Clinical trial results:
A Prospective, Open-Label Study To Assess The Pharmacokinetics, Safety & Efficacy Of Anidulafungin When Used To Treat Children With Invasive Candidiasis, Including Candidemia

Summary

EudraCT number	2008-004150-32
Trial protocol	ES DE FR PT IT GR Outside EU/EEA GB
Global end of trial date	14 February 2018

Results information

Result version number	v1
This version publication date	30 August 2018
First version publication date	30 August 2018

Trial information

Trial identification

Sponsor protocol code	A8851008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00761267
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000469-PIP01-08
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	17 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of anidulafungin in children 1 month to less than (<) 18 years of age with invasive candidiasis, including candidemia (ICC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 February 2009
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	Brazil: 17
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	68
EEA total number of subjects	19

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)	19
Children (2-11 years)	39
Adolescents (12-17 years)	10
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted in 10 countries between 27 Feb 2009 and 14 Feb 2018.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Anidulafungin:Subjects Aged 1 month to less than(<)2 Years

Arm description:

Subjects received Anidulafungin loading dose of 3 milligrams per kg(mg/kg) intravenously(IV) on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days.After >=10 days treatment, subjects with microbiologically confirmed invasive candidiasis/candidemia(ICC) and who fulfilled protocol specified criteria [1)afebrile for >=24 hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection] and after >=5 days treatment, subjects without microbiologically confirmed ICC,could switch to oral fluconazole(6-12 mg/kg/day,maximum 800mg/day) upto 49 days.First 6 subjects received second antifungal agent, if required at Investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Anidulafungin
Investigational medicinal product code	PF-03910960
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Anidulafungin at loading dose of 3mg/kg, IV on Day 1, then maintenance dose of 1.5 mg/kg, every 24 hours for a minimum of 10 days and maximum of 35 days.

Arm title	Anidulafungin: Subjects Aged 2 to <5 Years

Arm description:

Subjects received Anidulafungin loading dose of 3mg/kg, IV on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days. After >=10 days treatment, subjects with microbiologically confirmed ICC and who fulfilled protocol specified criteria [1)afebrile for >=24 2hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection] and after >=5 days treatment, subjects without microbiologically confirmed ICC, could switch to oral fluconazole (6-12 mg/kg/day, maximum 800mg/day) for upto 49 days.

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Investigational medicinal product name	Anidulafungin
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Dosage and administration details:

Anidulafungin at loading dose of 3 mg/kg, IV on Day 1, then maintenance dose of 1.5 mg/kg, every 24 hours for a minimum of 10 days and maximum of 35 days.

Arm title	Anidulafungin: Subjects Aged 5 to <18 Years

Arm description:

Subjects received Anidulafungin loading dose of 3mg/kg, IV on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days. After >=10 days treatment, subjects with microbiologically confirmed ICC and who fulfilled protocol specified criteria ([1)afebrile for >=24 hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection]and after >=5 days treatment, subjects without microbiologically confirmed ICC, could switch to oral fluconazole (6-12 mg/kg/day, maximum 800mg/day) upto 49 days.

Arm type	Experimental
Investigational medicinal product name	Anidulafungin
Investigational medicinal product code	PF-03910960
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Anidulafungin at loading dose of 3 mg/kg, IV on Day 1, then maintenance dose of 1.5 mg/kg, every 24 hours for a minimum of 10 days and maximum of 35 days.

Number of subjects in period 1	Anidulafungin:Subjects Aged 1 month to less than(<)2 Years	Anidulafungin: Subjects Aged 2 to <5 Years	Anidulafungin: Subjects Aged 5 to <18 Years
Started	19	19	30
Completed	18	16	24
Not completed	1	3	6
Consent withdrawn by subject	-	1	-
Lost to follow-up	-	-	1
Subject Died	1	2	5

Baseline characteristics

Reporting groups

Reporting group title	Anidulafungin:Subjects Aged 1 month to less than(<)2 Years

Reporting group description:

Subjects received Anidulafungin loading dose of 3 milligrams per kg(mg/kg) intravenously(IV) on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days.After >=10 days treatment, subjects with microbiologically confirmed invasive candidiasis/candidemia(ICC) and who fulfilled protocol specified criteria [1)afebrile for >=24 hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection] and after >=5 days treatment, subjects without microbiologically confirmed ICC,could switch to oral fluconazole(6-12 mg/kg/day,maximum 800mg/day) upto 49 days.First 6 subjects received second antifungal agent, if required at Investigator's discretion.

Reporting group title	Anidulafungin: Subjects Aged 2 to <5 Years

Reporting group description:

Subjects received Anidulafungin loading dose of 3mg/kg, IV on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days. After >=10 days treatment, subjects with microbiologically confirmed ICC and who fulfilled protocol specified criteria [1)afebrile for >=24 2hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection] and after >=5 days treatment, subjects without microbiologically confirmed ICC, could switch to oral fluconazole (6-12 mg/kg/day, maximum 800mg/day) for upto 49 days.

Reporting group title	Anidulafungin: Subjects Aged 5 to <18 Years

Reporting group description:

Subjects received Anidulafungin loading dose of 3mg/kg, IV on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days. After >=10 days treatment, subjects with microbiologically confirmed ICC and who fulfilled protocol specified criteria ([1)afebrile for >=24 hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection]and after >=5 days treatment, subjects without microbiologically confirmed ICC, could switch to oral fluconazole (6-12 mg/kg/day, maximum 800mg/day) upto 49 days.

Reporting group values	Anidulafungin:Subjects Aged 1 month to less than(<)2 Years	Anidulafungin: Subjects Aged 2 to <5 Years	Anidulafungin: Subjects Aged 5 to <18 Years
Number of subjects	19	19	30
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)	19	0	0
Children (2-11 years)	0	19	20
Adolescents (12-17 years)	0	0	10
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0

Age Continuous Units: years			
arithmetic mean	0.93	3.09	10.67
standard deviation	± 0.52	± 0.68	± 3.68
Sex: Female, Male Units: Subjects			
Female	9	8	13
Male	10	11	17
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	0
White	19	15	20
More than one race	0	0	0
Unknown or Not Reported	0	1	6

Reporting group values	Total		
Number of subjects	68		
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)	19		
Children (2-11 years)	39		
Adolescents (12-17 years)	10		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	30		
Male	38		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	6		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	54		
More than one race	0		
Unknown or Not Reported	7		

Subject analysis sets

Subject analysis set title	Anidulafungin PK subgroup: 1 month to <2 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

First 6 subjects received Anidulafungin at loading dose of 3 mg/kg, IV on Day 1, then maintenance dose of 1.5 mg/kg, every 24 hours for minimum of 10 days and maximum of 35 days. After >=10 days of IV treatment, subjects with microbiologically confirmed ICC and who fulfilled protocol specified criterion [1) afebrile for >=24 hours, 2) tolerate oral medication, 3)documentation of 2 blood cultures (24 hours apart) negative for Candida species,4) Eradication/presumed eradication of Candida species from any other sites of infection if identified at enrollment, 5) Specific Candida isolate was susceptible/presumed susceptible to fluconazole, 6) switched to oral fluconazole if improvement in signs, symptoms of Candida infection] and after >=5 days treatment, subjects without microbiologically confirmed ICC,could switch to oral fluconazole(6-12 mg/kg/day,maximum 800mg/day) upto 49 days.Subjects received a second systemic antifungal agent, if required at the Investigator's discretion.

Reporting group values	Anidulafungin PK subgroup: 1 month to <2 Years		
Number of subjects	6		
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)	6		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	±		
Sex: Female, Male Units: Subjects			
Female			
Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
More than one race			
Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	Anidulafungin:Subjects Aged 1 month to less than(<)2 Years

Reporting group description:

Subjects received Anidulafungin loading dose of 3 milligrams per kg(mg/kg) intravenously(IV) on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days.After >=10 days treatment, subjects with microbiologically confirmed invasive candidiasis/candidemia(ICC) and who fulfilled protocol specified criteria [1)afebrile for >=24 hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection] and after >=5 days treatment, subjects without microbiologically confirmed ICC,could switch to oral fluconazole(6-12 mg/kg/day,maximum 800mg/day) upto 49 days.First 6 subjects received second antifungal agent, if required at Investigator's discretion.

Reporting group title	Anidulafungin: Subjects Aged 2 to <5 Years

Reporting group description:

Subjects received Anidulafungin loading dose of 3mg/kg, IV on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days. After >=10 days treatment, subjects with microbiologically confirmed ICC and who fulfilled protocol specified criteria [1)afebrile for >=24 2hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection] and after >=5 days treatment, subjects without microbiologically confirmed ICC, could switch to oral fluconazole (6-12 mg/kg/day, maximum 800mg/day) for upto 49 days.

Reporting group title	Anidulafungin: Subjects Aged 5 to <18 Years

Reporting group description:

Subjects received Anidulafungin loading dose of 3mg/kg, IV on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days. After >=10 days treatment, subjects with microbiologically confirmed ICC and who fulfilled protocol specified criteria ([1)afebrile for >=24 hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection]and after >=5 days treatment, subjects without microbiologically confirmed ICC, could switch to oral fluconazole (6-12 mg/kg/day, maximum 800mg/day) upto 49 days.

Subject analysis set title	Anidulafungin PK subgroup: 1 month to <2 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

First 6 subjects received Anidulafungin at loading dose of 3 mg/kg, IV on Day 1, then maintenance dose of 1.5 mg/kg, every 24 hours for minimum of 10 days and maximum of 35 days. After >=10 days of IV treatment, subjects with microbiologically confirmed ICC and who fulfilled protocol specified criterion [1) afebrile for >=24 hours, 2) tolerate oral medication, 3)documentation of 2 blood cultures (24 hours apart) negative for Candida species,4) Eradication/presumed eradication of Candida species from any other sites of infection if identified at enrollment, 5) Specific Candida isolate was susceptible/presumed susceptible to fluconazole, 6) switched to oral fluconazole if improvement in signs, symptoms of Candida infection] and after >=5 days treatment, subjects without microbiologically confirmed ICC,could switch to oral fluconazole(6-12 mg/kg/day,maximum 800mg/day) upto 49 days.Subjects received a second systemic antifungal agent, if required at the Investigator's discretion.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 6 weeks after end of

treatment (EOT) (up to 91 days) that were absent before treatment or that worsened relative to pretreatment state. AEs included both SAEs and non-SAEs. EOT visit defined as last day of study treatment (IV or oral). The safety population included all randomized subjects who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Baseline up to 6 weeks after EOT (up to 91 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: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Anidulafungin: Subjects Aged 1 month to less than(<)2 Years	Anidulafungin: Subjects Aged 2 to <5 Years	Anidulafungin: Subjects Aged 5 to <18 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	19	30	
Units: subjects				
AEs|	17	19	30	
SAEs|	7	10	13	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Laboratory Abnormalities

End point title	Number of Subjects with Laboratory Abnormalities[2]

End point description:

Criteria for laboratory abnormalities: Hematology parameters:red blood cell count:<0.8*lower limit of normal (LLN); reticulocytes count(absolute or percent):<0.5*LLN or greater than (>) 1.5*upper limit of normal (ULN); Platelets: <0.5*LLN or >1.75*ULN; white blood cell count:<0.6*LLN or >1.5*ULN; neutrophils (absolute or percent):<0.8*LLN or >1.2*ULN; basophils (absolute or percent):>1.2*ULN; lymphocytes (absolute or percent):<0.8*LLN or >1.2*ULN; monocytes (absolute or percent):>1.2*ULN. Serum Chemistry parameters: sodium:<0.95*LLN or >1.05*ULN, potassium, chloride, bicarbonate, calcium:<0.9*LLN or >1.1*ULN; magnesium:>1.1*ULN or <0.9*LLN; BUN (blood urea nitrogen):>1.3* ULN, creatinine:>1.3*ULN; aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase:>3.0*ULN ; total bilirubin: >1.5*ULN; albumin:<0.8*LLN or >1.2*ULN and glucose: <0.6*LLN or >1.5*ULN.Safety population:all randomized subjects who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Baseline up to 6 weeks after EOT (up to 91 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: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Anidulafungin: Subjects Aged 1 month to less than(<)2 Years	Anidulafungin: Subjects Aged 2 to <5 Years	Anidulafungin: Subjects Aged 5 to <18 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	19	30	
Units: subjects	19	18	30	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Global Response

End point title	Number of Subjects With Global Response

End point description:

Global response categorized:success,failure,indeterminate.Success:clinical response(CR)of cure(resolution of sign, symptoms attributed to Candida infection[CI];no additional systemic/oral antifungal) or improvement(significant but incomplete resolution of signs,symptoms of CI;no additional systemic antifungal) and microbiological eradication/presumed eradication(Baseline pathogen not isolated from original site culture/ culture data not available for subject with successful outcome).Failure:CR of failure(no significant improvement in signs,symptoms/death due to CI)and/or microbiological failure(persistence/new infection/relapse at follow-up).Indeterminate:CR of indeterminate(evaluation not made due to withdrawal from study prior to cure or failure assessment)and/or microbiological response of indeterminate(Culture data not available for subject with clinical outcome of indeterminate)and neither response was failure.mITT population:atleast 1 dose of

End point type	Secondary

End point timeframe:

EOIVT (maximum of 35 days), EOT (maximum of 49 days), during 2 week follow-up (up to 63 days) and 6 week follow-up (up to 91 days) after EOT

End point values	Anidulafungin: Subjects Aged 1 month to less than(<)2 Years	Anidulafungin: Subjects Aged 2 to <5 Years	Anidulafungin: Subjects Aged 5 to <18 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	18	30	
Units: subjects				
EOIVT:Success	11	14	20	
EOIVT:Failure	2	1	3	
EOIVT:Indeterminate	3	3	7	
EOIVT:Missing	0	0	0	
EOT:Success	11	14	21	
EOT:Failure	2	1	3	
EOT:Indeterminate	3	3	6	
EOT:Missing	0	0	0	
2 week follow-up:Success	11	13	22	
2 week follow-up:Failure	2	1	4	
2 week follow-up:Indeterminate	3	1	0	
2 week follow-up:Missing	0	3	4	
6 week follow-up:Success	11	12	20	
6 week follow-up:Failure	2	2	6	
6 week follow-up:Indeterminate	3	2	0	
6 week follow-up:Missing	0	2	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Versus Time Curve From Time Zero to 24 Hours (AUC24) of Anidulafungin for Pharmacokinetic (PK) Subgroup

End point title	Area Under the Plasma Concentration Versus Time Curve From Time Zero to 24 Hours (AUC24) of Anidulafungin for Pharmacokinetic (PK) Subgroup

End point description:

The PK analysis set included the first 6 subjects aged between 1 month to <2 years. AUC24 PK time points were assessed on Day 1 and Day 2. Summarized data for both time points were reported

End point type	Secondary

End point timeframe:

Day 1: 2 minutes before the end of infusion, Day 2: pre- infusion, 6, 12 and 24 hours after the start of infusion and 2 minutes before the end of infusion

End point values	Anidulafungin PK subgroup: 1 month to <2 Years			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: nanogram*hour per milliliter (ng*hr/mL)				
geometric mean (geometric coefficient of variation)	66449.1 (± 28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Anidulafungin for Pharmacokinetic (PK) Subgroup

End point title	Maximum Plasma Concentration (Cmax) of Anidulafungin for Pharmacokinetic (PK) Subgroup

End point description:

The PK analysis set included the first 6 subjects aged between 1 month to <2 years. Cmax PK time points were assessed on Day 1 and Day 2. Summarized data for both time points were reported.

End point type	Secondary

End point timeframe:

Day 1: 2 minutes before the end of infusion, Day 2: pre- infusion, 6, 12 and 24 hours after the start of infusion and 2 minutes before the end of infusion

End point values	Anidulafungin PK subgroup: 1 month to <2 Years			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	5963.53 (± 29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Versus Time Curve From Time Zero to 24 Hours (AUC24) of Polysorbate 80 (PS 80) Following Infusion of Anidulafungin

End point title	Area Under the Plasma Concentration Versus Time Curve From Time Zero to 24 Hours (AUC24) of Polysorbate 80 (PS 80) Following Infusion of Anidulafungin[3]

End point description:

Excipient PS 80 is a solubilizing agent contained in the IV formulation of anidulafungin. The lower limit of quantitation (LLOQ) for all the observations of PS 80 was 5.0 milligram per milliliter (mg/mL). The geometric mean and coefficient of variation was not reported since only one value was above LLOQ, hence, AUC24 of polysorbate 80 could not be calculated and has been denoted by 99999. The PK population for PS80 included all subjects aged between 1 month to <2 years who had 1 or more PK sample available. AUC24 PK time points were assessed on at Day 1, Day 2, Day 5, Day 7 and Day 9. Summarized data for all the time points were reported.

End point type	Secondary

End point timeframe:

Day 1: 0 to 2 hours post dose; Day 3 and Day 9:pre-dose; Day 5: 0 to 3 hours post dose; Day 7: 6 to 12 hours delayed post-dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Subjects Aged 1 month to less than (<)2 Years were analyzed for this end point.

End point values	Anidulafungin: Subjects Aged 1 month to less than(<)2 Years			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Polysorbate 80 (PS 80) Following Infusion of Anidulafungin

End point title	Maximum Plasma Concentration (Cmax) of Polysorbate 80 (PS 80) Following Infusion of Anidulafungin[4]

End point description:

Excipient PS 80 is a solubilizing agent contained in the IV formulation of anidulafungin. The LLOQ for all the observations of PS 80 was 5.0 mg/ml. The geometric mean and coefficient of variation was not reported since only one value was above LLOQ, hence, Cmax of polysorbate 80 could not be calculated and has been denoted by 99999. The PK population for PS80 included all subjects aged between 1 month to <2 years who had 1 or more PK sample available. Cmax PK time points were assessed on at Day 1, Day 2, Day 5, Day 7 and Day 9. Summarized data for all the time points were reported.

End point type	Secondary

End point timeframe:

Day 1: 0 to 2 hours post dose; Day 3 and Day 9:pre-dose; Day 5: 0 to 3 hours post dose; Day 7: 6 to 12 hours delayed post-dose Day 1: 0 to

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects Aged 1 month to less than(<)2 Years were only analyzed for this end point.

End point values	Anidulafungin: Subjects Aged 1 month to less than(<)2 Years			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Relapsed Response

End point title	Percentage of Subjects With Relapsed Response

End point description:

Relapse:any baseline Candida species isolated following eradication (documented or presumed); or culture data not available for a subject with a clinical response of failure after a previous response of success. Clinical response of failure:no significant improvement in signs and symptoms, or death due to the Candida infection (CI). Subjects had received at least 3 doses of study medication to be classified as a failure. Clinical response of success: resolution of sign and symptoms attributed to Candida infection occurred with no additional systemic or oral antifungal treatment required to complete the course of therapy. Eradication or presumed eradication: baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful clinical outcome. End of treatment visit defined as last day of study treatment (IV or oral).mITT population:subjects who received at least 1 dose of study drug and had microbiological confirmation of CI.

End point type	Secondary

End point timeframe:

During 2 week follow-up (up to 63 days) and 6 week follow-up (up to 91 days) after EOT

End point values	Anidulafungin: Subjects Aged 1 month to less than(<)2 Years	Anidulafungin: Subjects Aged 2 to <5 Years	Anidulafungin: Subjects Aged 5 to <18 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	18	30	
Units: percentage of subjects				
number (not applicable)				
2 week follow-up|	0.0	0.0	0.0	
6 week follow-up|	0.0	5.6	6.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With New Infection

End point title	Percentage of Subjects With New Infection

End point description:

New infection was defined as a subject presenting with clinical failure with the emergence of new Candida species at the original site of infection or at a distant site of infection. Clinical response of failure was defined as no significant improvement in signs and symptoms, or death due to the Candida infection occurred. Subjects had received at least 3 doses of study medication to be classified as a failure. End of treatment visit defined as last day of study treatment (IV or oral). The mITT population was defined as all subjects who had received at least 1 dose of study drug and who had microbiological confirmation of Candida infection.

End point type	Secondary

End point timeframe:

follow-up (up to 91 days) after EOT During 2 week follow-up (up to 63 days) and 6 week follow-up (up to 91 days) after EOT

End point values	Anidulafungin: Subjects Aged 1 month to less than(<)2 Years	Anidulafungin: Subjects Aged 2 to <5 Years	Anidulafungin: Subjects Aged 5 to <18 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	18	30	
Units: percentage of subjects				
number (not applicable)				
2 week follow-up	0.0	0.0	0.0	
6 week follow-up	0.0	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: All-Cause Mortality - Number of Subjects Who Died During Overall Study Treatment Period and Follow-Up Visits

End point title	All-Cause Mortality - Number of Subjects Who Died During Overall Study Treatment Period and Follow-Up Visits

End point description:

The safety population included all randomized subjects who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Overall period (up to 49 days); during 2 week follow-up (up to 63 days) and 6 week follow-up (up to 91 days) after EOT

End point values	Anidulafungin: Subjects Aged 1 month to less than(<)2 Years	Anidulafungin: Subjects Aged 2 to <5 Years	Anidulafungin: Subjects Aged 5 to <18 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	19	30	
Units: subjects				
overall study treatment period	0	1	4	
2 Week FU	0	0	1	
6 Week FU	1	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 6 weeks after end of treatment (up to 91 days)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Anidulafungin:Subjects Aged 1 month to less than(<)2 Years

Reporting group description:

Subjects received Anidulafungin loading dose of 3 milligrams per kg(mg/kg) intravenously(IV) on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days.After >=10 days treatment, subjects with microbiologically confirmed invasive candidiasis/candidemia(ICC) and who fulfilled protocol specified criteria [1)afebrile for >=24 hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection] and after >=5 days treatment, subjects without microbiologically confirmed ICC,could switch to oral fluconazole(6-12 mg/kg/day,maximum 800mg/day) upto 49 days.First 6 subjects received second antifungal agent, if required at Investigator's discretion.

Reporting group title	Anidulafungin: Subjects Aged 5 to <18 Years

Reporting group description:

Subjects received Anidulafungin loading dose of 3mg/kg, IV on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days. After >=10 days treatment, subjects with microbiologically confirmed ICC and who fulfilled protocol specified criteria ([1)afebrile for >=24 hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection]and after >=5 days treatment, subjects without microbiologically confirmed ICC, could switch to oral fluconazole (6-12 mg/kg/day, maximum 800mg/day) upto 49 days.

Reporting group title	Anidulafungin: Subjects Aged 2 to <5 Years

Reporting group description:

Subjects received Anidulafungin loading dose of 3mg/kg, IV on Day 1 and maintenance dose of 1.5mg/kg, every 24 hours for minimum 10 and maximum 35 days. After >=10 days treatment, subjects with microbiologically confirmed ICC and who fulfilled protocol specified criteria [1)afebrile for >=24 2hours, 2)tolerate oral medication, 3)documentation of 2 blood cultures [24 hours apart] negative for Candida, 4)eradication/presumed eradication of Candida from other infection sites,identified at enrollment,5)specific Candida isolate susceptible/presumed susceptible to fluconazole, 6)switched to oral fluconazole if improvement in signs,symptoms of Candida infection] and after >=5 days treatment, subjects without microbiologically confirmed ICC, could switch to oral fluconazole (6-12 mg/kg/day, maximum 800mg/day) for upto 49 days.

Serious adverse events	Anidulafungin:Subjects Aged 1 month to less than(<)2 Years	Anidulafungin: Subjects Aged 5 to <18 Years	Anidulafungin: Subjects Aged 2 to <5 Years
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 19 (36.84%)	13 / 30 (43.33%)	10 / 19 (52.63%)

number of deaths (all causes)	1	5	2
number of deaths resulting from adverse events			
Investigations			
Aspiration bronchial			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Unintentional medical device removal			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Brachiocephalic vein thrombosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Seizure			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pancytopenia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic pseudocyst			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory failure			

subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			

subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	0 / 19 (0.00%)	2 / 30 (6.67%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 19 (5.26%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Anidulafungin:Subjects Aged 1 month to less than(<)2 Years	Anidulafungin: Subjects Aged 5 to <18 Years	Anidulafungin: Subjects Aged 2 to <5 Years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 19 (89.47%)	30 / 30 (100.00%)	17 / 19 (89.47%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial neoplasm			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 19 (0.00%)	3 / 30 (10.00%)	2 / 19 (10.53%)
occurrences (all)	0	3	3
Phlebitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Poor venous access			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Shock			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Thrombophlebitis superficial			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Deep vein thrombosis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Catheter site haematoma			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Catheter site haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Catheter site inflammation			

subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Catheter site pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Catheter site related reaction			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Catheter site rash			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Generalised oedema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Hyperpyrexia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Hypothermia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Infusion site extravasation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	4 / 19 (21.05%)	6 / 30 (20.00%)	3 / 19 (15.79%)
occurrences (all)	6	6	4
Oedema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Face oedema			

subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Genital erythema			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Penile oedema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Scrotal oedema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Uterine haematoma			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Epistaxis			

subjects affected / exposed	1 / 19 (5.26%)	5 / 30 (16.67%)	3 / 19 (15.79%)
occurrences (all)	1	6	3
Haemoptysis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Hypoxia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Lung disorder			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pneumonia aspiration			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Respiratory distress			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Rhinalgia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Tachypnoea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Bronchospasm			

subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Laryngospasm			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Respiratory disorder			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Tonsillar erythema			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	3 / 19 (15.79%)
occurrences (all)	0	1	3
Depression			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Product issues			
Device dislocation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Device malfunction			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 19 (10.53%)	3 / 30 (10.00%)	2 / 19 (10.53%)
occurrences (all)	3	3	2
Amylase increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 19 (10.53%)	2 / 30 (6.67%)	1 / 19 (5.26%)
occurrences (all)	4	2	1
C-reactive protein increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Bacterial test positive			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Liver function test abnormal			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Enterobacter test positive			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Klebsiella test positive			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Platelet count increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	1 / 19 (5.26%)	2 / 30 (6.67%)	0 / 19 (0.00%)
occurrences (all)	1	2	0
Urine output decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood bicarbonate decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase			

increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Candida test positive			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Carbon dioxide decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Liver function test increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Accidental overdose			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Excoriation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Post procedural haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 19 (0.00%)	2 / 30 (6.67%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Sinus arrhythmia			

subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 19 (0.00%)	2 / 30 (6.67%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Areflexia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	2
Headache			
subjects affected / exposed	0 / 19 (0.00%)	6 / 30 (20.00%)	1 / 19 (5.26%)
occurrences (all)	0	7	2
Loss of consciousness			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 19 (0.00%)	2 / 30 (6.67%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Anaemia			
subjects affected / exposed	5 / 19 (26.32%)	1 / 30 (3.33%)	3 / 19 (15.79%)
occurrences (all)	9	1	5
Febrile neutropenia			
subjects affected / exposed	0 / 19 (0.00%)	2 / 30 (6.67%)	1 / 19 (5.26%)
occurrences (all)	0	3	1
Leukopenia			

subjects affected / exposed	1 / 19 (5.26%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	1	1	2
Neutropenia			
subjects affected / exposed	1 / 19 (5.26%)	3 / 30 (10.00%)	0 / 19 (0.00%)
occurrences (all)	1	4	0
Pancytopenia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Thrombocytopenia			
subjects affected / exposed	2 / 19 (10.53%)	2 / 30 (6.67%)	1 / 19 (5.26%)
occurrences (all)	5	2	2
Splenomegaly			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Thrombocytosis			
subjects affected / exposed	1 / 19 (5.26%)	2 / 30 (6.67%)	0 / 19 (0.00%)
occurrences (all)	1	2	0
Lymphadenopathy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Eye disorders			
Pupil fixed			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Strabismus			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Eye discharge			
subjects affected / exposed	2 / 19 (10.53%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Eye irritation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Eyelid oedema			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0

Periorbital oedema			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 19 (0.00%)	3 / 30 (10.00%)	1 / 19 (5.26%)
occurrences (all)	0	4	1
Abdominal pain			
subjects affected / exposed	0 / 19 (0.00%)	3 / 30 (10.00%)	3 / 19 (15.79%)
occurrences (all)	0	3	4
Anorectal discomfort			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	3 / 19 (15.79%)	9 / 30 (30.00%)	2 / 19 (10.53%)
occurrences (all)	3	12	4
Dry mouth			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Dysphagia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gastric haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 19 (5.26%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ileus			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	3
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Mouth ulceration			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 19 (0.00%)	3 / 30 (10.00%)	1 / 19 (5.26%)
occurrences (all)	0	3	1
Pancreatic disorder			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Pancreatic pseudocyst			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Pancreatitis acute			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Saliva altered			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	4 / 19 (21.05%)	5 / 30 (16.67%)	7 / 19 (36.84%)
occurrences (all)	6	5	17
Food poisoning			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Salivary hypersecretion			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Hepatomegaly			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 19 (0.00%)	2 / 30 (6.67%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
Cholestasis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Ocular icterus			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Decubitus ulcer			

subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Ecchymosis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 30 (6.67%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Erythema			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Livedo reticularis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pruritus generalised			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	2 / 19 (10.53%)	2 / 30 (6.67%)	2 / 19 (10.53%)
occurrences (all)	3	2	2
Rash generalised			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Rash macular			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Scar pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Skin discolouration			

subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Skin haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin hyperpigmentation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Skin lesion			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Dermatitis diaper			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Toxic skin eruption			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Henoch-Schonlein purpura nephritis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Acute kidney injury			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	0 / 19 (0.00%)	2 / 30 (6.67%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Endocrine disorders			
Thyroiditis			

subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Muscular weakness			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Clostridium difficile colitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Enterococcal bacteraemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Enterococcal sepsis			

subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Herpes virus infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Liver abscess			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)	2 / 30 (6.67%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Otitis media acute			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Pneumonia			
subjects affected / exposed	0 / 19 (0.00%)	3 / 30 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Purulent discharge			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Relapsing fever			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Splenic abscess			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Staphylococcal infection			

subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Systemic candida			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	1 / 30 (3.33%)	2 / 19 (10.53%)
occurrences (all)	1	1	2
Viral infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Uterine abscess			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Atypical pneumonia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Bacteraemia			
subjects affected / exposed	2 / 19 (10.53%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
Catheter site infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Bacterial infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
catheter site cellulitis			

subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Device related infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pseudomonas infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pyelonephritis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Sepsis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Skin infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Dehydration			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Electrolyte imbalance			
subjects affected / exposed	1 / 19 (5.26%)	0 / 30 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0

Hyperglycaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypernatraemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 19 (5.26%)	2 / 30 (6.67%)	1 / 19 (5.26%)
occurrences (all)	1	2	1
Hypoglycaemia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 30 (3.33%)	2 / 19 (10.53%)
occurrences (all)	1	1	2
Hypokalaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Hypomagnesaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Hyponatraemia			
subjects affected / exposed	0 / 19 (0.00%)	4 / 30 (13.33%)	0 / 19 (0.00%)
occurrences (all)	0	5	0
Hypoproteinaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 30 (3.33%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Metabolic acidosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 30 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2008	Exclusion criterion to exclude premature neonates born at gestation of less than 36 weeks (unless the sum of gestational age plus chronological age was at least 44 weeks) was added, as well as a new section on central venous catheter management.
19 August 2010	(1)Enrollment of subjects with Candida endocarditis on the basis of at least 1 positive blood culture for Candida spp. and evidence of endocarditis on echocardiogram, and, enrollment of subjects with Candida osteomyelitis on the basis of at least 1 positive culture for Candida spp. from a bone biopsy or aspirate and evidence of osteomyelitis on Magnetic Resonance Imaging (MRI) was allowed; (2) Subjects in the PK subgroup (ie, the first 6 subjects between 1 month and <2 years of age enrolled at selected centers) could be given anidulafungin as either monotherapy or in combination with a second antifungal treatment, at the Investigator's discretion; (3) Clarified maximum total duration of treatment in the study was 49 days, and the maximum allowed treatment duration with anidulafungin was 35 days; (4) Modified oral fluconazole switch criteria, such that in addition to other criteria currently listed in the protocol, switching to fluconazole could occur if microbiological eradication was presumed based on clinical signs and symptoms, and if susceptibility to fluconazole was presumed based on the Candida species, identified and based on local Candida resistance patterns; (5) Clarified that subjects could have at least 1 clinical criterion present either at the time of study entry or within 96 hours prior to study entry.
08 December 2011	At the request of the Korean authorities, the Sponsor removed all aspects of the protocol related to the enrollment of subjects with Candida endocarditis and Candida osteomyelitis; study centers in Korea were not permitted to enroll subjects with these conditions.
07 January 2013	The protocol was updated to include: (1) the Sponsor's recent standard protocol template text, including language regarding females and males of childbearing potential, pregnancy testing and contraception; (2) expected SAEs and additional SAE reporting requirements; (3) medication error reporting requirements and (4) Portugal opted out of enrolling Candida endocarditis and Candida osteomyelitis subjects.
06 July 2015	Included measurement of plasma levels of the excipient polysorbate 80, a solubilizing agent contained in the intravenous (IV) formulation of anidulafungin, due to the lack of excipient exposure/response data of polysorbate 80 in very young children (eg, <2 years of age).
16 September 2016	(1) Study population was broadened to include children aged 1 month to <2 years only who were at high risk for candidiasis; (2)Amended exclusion criteria, including those related to prior systemic antifungal therapy and removal of prosthetic devices and/or vascular catheters at the suspected site of infection; (3) Added an interim analysis; (4) Reduced the volume of blood required for polysorbate 80 PK samples and added details for preferred sample collection times; (5) Provided instructions for withdrawal of subjects without microbiologically confirmed invasive candidiasis, including ICC.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Data for the end point of exposure-response relationships of anidulafungin will be estimated and reported separately as part of the Non-linear Mixed Effects Modeling analysis and will be provided once available.

Notes: