Clinical trial results:
A Phase 3, Randomized, Double-Blind, Multi-Center study to Compare the Efficacy and safety of Micafungin Versus Amphotericin B Deoxycholate for the Treatment of Neonatal Candidiasis

Summary

EudraCT number	2012-000780-24
Trial protocol	GR HU BG
Global end of trial date	15 December 2014

Results information

Result version number	v1 (current)
This version publication date	05 February 2016
First version publication date	05 February 2016

Trial information

Trial identification

Sponsor protocol code	9463-CL-2303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00815516
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development US
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development US, Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development US, 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	15 December 2014

Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 December 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The study evaluated how effective and how safe the drug micafungin is when compared to the drug amphotericin B deoxycholate in treating neonates and young infants with certain fungal infections.

Protection of trial subjects:

The study was conducted in accordance with the protocol, Good Clinical Practice (GCP), ICH (International Committee on Harmonisation) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.
The Independent Ethics Committee (IEC) or Institutional Review Board (IRB) reviewed the ethical, scientific and medical appropriateness of the study before it was conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, was obtained prior to the authorization of drug shipment to a study site.
Prior to any study-related screening procedures being performed on the subject, the informed consent statement was reviewed and signed and dated by subject's guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2013
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: 3
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Philippines: 1
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	Ukraine: 2
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	30
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	25
Infants and toddlers (28 days-23 months)	5
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Infants greater than 48 hours of life through day of life (DOL) 120 with a diagnosis of invasive candidiasis were eligible for this study.

Pre-assignment

Screening details:

In total, 31 infants were screened and 30 were randomized in a 2:1 ratio to receive micafungin or amphotericin B deoxycholate. Randomization was stratified by estimated gestational age (< 27 weeks, ≥ 27 weeks) and by region (North America/Europe, Latin America / Mexico, other region).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Micafungin

Arm description:

Infants received micafungin at a dose of 10 mg/kg per day by intravenous infusion for a minimum of 21 days to a maximum of 28 days for infants without end-organ dissemination or for a maximum of 42 days for infants with end-organ dissemination.

Arm type	Experimental
Investigational medicinal product name	Micafungin
Investigational medicinal product code	FK463
Other name	Mycamine
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion

Arm title	Amphotericin B

Arm description:

Infants received amphotericin B deoxycholate (CAB) at a dose of 1.0 mg/kg per day by intravenous infusion for a minimum of 21 days to a maximum of 28 days for infants without end-organ dissemination or for a maximum of 42 days for infants with end-organ dissemination.

Arm type	Active comparator
Investigational medicinal product name	Amphotericin B deoxycholate
Investigational medicinal product code	
Other name	Fungizone, conventional amphotericin B, CAB
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion

Number of subjects in period 1	Micafungin	Amphotericin B
Started	20	10
Completed	16	9
Not completed	4	1
Death	3	1
Physician decision	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Micafungin
Reporting group description:	
Infants received micafungin at a dose of 10 mg/kg per day by intravenous infusion for a minimum of 21 days to a maximum of 28 days for infants without end-organ dissemination or for a maximum of 42 days for infants with end-organ dissemination.	
Reporting group title	Amphotericin B
Reporting group description:	
Infants received amphotericin B deoxycholate (CAB) at a dose of 1.0 mg/kg per day by intravenous infusion for a minimum of 21 days to a maximum of 28 days for infants without end-organ dissemination or for a maximum of 42 days for infants with end-organ dissemination.	

Reporting group values	Micafungin	Amphotericin B	Total
Number of subjects	20	10	30
Age categorical Units: Subjects			
≤ 4 weeks	15	10	25
> 4 weeks to 4 months	5	0	5
Age Continuous Units: days			
arithmetic mean	30.2	16.9	
standard deviation	± 27.99	± 5.13	-
Gender, Male/Female Units: participants			
Female	12	4	16
Male	8	6	14
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	3	6
Not Hispanic or Latino	4	3	7
Unknown or Not Reported	13	4	17
Race/Ethnicity, Customized Units: Subjects			
White	18	9	27
Black or African American	0	1	1
Asian	1	0	1
Other	1	0	1
Gestational Age Units: Subjects			
< 27 Weeks	3	2	5
≥ 27 Weeks	17	8	25
Region of Enrollment Units: Subjects			
North America /Europe	15	9	24
Latin America /Mexico	4	1	5
Other	1	0	1
Fungal Infection Type			
Candidemia: diagnosed if Candida isolated from blood only;			

Invasive candidiasis: diagnosed if Candida isolated from blood in addition to other body fluids such as cerebrospinal fluid (CSF), peritoneal fluid, or urine.			
Units: Subjects			
Candidemia	12	7	19
Invasive Candidiasis	8	2	10
Missing	0	1	1
Presence of End-Organ Dissemination (EOD)			
End-organ dissemination was assessed using echocardiogram, abdominal ultrasound, including evaluation of the liver, spleen, and kidneys, head ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI), and retinal exam (if clinically feasible). End-organ dissemination was assessed by the independent data review panel (DRP). Missing for the DRP assessment means that no evidence for EOD was documented.			
Units: Subjects			
Yes	7	3	10
Missing	13	7	20
Birth Weight			
Units: grams			
arithmetic mean	1807.3	2171.4	
standard deviation	± 879.03	± 1008.79	-

End points

End points reporting groups

Reporting group title	Micafungin

Reporting group description:

Infants received micafungin at a dose of 10 mg/kg per day by intravenous infusion for a minimum of 21 days to a maximum of 28 days for infants without end-organ dissemination or for a maximum of 42 days for infants with end-organ dissemination.

Reporting group title	Amphotericin B

Reporting group description:

Infants received amphotericin B deoxycholate (CAB) at a dose of 1.0 mg/kg per day by intravenous infusion for a minimum of 21 days to a maximum of 28 days for infants without end-organ dissemination or for a maximum of 42 days for infants with end-organ dissemination.

Primary: Fungal-free survival

End point title	Fungal-free survival[1]

End point description:

Fungal-free survival was assessed by an independent data review panel (DRP).
Fungal-free survival is defined as the percentage of participants alive at one week following the last dose of study drug with a mycological response of eradication and no requirement for alternative systemic antifungal therapy for continued treatment.
Eradication was defined as culture or histologically documented absence of the infecting Candida species from all positive normally sterile sites during therapy, documented by 2 negative samples, drawn at least 24 hours apart, or for Candida meningitis and/or candiduria, 1 negative culture.
This endpoint was analyzed using the full analysis set (all randomized infants who were administered any amount of study drug).

End point type	Primary

End point timeframe:

One week after the last dose of study drug (maximum of 49 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: Since this study was terminated early, the total number of evaluable subjects was far below the fully powered sample size. For this circumstance, the statistical inference based on the planned hypothesis was not applicable and not performed.

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: percentage of participants				
number (confidence interval 95%)	60 (36.1 to 80.9)	70 (34.8 to 93.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to mycological clearance of invasive candidiasis

End point title	Time to mycological clearance of invasive candidiasis

End point description:

Time to mycological clearance of invasive candidiasis is defined as the time from first dose to the day of mycological eradication for baseline invasive candidiasis infection.
Eradication was defined as a culture or histologically documented absence of the infecting Candida species from all positive normally sterile sites during therapy, documented by 2 negative samples, drawn at least 24 hours apart, or for for Candida meningitis and/or candiduria, 1 negative culture.
Infants without eradication during the treatment period and who survived were censored at one day after the end of treatment. Infants without eradication who died before completing the treatment period or were lost to follow-up during the treatment were censored at their death or last contact day.
"99999" indicates data could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From first dose up to 30 days after the last dose of study drug (maximum of 72 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: days				
median (confidence interval 95%)	6 (3 to 99999)	3 (0 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fungal-free survival at end of study drug therapy in infants with end-organ dissemination

End point title	Fungal-free survival at end of study drug therapy in infants with end-organ dissemination

End point description:

Fungal-free survival was assessed by an independent data review panel (DRP). Fungal-free survival is defined as the percentage of participants alive at the end of study drug therapy with a mycological response of eradication based upon the DRP assessment and no requirement for alternative systemic antifungal therapy for continued treatment.
This endpoint was analyzed for participants in the full analysis set with end-organ dissemination.

End point type	Secondary

End point timeframe:

The end of study drug therapy (maximum of 42 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	3		
Units: percentage of participants				
number (confidence interval 95%)	42.9 (9.9 to 81.6)	33.3 (0.8 to 90.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fungal-free survival one week after last dose of study drug in infants with end-organ dissemination

End point title	Fungal-free survival one week after last dose of study drug in infants with end-organ dissemination

End point description:

Fungal-free survival was assessed by an independent data review panel (DRP). Fungal-free survival is defined as the percentage of participants alive one week after last dose of study drug with a mycological response of eradication based upon the DRP assessment and no requirement for alternative systemic antifungal therapy for continued treatment.
This endpoint was analyzed for participants in the full analysis set with end-organ dissemination.

End point type	Secondary

End point timeframe:

One week after the last dose of study drug (maximum of 49 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	3		
Units: percentage of participants				
number (confidence interval 95%)	42.9 (9.9 to 81.6)	33.3 (0.8 to 90.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with emergent fungal infections

End point title	Percentage of participants with emergent fungal infections

End point description:

An emergent fungal infection is defined as
● An invasive fungal infection which is detected at any time during the study that is a non-Candida organism, or
● An invasive fungal infection which is detected during the treatment or post-treatment period with a Candida species identified other than those detected at Baseline. If this occurred within 96 hours of the first dose of study drug, the infection was considered part of the final diagnosis of enrolling infection and not an emergent infection.
"99999" indicates values that could not be estimated.

End point type	Secondary

End point timeframe:

Up to 30 days after the last dose of study drug (maximum of 72 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: percentage of participants				
number (confidence interval 95%)	5 (0.1 to 24.9)	0 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with recurrent fungal infections

End point title	Percentage of participants with recurrent fungal infections

End point description:

A recurrent infection is defined as a systemic fungal infection in an infant with eradication at the end of study drug therapy, who developed positive blood cultures or a mycologically confirmed deep-seated Candida infection, with the same species as the enrolling infection.
This endpoint was analyzed for participants in the full analysis set with eradication at the end of study drug therapy. "99999" indicates values that could not be estimated.

End point type	Secondary

End point timeframe:

Up to 30 days after the last dose of study drug (maximum of 72 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: percentage of participants				
number (confidence interval 95%)	0 (-99999 to 99999)	12.5 (0.3 to 52.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to positive clinical response

End point title	Time to positive clinical response

End point description:

Time to a positive clinical response is defined as the time from the first dose to the day during the treatment period that a positive clinical response (defined as a complete response or partial response) is observed for the first time, assessed by the Investigator.
Complete Response is defined as the resolution of all attributable signs related to fungal infection, if present at baseline and Partial Response is defined as improvement in attributable signs related to the fungal infection, if present at baseline.
Infants without positive responses and who survived were censored at one day post the end of treatment. Infants without positive responses who died before completing the treatment period, or were lost to follow-up during the treatment were censored at their death or last contact day.
This endpoint was analyzed in full analysis set participants with clinical signs and symptoms related to the fungal Infection at Baseline.

End point type	Secondary

End point timeframe:

From first dose up to 30 days after the last dose of study drug (maximum of 72 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	10		
Units: days				
median (confidence interval 95%)	8 (7 to 15)	11 (7 to 14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response at the end of study drug therapy

End point title	Clinical response at the end of study drug therapy

End point description:

Clinical response assessments were based on the following definitions and assessed by the DRP:

• Complete Response: Resolution of all attributable signs related to fungal infection, if present at baseline.

• Partial Response: Improvement in attributable signs related to the fungal infection, if present at baseline.

• Stabilization: Minor improvement or no change in attributable signs related to the fungal infection, if present at baseline, and infant continued on therapy without deterioration.

• Progression: Deterioration in attributable signs related to the fungal infection, if present at baseline; or if death occurred presumably related to a fungal infection.

This endpoint was analyzed in full analysis set participants with clinical signs and symptoms related to the fungal Infection at Baseline.

End point type	Secondary

End point timeframe:

Baseline and end of study drug therapy (maximum of 42 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	10		
Units: percentage of participants				
number (not applicable)				
Complete	55.6	70		
Partial	5.6	0		
Stable	5.6	10		
Progression	16.7	20		
Missing	16.7	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response one week after last dose of study drug

End point title	Clinical response one week after last dose of study drug

End point description:

Clinical response assessments were based on the following definitions and assessed by the DRP:

• Complete Response: Resolution of all attributable signs related to fungal infection, if present at baseline.

• Partial Response: Improvement in attributable signs related to the fungal infection, if present at baseline.

• Stabilization: Minor improvement or no change in attributable signs related to the fungal infection, if present at baseline, and infant continued on therapy without deterioration.

• Progression: Deterioration in attributable signs related to the fungal infection, if present at baseline; or if death occurred presumably related to a fungal infection.

This endpoint was analyzed in full analysis set participants with clinical signs and symptoms related to the fungal Infection at Baseline.

End point type	Secondary

End point timeframe:

Baseline and one week after the last dose of study drug (maximum of 49 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	10		
Units: percentage of participants				
number (not applicable)				
Complete	55.6	70		
Partial	5.6	0		
Stable	5.6	10		
Progression	5.6	20		
Missing	27.8	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mycological response at end of study drug therapy

End point title	Mycological response at end of study drug therapy

End point description:

Mycological response assessments were based on the following definitions and assessed by the DRP:
• Eradication: Culture or histologically documented absence of the infecting Candida species from all positive normally sterile sites during therapy, documented by 2 negative samples, drawn at least 24 h apart; for Candida meningitis and/or candiduria, 1 negative culture.
• Persistence: Continued isolation or histological documentation from a normally sterile site.

End point type	Secondary

End point timeframe:

End of study drug therapy (maximum of 42 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: percentage of participants				
number (not applicable)				
Eradication	55	80		
Persistence	10	20		
Not Assessed	35	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mycological response one week after last dose of study drug

End point title	Mycological response one week after last dose of study drug

End point description:

Mycological response assessments were based on the following definitions and assessed by the DRP:
• Eradication: Culture or histologically documented absence of the infecting Candida species from all positive normally sterile sites during therapy, documented by 2 negative samples, drawn at least 24 h apart; for Candida meningitis and/or candiduria, 1 negative culture.
• Persistence: Continued isolation or histological documentation from a normally sterile site.

End point type	Secondary

End point timeframe:

One week after the last dose of study drug (maximum of 49 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: percentage of participants				
number (not applicable)				
Continuing Eradication/Eradication	55	80		
Persistence	10	20		
Not Assessed	35	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Follow-up status for infants with end-organ assessments

End point title	Follow-up status for infants with end-organ assessments

End point description:

End-organ dissemination was assessed through abdominal ultrasound and/or computed tomography (CT), echocardiogram, head imaging and retinal exam. Each specific finding, documented by 1 of these techniques, was evaluated as follows:
• Improvement: Improvement in size, number or density of identified lesions. Complete response was not expected but may have been documented.
• Stabilization: Minor improvement or no change in size, number or density of identified lesions.
• Worsening: Increase in size or number of identified lesions.
This endpoint was analyzed in full analysis set participants with end-organ assessments.

End point type	Secondary

End point timeframe:

Baseline and 30 days after the last dose of study drug (maximum of 72 days)

End point values	Micafungin	Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	3		
Units: percentage of participants				
number (not applicable)				
Improved	57.1	33.3		
Stable	14.3	0		
Worsened	14.3	66.7		
Not Assessed	14.3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Micafungin Concentration

End point title	Plasma Micafungin Concentration[2]

End point description:

This endpoint was analyzed in the pharmacokinetics (PK) analysis set, including those infants who received any amount of study drug, have at least one study drug concentration, and have dosing and blood collection date and time data sufficient for inclusion in a population pharmacokinetic analysis.

End point type	Secondary

End point timeframe:

15 minutes post intravenous infusion (IV), 4-8 hours post IV and 15-24 hours post IV

Notes:

[2] - 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: PK analyses were performed in the micafungin treatment group only.

End point values	Micafungin			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
arithmetic mean (standard deviation)				
Within 15 Minutes Post IV	25130.5 (± 13964.3)			
4-8 Hours Post IV	23751.7 (± 9547.7)			
15-24 Hours Post IV	14118.3 (± 12396)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 72 hours after the last dose; mean duration of study drug exposure among micafungin-treated patients was 18.6 days and 15.5 days for Amphotericin B-treated patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Amphotericin B

Reporting group description:

Infants received amphotericin B deoxycholate (CAB) at a dose of 1.0 mg/kg per day by intravenous infusion for a minimum of 21 days to a maximum of 28 days for infants without end-organ dissemination or for a maximum of 42 days for infants with end-organ dissemination.

Reporting group title	Micafungin

Reporting group description:

Infants received micafungin at a dose of 10 mg/kg per day by intravenous infusion for a minimum of 21 days to a maximum of 28 days for infants without end-organ dissemination or for a maximum of 42 days for infants with end-organ dissemination.

Serious adverse events	Amphotericin B	Micafungin	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	12 / 20 (60.00%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Obstructive airways disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (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 / 10 (10.00%)	4 / 20 (20.00%)	
occurrences causally related to treatment / all	0 / 1	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intraventricular haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis neonatal			
subjects affected / exposed	2 / 10 (20.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	0 / 10 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Amphotericin B	Micafungin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	14 / 20 (70.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Thrombophlebitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 20 (5.00%)	
occurrences (all)	2	2	
Hypothermia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infusion related reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Infusion site rash			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infusion site extravasation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			

Agitation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Galactorrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Medical device complication			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Post procedural haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Bacteria blood identified			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Antithrombin III decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	

occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Neutrophil count increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Liver function test abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Oxygen consumption increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Serum ferritin increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 10 (20.00%)	5 / 20 (25.00%)	
occurrences (all)	2	5	

Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Thrombocytopenia			
subjects affected / exposed	3 / 10 (30.00%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Leukocytosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Eosinophilia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Anaemia neonatal			
subjects affected / exposed	1 / 10 (10.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypercapnia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Intraventricular haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	2 / 10 (20.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Dermatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Osteopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hyperphosphataemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypochloraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Staphylococcal infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Endocarditis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

Urinary tract infection bacterial			
subjects affected / exposed	0 / 10 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	3	
Neonatal infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Staphylococcal sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2013	- Add clarifying language for a negative or positive culture and a time window of ± 3 h to the treatment period collection of every 48 h. - Time windows added to Schedule of Assessments. - Include a new criterion prohibiting participation in another interventional study while on treatment. - Provide clarity around qualifying specimens from an indwelling catheter. - Clarify that there are limited amount of antifungal therapies approved in the introduction. - Provide further clarifying details on non-GLP studies. - Replace 'subject' with 'infant' under discontinuation criteria and include clarification of the end of study visit (ESV) procedure window. - Update study drug handling. - Provide clarity on dilution requirements, flushing technique, clarification on color of coverings and consistency in instructions on the administration of micafungin and of CAB. - Add details for unblinded personnel on maintaining blind for study drug materials. -Provide guidance during treatment for removal and replacement of existing central lines. - Ensure the collection of all antifungal treatment provided. - Added the volume of blood to be drawn for blood culture. - Clarify pharmacoeconomic data collection on length of stay. - Update to definition of adverse events. - Definition of infusion related reaction is provided with guidance on what is to be documented around the reaction. - Additional information on AEs specific to the comparator. - Include revisions regarding notification of SAEs in the study, investigators responsibility for IRB/IEC notification and information on CIOMS in a blinded study. - Addition of protocol deviation information and definition. - Addition of definition of End of Study. - Informed consent requirements are updated. - Added clarification of requirements if there is new or important information. - Additional information provided regarding sponsor insurance for study subjects. - Updated clinical study report signatory.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported