Clinical trial results:
Determination of Plasmatic and CSF Levels of High Doses of Micafungin in Neonates Suffering from Systemic Candidiasis and/or Candida Meningitis

Summary

EudraCT number	2014-003087-20
Trial protocol	IT
Global end of trial date	10 April 2018

Results information

Result version number	v1
This version publication date	18 October 2018
First version publication date	18 October 2018

Trial information

Trial identification

Sponsor protocol code	9463-CL-6001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03421002
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc. (APGD)
Sponsor organisation address	1 Astellas Way, Northbrook, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to study pharmacokinetic (PK) profile of micafungin administered at a dose of 8 mg/kg per day to infants suffering from systemic candidiasis.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	8
Infants and toddlers (28 days-23 months)	27
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:

Infant participants with Systemic Candidiasis and/or Candida Meningitis were enrolled in this study.

Pre-assignment

Screening details:

Eligible participants who met inclusion criteria and none of the exclusion criteria were enrolled. A total of 35 participants were enrolled in this study.

Period 1

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

Arms

Arm title	Micafungin

Arm description:

Participants received micafungin 8 mg/kg per day via intravenous infusion for approximately 1 hour. Micafungin was administered for a minimum of 14 days until 1 of the following conditions applied: •Negative results (absence of Candida growth) from at least 2 consecutive blood cultures and/or resolution of clinical and laboratory symptoms and reduction of mannan antigen blood level (< 125 pg/mL) were obtained. •In case of meningitis, hydrocephalus and external ventricular derivation, negative results (absence of Candida growth) from at least 2 consecutive cerebral spinal fluid (CSF) cultures associated with resolution of clinical and laboratory symptoms. •Interruption (including addition or switch to another antifungal agent or dosage change of micafungin) due to demonstration of therapy failure.

Arm type	Experimental
Investigational medicinal product name	Micafungin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received micafungin 8 mg/kg per day via intravenous infusion for approximately 1 hour.

Number of subjects in period 1	Micafungin
Started	35
Treated	35
Completed	20
Not completed	15
Death	3
Miscellaneous	4
Infection not confirmed	4
Lack of efficacy	4

Baseline characteristics

Reporting groups	
Reporting group title	Micafungin
Reporting group description:	
Participants received micafungin 8 mg/kg per day via intravenous infusion for approximately 1 hour. Micafungin was administered for a minimum of 14 days until 1 of the following conditions applied: •Negative results (absence of Candida growth) from at least 2 consecutive blood cultures and/or resolution of clinical and laboratory symptoms and reduction of mannan antigen blood level (< 125 pg/mL) were obtained. •In case of meningitis, hydrocephalus and external ventricular derivation, negative results (absence of Candida growth) from at least 2 consecutive cerebral spinal fluid (CSF) cultures associated with resolution of clinical and laboratory symptoms. •Interruption (including addition or switch to another antifungal agent or dosage change of micafungin) due to demonstration of therapy failure.	

Reporting group values	Micafungin	Total	
Number of subjects	35	35	
Age categorical Units: Subjects			
Age continuous Units: months arithmetic mean standard deviation	 2.53 ± 2.11	 -	
Gender categorical Units:			
Male	20	20	
Female	15	15	
Race Units: Subjects			
Caucasian	32	32	
Black	2	2	
Other	1	1	

End points

End points reporting groups

Reporting group title	Micafungin

Reporting group description:

Participants received micafungin 8 mg/kg per day via intravenous infusion for approximately 1 hour. Micafungin was administered for a minimum of 14 days until 1 of the following conditions applied: •Negative results (absence of Candida growth) from at least 2 consecutive blood cultures and/or resolution of clinical and laboratory symptoms and reduction of mannan antigen blood level (< 125 pg/mL) were obtained. •In case of meningitis, hydrocephalus and external ventricular derivation, negative results (absence of Candida growth) from at least 2 consecutive cerebral spinal fluid (CSF) cultures associated with resolution of clinical and laboratory symptoms. •Interruption (including addition or switch to another antifungal agent or dosage change of micafungin) due to demonstration of therapy failure.

Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF consisted of all enrolled (intent to treat [ITT]) participants who had received at least 1 dose of study drug.

Primary: Concentration of Micafungin in Blood

End point title	Concentration of Micafungin in Blood[1]

End point description:

Concentration was determined from the PK blood samples collected via capillary micro-method (draws from the heel). The analysis population consisted of the pharmacokinetic analysis set (PKAS) which was defined as a subset of the SAF who had at least one blood draw.

End point type	Primary

End point timeframe:

Predose and after 1, 3, and 8 hours post-dose on one of treatment days from Day 3 to Day 10

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: All variables were presented using descriptive statistics only.

End point values	Micafungin			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Pre-dose	5.702 (± 2.685)			
1 hour post-dose	17.233 (± 6.296)			
3 hours post-dose	15.591 (± 5.988)			
8 hours post-dose	10.273 (± 3.346)			

Statistical analyses

No statistical analyses for this end point

Primary: Concentration of Micafungin in CSF

End point title	Concentration of Micafungin in CSF[2]

End point description:

Concentration was to be determined from the CSF samples collected. The analysis population consisted of the SAF (only participants that had CSF samples collected). Data for concentration of micafungin in CSF was not evaluable due to insufficient number of participants with CSF samples collected. Data not evaluable denoted as "99999."

End point type	Primary

End point timeframe:

Predose and after 1, 3, and 8 hours post-dose on one of treatment days from Day 3 to Day 10

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: All variables were presented using descriptive statistics only.

End point values	Micafungin			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: mg/mL				
arithmetic mean (standard deviation)				
Pre-dose	99999 (± 99999)			
1 hour post-dose	99999 (± 99999)			
3 hours post-dose	99999 (± 99999)			
8 hours post-dose	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with A Response at End of Treatment (EOT) - Success of Therapy (SOT)

End point title	Percentage of Participants with A Response at End of Treatment (EOT) - Success of Therapy (SOT)

End point description:

For systemic candidiasis (SC) participants, SOT was determined by survival associated with negative Candida test results of 2 consecutive blood cultures, completed at start of treatment, or resolution of clinical & laboratory symptoms together with reduction of mannan antigen blood level (MABL) (<125 pg/ml). For Candida meningitis (CM), SOT was determined by survival associated with negative Candida test results of at least 2 consecutive CSF cultures, completed at start of treatment and resolution of clinical & lab symptoms. For hydrocephalus due to Candida infection (CI) and/or external ventricular derivation (EVD), SOT was determined by survival associated with negative Candida test results of at least 2 consecutive CSF cultures, completed at start of treatment. The analysis population consisted of the SAF (only participants that completed 14 days of treatment), 20 participants completed treatment and 16 had SOT.

End point type	Secondary

End point timeframe:

Up to day 14

End point values	Micafungin			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percentage of participants				
number (confidence interval 95%)				
Success	80 (56.34 to 94.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with A Response at EOT - Failure of Therapy (FOT)

End point title	Percentage of Participants with A Response at EOT - Failure of Therapy (FOT)

End point description:

For SC participants, FOT was determined by death due to Candida sepsis, by confirmation of persistence of positive Candida test results from 1 blood culture completed by need to add/switch to another antifungal agent (AA) and/or change of micafungin dose for resolution of infection at any time or by the persistence of Candida colonization in different indicated sites associated with persistence of clinical & lab symptoms & with high (MABL) (≥ 125 pg/ml). For CM, FOT was determined by death due to CM, by persistence of CI from confirmation of positive CSF culture or by need to add/switch to another AA or dose change of micafungin for resolution of CI at any time. For hydrocephalus due to CI and/or EVD, FOT was determined by death due to CI, by need to add/switch to another AA or dose change of micafungin for resolution of CI at any time or by persistence of CI as from confirmation of positive CSF culture. SAF (those that completed 14 days of treatment (20)), 4 had FOT.

End point type	Secondary

End point timeframe:

Up to day 14

End point values	Micafungin			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percentage of participants				
number (not applicable)				
Failure	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a participant administered a study drug or who had undergone study procedures which did not necessarily have a causal relationship with this treatment. This included abnormal laboratory tests, vital signs, electrocardiogram data or physical examinations that were defined as AEs if the abnormality induced clinical signs or symptoms, required active intervention, interruption or discontinuation of study drug or was clinically significant in the investigator's opinion. The following standard with 3 grades was used to measure the severity of AEs, including abnormal clinical laboratory values: • Mild: No disruption of normal daily activities • Moderate: Affected normal daily activities • Severe: Inability to perform daily activities. A treatment-emergent adverse event (TEAE) was defined as an AE observed after starting administration of the test drug/comparative drug. The analysis population consisted of the SAF.

End point type	Secondary

End point timeframe:

From the first dose of study drug administration up 72 hours after the last dose, up to 17 days.

End point values	Micafungin			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: participants				
Any TEAE	31			
Drug-related TEAEs	1			
TEAE with Unknown Relationship to Study Drug	15			
Serious TEAEs	12			
Drug-related Serious TEAEs	0			
Serious TEAEs with Unk. Relationship to Study Drug	3			
TEAEs Leading to Death	3			
Drug-related TEAEs Leading to Death	0			
TEAEs Leading to Death - Unk. Rel. to Study Drug	0			
TEAEs Leading to Withdrawal of Treatment (Tx)	0			
Drug-Related TEAE Leading to Withdrawal of Tx	0			
TEAE Leading to Wdl. of Tx Unk. Rel. to Study Drug	0			
Death	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of Concentration

End point title	Comparison of Concentration

End point description:

Concentration was determined from the PK blood samples collected via both capillary micro-method (draws from the heel) and venous methods. The analysis population consisted of the SAF (only participants where blood was withdrawn by both capillary and venous methods), 8 participants had blood withdrawn by both methods. N = number of participants.

End point type	Secondary

End point timeframe:

Predose and after 1, 3, and 8 hours post-dose on one of treatment days from Day 3 to Day 10

End point values	Micafungin			
Subject group type	Reporting group			
Number of subjects analysed	8[3]			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Capillary - Pre-dose	6.179 (± 2.864)			
Capillary - 1 hour post-dose	19.196 (± 5.659)			
Capillary - 3 hours post-dose	16.935 (± 4.075)			
Capillary - 8 hours post-dose	11.834 (± 2.433)			
Venous - Pre-dose	6.431 (± 2.841)			
Venous - 1 hour post-dose	22.390 (± 4.972)			
Venous - 3 hours post-dose	19.000 (± 3.945)			
Venous - 8 hours post-dose	12.994 (± 2.765)			

Notes:

[3] - For venous 1, 3 and 8 hours post-dose, n=7.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first dose of study drug administration up 72 hours after the last dose, up to 17 days.	
Adverse event reporting additional description:	
The total number of deaths (all causes) includes deaths reported after the time frame above.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Micafungin
Reporting group description:	
Participants received micafungin 8 mg/kg per day via intravenous infusion for approximately 1 hour.	

Serious adverse events	Micafungin		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 35 (34.29%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	3		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			

subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anuria			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Candida sepsis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Klebsiella sepsis			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Septic shock			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		

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

Non-serious adverse events	Micafungin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 35 (71.43%)		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
C-reactive protein increased			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 35 (25.71%)		
occurrences (all)	11		
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Blood and lymphatic system disorders			

Leukopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2 3 / 35 (8.57%) 3		
General disorders and administration site conditions Oedema subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Hepatobiliary disorders Cholestasis subjects affected / exposed occurrences (all) Hypertransaminasaemia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3 2 / 35 (5.71%) 2		
Infections and infestations Sepsis subjects affected / exposed occurrences (all) Urinary tract infection bacterial subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2 2 / 35 (5.71%) 2		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2 3 / 35 (8.57%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2015	The changes include: ● Changed the cutoff for positive mannan antigen test results from 250 to 125 pg/mL ● Specified that absence of Candida growth in case of Candida meningitis, hydrocephalus due to Candida infection and/or external ventricular derivation could be based on negative results from 2 instead of 3 consecutive CSF cultures ● Changed the age of patients to be enrolled from 90 to 180 days and specified the age calculation based on gestational age. ● Specified that at least 4 neonates with Candida meningitis, hydrocephalus due to Candida infection and/or external ventricular derivation were to be enrolled ● Updated the exclusion criteria ● Allowed patient to start study drug administration as soon as possible after screening rather than the day of screening ● Added anthropometric parameters at birth as a screening/baseline evaluation
13 September 2017	The changes include: ● Updated contact information of sponsor and contract research organization ● Clarified that neonates with Candida meningitis, hydrocephalus due to Candida infection and/or external ventricular derivation would only be included if available during the enrollment period ● Added in vitro susceptibility testing of the collected Candida spp isolates to determine the MIC for micafungin ● Extended the trial end date ● Updated the information on labeling of primary and secondary packages and syringes ● Updated the information on the reporting of SAEs

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.

Participants were re-consented under Astellas sponsorship, the last informed consent (ICF) was collected on 10APR2018, this is considered the global end of trial date.

Notes: