or Latino	124	124	
Not Recorded	3	3	
Therapy Status			
Intent to Treat Population. (ITT)			
Units: Subjects			
Primary Therapy	93	93	

Refractory	38	38	
Intolerant	12	12	
Missing	3	3	
Not Recorded	3	3	
Hematologic malignancy			
Units: Subjects			
Yes	63	63	
No	83	83	
Not Recorded	3	3	
Allogeneic BMT/HSCT			
Units: Subjects			
Yes	26	26	
No	120	120	
Not Recorded	3	3	
Uncontrolled malignancy status			
Units: Subjects			
Yes	46	46	
No	100	100	
Not Recorded	3	3	
Corticosteroid use			
Intent-to-Treat Analysis Set			
Units: Subjects			
Yes	35	35	
No	111	111	
Not Recorded	3	3	
T-cell immunosuppressant use			
Intent-to-Treat Analysis Set			
Units: Subjects			
Yes	61	61	
No	48	48	
Missing	37	37	
Not Recorded	3	3	
Neutropenic			
Units: Subjects			
Yes	38	38	
No	66	66	
Missing	42	42	
Not Recorded	3	3	

Subject analysis sets

Subject analysis set title	mITT- Aspergillus [Renally Impaired]
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Aspergillus - Renally Impaired mITT population consisted of participants who have had proven, probable or possible IFD as determined by the DRC. Classification by the DRC was based on the type of pathogen which was found to be the cause of participants IFD. The Aspergillus-mITT population was presented by renal status, renally impaired and not renally impaired. Renal impairment was defined as yes for patients who have a baseline eGFR-MDRD < 60 mL/min/1.73 m ² , no for patients who have a baseline eGFR-MDRD ≥ 60 mL/min/1.73 m ² . Overall there were 24 participants in the mITT-Aspergillus population out of which 20 participants were classified as Renally Impaired (RI).	
Subject analysis set title	mITT- Aspergillus [Not Renally Impaired]
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Aspergillus - Renally Impaired mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Classification by the DRC was based on the type of pathogen which was found to be the cause of participants IFD. The Aspergillus-mITT population was presented by renal status, renally impaired and not renally impaired. Overall there were 24 participants in the mITT-Aspergillus population out of which 4 participants were classified as Not Renally Impaired (NRI).

Subject analysis set title	mITT- Mucorales [Primary Therapy]
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Mucorales – Primary Therapy mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participants had proven and 5 participants had probable invasive mucormycosis). The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 21 participants receiving isavuconazole as a primary therapy.

Subject analysis set title	mITT- Mucorales [Refractory]
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Mucorales – Refractory Therapy mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participants had proven and 5 participants had probable invasive mucormycosis). The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 11 participants whose IFD was refractory to prior AFT.

Subject analysis set title	mITT - Mucorales [Intolerant]
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Mucorales – Intolerant mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participants had proven and 5 participants had probable invasive mucormycosis). The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 5 participants who were intolerant to prior AFT.

Subject analysis set title	mITT- Other Filamentous Fungi
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Other Filamentous Fungi mITT population consisted of 17 participants who have had proven or probable IFD as determined by the DRC caused by other filamentous fungi (4 Fusarium, 2 Exophiala, 2 Cladosporium, 2 Scopulariopsis and 1 each of Acremonium, Alternaria, Curvularia, Exserohilum, Paecilomyces, Pseudallescheria and Scedosporium).

Subject analysis set title	mITT- Mould Species
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Other Mould Species mITT population consisted of 7 participants who have had proven or probable IFD as determined by the DRC caused by mould species.

Subject analysis set title	mITT- Dimorphic Fungi
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Other Dimorphic Fungi mITT population consisted of 29 participants who have had proven or probable IFD as determined by the DRC caused by dimorphic fungi (10 Paracoccidioides, 9 Coccidioides, 7 Histoplasma, 3 Blastomyces).

Subject analysis set title	mITT- Non Candida Yeast
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Other Non Candida Yeast mITT population consisted of 11 participants who have had proven or probable IFD as determined by the DRC caused by non-Candida yeast (4 Cryptococcus neoformans, 3 Cryptococcus gatii, 2 Cryptococcus NOS and 2 Trichosporon).

Subject analysis set title	mITT-Mixed Infections
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Other Mixed Infections mITT population consisted of 15 participants who have had proven or probable IFD as determined by the DRC caused by mixed infections aspergillosis/mucormycosis.

Reporting group values	mITT- Aspergillus [Renally Impaired]	mITT- Aspergillus [Not Renally Impaired]	mITT- Mucorales [Primary Therapy]
Number of subjects	20	4	21
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	3	17
From 65-84 years	6	1	4
85 years and over	1	0	0
Not Recorded	0	0	0
Age continuous			
Units: years			
arithmetic mean	55.7	41.5	51.7
standard deviation	± 20.65	± 25.72	± 14.72
Gender categorical			
Units: Subjects			
Female	8	1	4
Male	12	3	17
Not Recorded	0	0	0
Race			
Race			
Units: Subjects			
White	17	4	12
Black or African American	0	0	1
Asian	3	0	8
Other	0	0	0
Not Recorded	0	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	19	4	20
Not Recorded	0	0	0
Therapy Status			
Intent to Treat Population. (ITT)			
Units: Subjects			
Primary Therapy			
Refractory			
Intolerant			
Missing			
Not Recorded			
Hematologic malignancy			

Units: Subjects			
Yes	11	3	11
No	9	1	10
Not Recorded	0	0	0
Allogeneic BMT/HSCT			
Units: Subjects			
Yes	7	2	4
No	13	2	17
Not Recorded	0	0	0
Uncontrolled malignancy status			
Units: Subjects			
Yes	5	2	11
No	15	2	10
Not Recorded	0	0	0
Corticosteroid use			
Intent-to-Treat Analysis Set			
Units: Subjects			
Yes	12	1	5
No	8	3	16
Not Recorded	0	0	0
T-cell immunosuppressant use			
Intent-to-Treat Analysis Set			
Units: Subjects			
Yes	15	3	7
No	5	1	14
Missing	0	0	0
Not Recorded	0	0	0
Neutropenic			
Units: Subjects			
Yes	5	3	4
No	15	1	17
Missing	0	0	0
Not Recorded	0	0	0

Reporting group values	mITT- Mucorales [Refractory]	mITT - Mucorales [Intolerant]	mITT- Other Filamentous Fungi
Number of subjects	11	5	17
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	5	15
From 65-84 years	1	0	2
85 years and over	0	0	0
Not Recorded	0	0	0

Age continuous Units: years arithmetic mean standard deviation	46.4 ± 16.55	39.6 ± 15.22	47.5 ± 14.26
Gender categorical Units: Subjects			
Female	3	0	7
Male	8	5	10
Not Recorded	0	0	0
Race			
Race			
Units: Subjects			
White	10	3	13
Black or African American	1	2	1
Asian	0	0	3
Other	0	0	0
Not Recorded	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	11	5	16
Not Recorded	0	0	0
Therapy Status			
Intent to Treat Population. (ITT)			
Units: Subjects			
Primary Therapy			
Refractory			
Intolerant			
Missing			
Not Recorded			
Hematologic malignancy Units: Subjects			
Yes	7	4	
No	4	1	
Not Recorded	0	0	
Allogeneic BMT/HSCT Units: Subjects			
Yes	4	5	
No	7	0	
Not Recorded	0	0	
Uncontrolled malignancy status Units: Subjects			
Yes	6	1	
No	5	4	
Not Recorded	0	0	
Corticosteroid use			
Intent-to-Treat Analysis Set			
Units: Subjects			
Yes	3	2	
No	8	3	
Not Recorded	0	0	

T-cell immunosuppressant use			
Intent-to-Treat Analysis Set			
Units: Subjects			
Yes	6	5	
No	5	0	
Missing	0	0	
Not Recorded	0	0	
Neutropenic			
Units: Subjects			
Yes	5	1	
No	6	4	
Missing	0	0	
Not Recorded	0	0	

Reporting group values	mITT- Mould Species	mITT- Dimorphic Fungi	mITT- Non Candida Yeast
Number of subjects	7	29	11
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	24	7
From 65-84 years	3	5	4
85 years and over	0	0	0
Not Recorded	0	0	0
Age continuous			
Units: years			
arithmetic mean	58.6	45.7	52.5
standard deviation	± 18.27	± 14.79	± 17.25
Gender categorical			
Units: Subjects			
Female	2	7	5
Male	5	22	6
Not Recorded	0	0	0
Race			
Race			
Units: Subjects			
White	5	20	6
Black or African American	1	2	1
Asian	1	4	3
Other	0	3	1
Not Recorded	0	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	17	2
Not Hispanic or Latino	7	12	9
Not Recorded	0	0	0

Therapy Status			
Intent to Treat Population. (ITT)			
Units: Subjects			
Primary Therapy			
Refractory			
Intolerant			
Missing			
Not Recorded			
Hematologic malignancy			
Units: Subjects			
Yes			
No			
Not Recorded			
Allogeneic BMT/HSCT			
Units: Subjects			
Yes			
No			
Not Recorded			
Uncontrolled malignancy status			
Units: Subjects			
Yes			
No			
Not Recorded			
Corticosteroid use			
Intent-to-Treat Analysis Set			
Units: Subjects			
Yes			
No			
Not Recorded			
T-cell immunosuppressant use			
Intent-to-Treat Analysis Set			
Units: Subjects			
Yes			
No			
Missing			
Not Recorded			
Neutropenic			
Units: Subjects			
Yes			
No			
Missing			
Not Recorded			

Reporting group values	mITT-Mixed Infections		
Number of subjects	15		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	13		
From 65-84 years	2		
85 years and over	0		
Not Recorded	0		
Age continuous			
Units: years			
arithmetic mean	49.8		
standard deviation	± 16.68		
Gender categorical			
Units: Subjects			
Female	7		
Male	8		
Not Recorded	0		
Race			
Race			
Units: Subjects			
White	12		
Black or African American	1		
Asian	2		
Other	0		
Not Recorded	0		
Ethnicity			
Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	15		
Not Recorded	0		
Therapy Status			
Intent to Treat Population. (ITT)			
Units: Subjects			
Primary Therapy			
Refractory			
Intolerant			
Missing			
Not Recorded			
Hematologic malignancy			
Units: Subjects			
Yes			
No			
Not Recorded			
Allogeneic BMT/HSCT			
Units: Subjects			
Yes			
No			
Not Recorded			
Uncontrolled malignancy status			
Units: Subjects			
Yes			
No			

Not Recorded			
Corticosteroid use			
Intent-to-Treat Analysis Set			
Units: Subjects			
Yes			
No			
Not Recorded			
T-cell immunosuppressant use			
Intent-to-Treat Analysis Set			
Units: Subjects			
Yes			
No			
Missing			
Not Recorded			
Neutropenic			
Units: Subjects			
Yes			
No			
Missing			
Not Recorded			

End points

End points reporting groups

Reporting group title	Isavuconazole
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Reporting group description:

Isavuconazole (BAL4815) is a broad spectrum triazole. It inhibits sterol 14 α -demethylase, a microsomal P450 enzyme (P45014DM) essential for ergosterol biosynthesis in fungi.

Subject analysis set title	mITT- Aspergillus [Renally Impaired]
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Aspergillus - Renally Impaired mITT population consisted of participants who have had proven, probable or possible IFD as determined by the DRC. Classification by the DRC was based on the type of pathogen which was found to be the cause of participants IFD. The Aspergillus-mITT population was presented by renal status, renally impaired and not renally impaired. Renal impairment was defined as yes for patients who have a baseline eGFR-MDRD < 60 mL/min/1.73 m², no for patients who have a baseline eGFR-MDRD ≥ 60 mL/min/1.73 m². Overall there were 24 participants in the mITT-Aspergillus population out of which 20 participants were classified as Renally Impaired (RI).

Subject analysis set title	mITT- Aspergillus [Not Renally Impaired]
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Aspergillus - Renally Impaired mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Classification by the DRC was based on the type of pathogen which was found to be the cause of participants IFD. The Aspergillus-mITT population was presented by renal status, renally impaired and not renally impaired. Overall there were 24 participants in the mITT-Aspergillus population out of which 4 participants were classified as Not Renally Impaired (NRI).

Subject analysis set title	mITT- Mucorales [Primary Therapy]
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Mucorales – Primary Therapy mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participants had proven and 5 participants had probable invasive mucormycosis). The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 21 participants receiving isavuconazole as a primary therapy.

Subject analysis set title	mITT- Mucorales [Refractory]
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Mucorales – Refractory Therapy mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participants had proven and 5 participants had probable invasive mucormycosis). The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 11 participants whose IFD was refractory to prior AFT.

Subject analysis set title	mITT - Mucorales [Intolerant]
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Mucorales – Intolerant mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participant had proven and 5 participants had probable invasive mucormycosis). The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 5 participants who were intolerant to prior AFT.

Subject analysis set title	mITT- Other Filamentous Fungi
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Other Filamentous Fungi mITT population consisted of 17 participants who have had proven or probable IFD as determined by the DRC caused by other filamentous fungi (4 Fusarium, 2 Exophiala, 2 Cladosporium, 2 Scopulariopsis and 1 each of Acremonium, Alternaria, Curvularia, Exserohilum, Paecilomyces, Pseudallescheria and Scedosporium).

Subject analysis set title	mITT- Mould Species
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Other Mould Species mITT population consisted of 7 participants who have had proven or probable IFD as determined by the DRC caused by mould species.	
Subject analysis set title	mITT- Dimorphic Fungi
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Other Dimorphic Fungi mITT population consisted of 29 participants who have had proven or probable IFD as determined by the DRC caused by dimorphic fungi (10 Paracoccidioides, 9 Coccidioides, 7 Histoplasma, 3 Blastomyces).	
Subject analysis set title	mITT- Non Candida Yeast
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Other Non Candida Yeast mITT population consisted of 11 participants who have had proven or probable IFD as determined by the DRC caused by non-Candida yeast (4 Cryptococcus neoformans, 3 Cryptococcus gatii, 2 Cryptococcus NOS and 2 Trichosporon).	
Subject analysis set title	mITT-Mixed Infections
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Other Mixed Infections mITT population consisted of 15 participants who have had proven or probable IFD as determined by the DRC caused by mixed infections aspergillosis/mucormycosis.	

Primary: Crude success rate of overall outcome of treatment evaluated by the Data Review Committee (DRC) Day 42, Day 84 and EOT (mITT)

End point title	Crude success rate of overall outcome of treatment evaluated by the Data Review Committee (DRC) Day 42, Day 84 and EOT (mITT) ^[1]
End point description:	
The DRC assessed overall response based on individual clinical, mycological and radiological response assessments. Participants with a complete or partial response were considered a success.	
End point type	Primary
End point timeframe:	
Day 42, Day 84 and End of Treatment [EOT]	

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: No statistical inferences were made due to the non-comparative study design. However, study outcomes were tabulated by renal status and baseline organism to provide context to historic literature.

End point values	mITT- Aspergillus [Renally Impaired]	mITT- Aspergillus [Not Renally Impaired]	mITT- Mucorales [Primary Therapy]	mITT- Mucorales [Refractory]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	4	21	11
Units: Percent				
number (not applicable)				
Day 42 [Success]	25	50	14.3	9.1
Day 84 [Success]	30	25	9.5	36.4
End of Treatment [EOT Success]	30	66.7	31.6	36.4

End point values	mITT - Mucorales [Intolerant]	mITT- Other Filamentous Fungi	mITT- Mould Species	mITT- Dimorphic Fungi
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	17	7	29
Units: Percent				
number (not applicable)				
Day 42 [Success]	0	47.1	28.6	41.4
Day 84 [Success]	20	41.2	28.6	44.8
End of Treatment [EOT Success]	20	64.7	28.6	64.3

End point values	mITT- Non Candida Yeast	mITT-Mixed Infections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	15		
Units: Percent				
number (not applicable)				
Day 42 [Success]	36.4	13.3		
Day 84 [Success]	36.4	13.3		
End of Treatment [EOT Success]	72.7	14.3		

Statistical analyses

No statistical analyses for this end point

Secondary: All-Cause Crude Mortality Through Day 42 and Day 84 (ITT)

End point title All-Cause Crude Mortality Through Day 42 and Day 84 (ITT)

End point description:

All-cause Mortality was assessed through Day 42 and Day 84 and summarized for ITT population.

End point type Secondary

End point timeframe:

Baseline to End of Treatment (EOT [Day 180]).

End point values	mITT- Aspergillus [Renally Impaired]	mITT- Aspergillus [Not Renally Impaired]	mITT- Mucorales [Primary Therapy]	mITT- Mucorales [Refractory]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	4	21	4
Units: Percent				
number (not applicable)				
All-cause Mortality Through Day 42	15	0	33.3	45.5

All-cause Mortality Through Day 84	25	25	42.9	45.5
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End point values	mITT - Mucorales [Intolerant]	mITT- Other Filamentous Fungi	mITT- Mould Species	mITT- Dimorphic Fungi
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	17	7	29
Units: Percent				
number (not applicable)				
All-cause Mortality Through Day 42	40	11.8	0	6.9
All-cause Mortality Through Day 84	40	17.6	14.3	6.9

End point values	mITT- Non Candida Yeast	mITT-Mixed Infections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	15		
Units: Percent				
number (not applicable)				
All-cause Mortality Through Day 42	9.1	20		
All-cause Mortality Through Day 84	9.1	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Crude success rate of clinical response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT)

End point title	Crude success rate of clinical response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT)
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End point description:

The DRC evaluated clinical response to treatment for patients at day 42, day 84 and EOT. The list of possible clinical responses to treatment as assessed by the DRC is as follows; Success [Resolution of all attributable clinical symptoms and physical findings and Partial resolution of attributable clinical symptoms and physical findings], Failure [No resolution of any attributable clinical symptoms and physical findings and/or worsening and Not done or missing] and Not applicable [No attributable signs and symptoms present at baseline and no symptoms attributable to IFD developed post baseline]. Each type of clinical response to treatment evaluated by the DRC at day 42, day 84 and EOT were summarized.

End point type	Secondary
End point timeframe:	
Day 42, Day 84 and EOT	

End point values	mITT- Aspergillus [Renally Impaired]	mITT- Aspergillus [Not Renally Impaired]	mITT- Mucorales [Primary Therapy]	mITT- Mucorales [Refractory]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	4	21	11
Units: percent				
number (not applicable)				
Day 42 [Success]	55	75	50	33.3
Day 42 [Failure]	45	25	50	66.7
Day 84 [Success]	45	25	40	22.2
Day 84 [Failure]	55	75	60	77.8
EOT [Success]	55	66.7	55.6	22.2
EOT [Failure]	45	33.3	44.4	77.8

End point values	mITT - Mucorales [Intolerant]	mITT- Other Filamentous Fungi	mITT- Mould Species	mITT- Dimorphic Fungi
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	17	7	29
Units: percent				
number (not applicable)				
Day 42 [Success]	50	78.6	71.4	85.2
Day 42 [Failure]	50	21.4	28.6	14.8
Day 84 [Success]	50	76.9	50	88.9
Day 84 [Failure]	50	23.1	50	11.1
EOT [Success]	50	81.3	85.7	82.1
EOT [Failure]	50	18.8	14.3	17.9

End point values	mITT- Non Candida Yeast	mITT-Mixed Infections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	15		
Units: percent				
number (not applicable)				
Day 42 [Success]	77.8	50		
Day 42 [Failure]	22.2	50		
Day 84 [Success]	77.8	50		
Day 84 [Failure]	22.2	50		
EOT [Success]	70	38.5		
EOT [Failure]	30	61.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Crude success rate of mycological response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT)

End point title	Crude success rate of mycological response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT)
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End point description:

The DRC evaluated mycological response to treatment for patients at day 42, day 84 and EOT. The list of possible mycological responses to treatment is as follows, Success [Eradication and Presumed eradication], Failure [Persistence, Presumed persistence and Not done or missing] and Not applicable [No mycological evidence available at baseline]. Each type of mycological response to treatment evaluated by the DRC at day 42, day 84 and EOT was summarized.

End point type	Secondary
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End point timeframe:

Day 42, Day 84 and End of Treatment (EOT).

End point values	mITT-Aspergillus [Renally Impaired]	mITT-Aspergillus [Not Renally Impaired]	mITT-Mucorales [Primary Therapy]	mITT-Mucorales [Refractory]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	4	21	11
Units: percent				
number (not applicable)				
Day 42 [Success]	30	50	4.8	0
Day 42 [Failure]	70	50	95.2	100
Day 84 [Success]	35	25	9.5	27.3
Day 84 [Failure]	65	75	90.5	72.7
EOT [Success]	35	66.7	31.6	36.4
EOT [Failure]	65	33.3	68.4	63.6

End point values	mITT - Mucorales [Intolerant]	mITT- Other Filamentous Fungi	mITT- Mould Species	mITT- Dimorphic Fungi
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	17	7	29
Units: percent				
number (not applicable)				
Day 42 [Success]	0	29.4	28.6	27.6
Day 42 [Failure]	100	70.6	71.4	72.4
Day 84 [Success]	40	35.3	28.6	27.6
Day 84 [Failure]	60	64.7	71.4	72.4
EOT [Success]	40	70.6	28.6	53.6
EOT [Failure]	60	29.4	71.4	46.4

End point values	mITT- Non Candida Yeast	mITT-Mixed Infections		
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Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	15		
Units: percent				
number (not applicable)				
Day 42 [Success]	45.5	13.3		
Day 42 [Failure]	54.5	86.7		
Day 84 [Success]	45.5	13.3		
Day 84 [Failure]	54.5	86.7		
EOT [Success]	81.8	14.3		
EOT [Failure]	18.2	85.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Crude success rate of radiological response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT)

End point title	Crude success rate of radiological response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT)
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End point description:

Radiological responses to treatment as assessed by the DRC at different time points are as follows, Day 42-Success [Improvement of at least 25% from baseline for invasive aspergillosis and other filamentous mold infections], Failure [No postbaseline radiology available]; Day 84-Success [Improvement of at least 50% from baseline for invasive aspergillosis and other filamentous mold infections], Failure [No postbaseline radiology available for patient with baseline evidence of radiologic disease]; EOT-Success [Improvement of at least 25% from baseline if EOT occurs prior to day 42 and at least 50% improvement from baseline if EOT occurs after day 42 for invasive aspergillosis and other filamentous mold infections], Failure [No postbaseline radiology available].

End point type	Secondary
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End point timeframe:

Day 42, Day 84 and EOT

End point values	mITT-Aspergillus [Renally Impaired]	mITT-Aspergillus [Not Renally Impaired]	mITT-Mucorales [Primary Therapy]	mITT-Mucorales [Refractory]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	4	21	11
Units: percent				
number (not applicable)				
Day 42 [Success]	30	25	0	10
Day 42 [Failure]	70	75	100	90
Day 84 [Success]	20	25	4.8	20
Day 84 [Failure]	80	75	95.2	80
EOT [Success]	15	66.7	16.7	20
EOT [Failure]	85	33.3	83.3	80

End point values	mITT - Mucorales [Intolerant]	mITT- Other Filamentous Fungi	mITT- Mould Species	mITT- Dimorphic Fungi
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	17	7	29
Units: percent				
number (not applicable)				
Day 42 [Success]	0	25	16.7	21.4
Day 42 [Failure]	100	75	83.3	78.6
Day 84 [Success]	20	6.3	0	28.6
Day 84 [Failure]	80	93.8	100	71.4
EOT [Success]	20	50	0	33.3
EOT [Failure]	80	50	100	66.7

End point values	mITT- Non Candida Yeast	mITT-Mixed Infections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	15		
Units: percent				
number (not applicable)				
Day 42 [Success]	0	7.1		
Day 42 [Failure]	100	92.9		
Day 84 [Success]	10	14.3		
Day 84 [Failure]	90	85.7		
EOT [Success]	10	7.7		
EOT [Failure]	90	92.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients were assessed for the occurrence of AEs on an ongoing basis during the course of the study and up to follow-up visit 1 (28 days after the last administration of study drug).

Adverse event reporting additional description:

All adverse events analysis was completed on Safety Analysis Set (SAF) population. Adverse events reported are Treatment Emergent Adverse Events (TEAEs). A treatment- emergent adverse event is any adverse event that starts after the first administration of study medication until 28 days after the last dose of study medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Not Renally Impaired
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Reporting group description: -

Reporting group title	Renally Impaired
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Reporting group description: -

Serious adverse events	Not Renally Impaired	Renally Impaired	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 87 (52.87%)	43 / 59 (72.88%)	
number of deaths (all causes)	23	24	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myeloid leukaemia recurrent			
subjects affected / exposed	2 / 87 (2.30%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic lymphocytic leukaemia			

subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukaemia recurrent			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant neoplasm progression			
subjects affected / exposed	2 / 87 (2.30%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Vascular disorders			
Arteritis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 87 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 87 (2.30%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
General physical health deterioration			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Multi-organ failure			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	0 / 87 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung transplant rejection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	3 / 87 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypercapnia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary infarction			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 87 (1.15%)	4 / 59 (6.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus disorder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Abnormal behaviour			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 87 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			

subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Electromechanical dissociation			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 87 (1.15%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	2 / 87 (2.30%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			

subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 87 (3.45%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			

subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 87 (2.30%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis relapsing			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 87 (4.60%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiolitis			

subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 87 (1.15%)	4 / 59 (6.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 87 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillosis			
subjects affected / exposed	2 / 87 (2.30%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
BK virus infection			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 87 (0.00%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchiectasis			

subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus enteritis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 87 (1.15%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			

subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 87 (2.30%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mucormycosis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 87 (6.90%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 87 (2.30%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia blastomyces			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia fungal			
subjects affected / exposed	2 / 87 (2.30%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia influenzal			

subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia primary atypical			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pseudomonal sepsis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomonas bronchitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 87 (1.15%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	0 / 87 (0.00%)	6 / 59 (10.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	1 / 4	
Sinusitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis fungal			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral diarrhoea			

subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Zygomycosis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 87 (1.15%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 87 (1.15%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Not Renally Impaired	Renally Impaired	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 87 (78.16%)	54 / 59 (91.53%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 87 (5.75%)	3 / 59 (5.08%)	
occurrences (all)	5	3	
Hypotension			
subjects affected / exposed	5 / 87 (5.75%)	5 / 59 (8.47%)	
occurrences (all)	5	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 87 (8.05%)	1 / 59 (1.69%)	
occurrences (all)	8	1	
Chills			
subjects affected / exposed	3 / 87 (3.45%)	5 / 59 (8.47%)	
occurrences (all)	3	8	
Fatigue			
subjects affected / exposed	2 / 87 (2.30%)	4 / 59 (6.78%)	
occurrences (all)	2	5	
Oedema peripheral			
subjects affected / exposed	8 / 87 (9.20%)	8 / 59 (13.56%)	
occurrences (all)	8	11	
Pain			
subjects affected / exposed	2 / 87 (2.30%)	3 / 59 (5.08%)	
occurrences (all)	3	4	
Pyrexia			
subjects affected / exposed	15 / 87 (17.24%)	9 / 59 (15.25%)	
occurrences (all)	27	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 87 (13.79%)	3 / 59 (5.08%)	
occurrences (all)	14	3	
Dyspnoea			
subjects affected / exposed	7 / 87 (8.05%)	6 / 59 (10.17%)	
occurrences (all)	7	6	

Epistaxis			
subjects affected / exposed	5 / 87 (5.75%)	2 / 59 (3.39%)	
occurrences (all)	6	2	
Haemoptysis			
subjects affected / exposed	1 / 87 (1.15%)	3 / 59 (5.08%)	
occurrences (all)	1	3	
Oropharyngeal pain			
subjects affected / exposed	2 / 87 (2.30%)	4 / 59 (6.78%)	
occurrences (all)	3	4	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 87 (2.30%)	7 / 59 (11.86%)	
occurrences (all)	2	9	
Insomnia			
subjects affected / exposed	8 / 87 (9.20%)	5 / 59 (8.47%)	
occurrences (all)	9	8	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 87 (2.30%)	3 / 59 (5.08%)	
occurrences (all)	2	4	
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 87 (6.90%)	4 / 59 (6.78%)	
occurrences (all)	6	4	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 87 (1.15%)	4 / 59 (6.78%)	
occurrences (all)	2	4	
Sinus tachycardia			
subjects affected / exposed	2 / 87 (2.30%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Tachycardia			
subjects affected / exposed	4 / 87 (4.60%)	4 / 59 (6.78%)	
occurrences (all)	5	4	
Nervous system disorders			
Dizziness			

subjects affected / exposed	5 / 87 (5.75%)	3 / 59 (5.08%)	
occurrences (all)	5	3	
Headache			
subjects affected / exposed	14 / 87 (16.09%)	11 / 59 (18.64%)	
occurrences (all)	19	13	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 87 (2.30%)	4 / 59 (6.78%)	
occurrences (all)	2	4	
Neutropenia			
subjects affected / exposed	2 / 87 (2.30%)	6 / 59 (10.17%)	
occurrences (all)	2	6	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 87 (4.60%)	7 / 59 (11.86%)	
occurrences (all)	4	8	
Abdominal pain upper			
subjects affected / exposed	5 / 87 (5.75%)	1 / 59 (1.69%)	
occurrences (all)	5	2	
Constipation			
subjects affected / exposed	10 / 87 (11.49%)	5 / 59 (8.47%)	
occurrences (all)	11	5	
Diarrhoea			
subjects affected / exposed	10 / 87 (11.49%)	16 / 59 (27.12%)	
occurrences (all)	11	22	
Haematochezia			
subjects affected / exposed	1 / 87 (1.15%)	3 / 59 (5.08%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	14 / 87 (16.09%)	19 / 59 (32.20%)	
occurrences (all)	19	23	
Stomatitis			
subjects affected / exposed	0 / 87 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Vomiting			

subjects affected / exposed occurrences (all)	17 / 87 (19.54%) 26	16 / 59 (27.12%) 24	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	7 / 87 (8.05%) 7	2 / 59 (3.39%) 2	
Renal and urinary disorders Oliguria subjects affected / exposed occurrences (all) Renal impairment subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0 1 / 87 (1.15%) 1	3 / 59 (5.08%) 3 3 / 59 (5.08%) 3	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	8 / 87 (9.20%) 8 5 / 87 (5.75%) 5 2 / 87 (2.30%) 2 3 / 87 (3.45%) 4	6 / 59 (10.17%) 6 3 / 59 (5.08%) 4 3 / 59 (5.08%) 4 4 / 59 (6.78%) 4	
Infections and infestations Clostridial infection subjects affected / exposed occurrences (all) Clostridium difficile colitis subjects affected / exposed occurrences (all) Herpes zoster subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0 1 / 87 (1.15%) 1 5 / 87 (5.75%) 7	3 / 59 (5.08%) 3 3 / 59 (5.08%) 4 1 / 59 (1.69%) 1	

Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 7	5 / 59 (8.47%) 6	
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2	7 / 59 (11.86%) 7	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 7	4 / 59 (6.78%) 4	
Hyperglycaemia subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 6	3 / 59 (5.08%) 3	
Hyperkalaemia subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 5	7 / 59 (11.86%) 8	
Hypernatraemia subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	3 / 59 (5.08%) 3	
Hypocalcaemia subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 3	3 / 59 (5.08%) 3	
Hypokalaemia subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 8	6 / 59 (10.17%) 6	
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	3 / 59 (5.08%) 3	
Hypomagnesaemia subjects affected / exposed occurrences (all)	7 / 87 (8.05%) 7	2 / 59 (3.39%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2007	Amendment 1 issued on October 16, 2007, clarified the type of participants to be enrolled, including changes requested by Regulatory Authorities. Clarifications were made to the duration of study drug, clinical and mycological responses, and to the timing of evaluations for secondary efficacy variables including the addition that survival status should be assessed for all participants, including those discontinued prior to day 42 or day 84 due to an unsuccessful outcome. The ceiling for total bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT) abnormalities were decreased per regulatory advice. The estimated number of centers that participated in the study was adjusted from 200 to 150.
27 May 2010	Amendment 2 issued on May 27, 2010, identified the change in the study sponsorship from Basilea to Astellas. The project physician, biostatistician and clinical pharmacologist were also changed. Isavuconazole dosing and the fasting requirement for oral isavuconazole administration were amended. The prohibited concomitant drugs were updated. The European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions of IFD were changed from 2002 to the revised 2008 criteria.
17 November 2010	Amendment 3 issued on November 17, 2010, amended maximum duration of therapy from 84 days up to 180 days and the timing of the first study drug maintenance dose was also amended. The primary and secondary analysis and efficacy variables were amended to specify that outcome criteria were assessed by the DRC and Investigator and to add additional time points for analysis. The exploratory analysis variables were amended to specify pharmacokinetic analysis and the addition of analysis of serum galactomannan (GM) as a biomarker for treatment of invasive aspergillosis. The inclusion and exclusion criteria were also amended and clarified. The criterion for withdrawing participants with possible IFD was removed, and prohibited and cautionary drugs and drug-drug interactions (DDIs) were updated. Various study procedures in the Schedule of Assessments were amended, clarified and added. Bronchoalveolar lavage (BAL) galactomannan (GM) was clarified as mycological criteria for enrollment of participants with invasive aspergillosis. The Protocol was amended to classify these participants as possible versus probable cases of IFD. Additional follow-up criteria for enrollment of these participants were also added. The CLCr calculation was amended to standardize reporting; ideal rather than actual BW was used in the calculation. The laboratory tests albumin, p-amylase and lipase were also added, and an improvement of < 25% was included in radiological response criteria.
11 June 2012	Amendment 5 issued on June 11, 2012, amended and clarified the efficacy variables and analysis sets and modified the entry criteria. Entry criteria changes included allowance of enrollment of participants on dialysis and of participants with proven or probable invasive mucormycosis who required primary therapy, and exclusion of participants who were enrolled in previous isavuconazole trials. Sirolimus and tyrosine kinase inhibitors were added as medications to use with caution, and clarification was added that statins could be discontinued at time of first dose. Various study procedures were amended, clarified and added to the Schedule of Assessments. The laboratory tests hematocrit and blood, urea and nitrogen test (BUN) were added.

06 February 2013	Amendment 6.1 issued on February 06, 2013, added inclusion criterion 7, stating that participants were not to participate in any other clinical trial within 30 days prior to first administration of study drug. Exclusion criterion 12 was revised to remove the exception that allowed concurrent participation in open-label protocols; limited the enrollment to participants that had proven or probable IFD caused by rare molds, yeasts or dimorphic fungi and participants who had proven or probable invasive zycomycosis who required primary treatment; relabeled inclusion criterion 5 as inclusion criterion 6; and clarified that no waivers to inclusion or exclusion criteria were permitted. The total sample size was increased from 100 participants to 150 participants to allow enrollment of specified subsets of participants requiring primary therapy. As the sample size was increased and the inclusion of participants with specific infections was limited, the sections of the Protocol that were no longer relevant to participants to be enrolled under this amendment were identified, and exclusion criterion 15 was removed to allow the inclusion of participants with invasive aspergillosis. A section entitled End of Trial in All Participating Countries was added to the Protocol, to define the end of trial for this Protocol and allow for consistency throughout participating countries. The Protocol was also updated to indicate that preliminary data suggested isavuconazole may shorten the QT interval.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 January 2009	Enrollment in the clinical study was suspended in January 2009 pending further characterization of newly identified impurities. After successful completion of the studies, regulatory notifications, and transfer of Sponsorship from Basilea to Astellas, resumption of enrollment occurred in April 2011 for the 9766-CL-0103/WSA-CS-003 study (hereafter referred to as 9766-CL-0103).	01 April 2011

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Primary limitation is the non-comparative design. Conduct of a large randomized controlled study in these rare diseases was not considered feasible. The results provide evidence that CRESEMBA is effective for the treatment for mucormycosis.

Notes: