17 December 2015
EMA/CHMP/804861/2015
Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Mycamine

micafungin

Procedure no: EMEA/H/C/000734/P46/038

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

On 1st of October 2015, the MAH submitted a completed paediatric study for micafungin, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the Follow-up information Art 46 paediatric study (P46-038) CSR 9463-CL-2303.

A short critical expert overview has also been provided.

Scientific discussion

Information on the development program

The MAH stated that 'Multicenter, blinded, randomized-controlled trial comparing efficacy and safety of micafungin to conventional amphotericin B (CAB) in infants < 4 months of age with Invasive candidiasis (IC). Study number 9463-CL-2303' is a stand-alone study.

Information on the pharmaceutical formulation used in the study

Test Product: Micafungin was manufactured by Astellas Pharma, Inc., Tokyo, Japan, and was supplied by the Sponsor or its designee.

Micafungin was packaged in a glass vial covered with a light-protective film. Each vial contained 50 mg of lyophilized micafungin and 200 mg lactose.

Each vial and outer box bore a label conforming to regulatory guidelines, which identified the contents as an investigational drug.

Reference Product: CAB was to be supplied by the Sponsor or its designee. CAB was packaged in glass vials containing a sterile, lyophilized cake providing 50 mg of amphotericin B and 41 mg of sodium desoxycholate buffered with 20.2 mg of sodium phosphates.

Clinical aspects

1. Introduction

The MAH submitted a final clinical study report for:

- S**tudy number 9463-CL-2303:**

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

2. Clinical study

Study number 9463-CL-2303:
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

Description

S**tudy 9463-CL-2303** was 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. The centers of this multinational study were located Africa (South Africa), Asia Pacific (Philippines, Taiwan), Europe (Bulgaria, Croatia, Greece, Hungary, Romania and Ukraine), Latin America (Argentina, Brazil, Chile, Colombia, Mexico and Peru), Middle East (Israel and Turkey) and North America (Canada and United States).

Study Initiation Date (Date of First Enrollment) was 23 Feb 2013 and Completion Date (Date of Last Evaluation) was 15 Dec 2014.

Note:

GLP Compliance has been stated by the MAH.

Methods

- Objectives
  - The primary objective was to evaluate the efficacy and safety of micafungin in comparison to amphotericin B deoxycholate (**CAB**) in the treatment of proven neonatal candidiasis.
  - The secondary objective was to further evaluate the pharmacokinetics of micafungin, as well as CAB, in this subject population.
- Study design

This was a phase 3, randomized (2:1) multi-center, double-blind, parallel group, non-inferiority study comparing the safety, efficacy and pharmacokinetics of micafungin to that of CAB as a treatment for candidiasis in neonates and young infants.

- Study population /Sample size

Main inclusion criteria:

- infant must have been greater than 48 h of life up to day of life 120 at the time of culture acquisition, had a diagnosis of invasive candidiasis (IC) by either proven candidemia, proven candiduria, proven *C.* meningitis, or C*andida* other focus.
- infant must have had sufficient venous access to permit administration of study medication and monitoring of safety variables.
- IRB-/IEC-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must have been obtained from legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable) and subject's parent or legal guardian must have agreed not to allow subject to participate in another study with another investigational drug while on treatment.

Main exclusion criteria were:

- Infant with any history of a hypersensitivity or severe vasomotor reaction to any echinocandin or systemic CAB product.
- Infant who has received more than 48 h of systemic antifungal therapy prior to the first dose of study drug for treatment of the current *Candida* infection. Cumulative doses were not to exceed 2 mg/kg of CAB. For systemic antifungal therapy not specifically stated here, infants with more than 2 therapeutic daily doses within the 48 h prior to the first dose of study drug were not eligible.
- Infant who had a breakthrough systemic fungal infection while receiving a CAB product or an echinocandin as prophylaxis. *NB: Infants with a breakthrough fungal infection while receiving azole prophylaxis were eligible for enrollment.*
- Infant who has failed prior systemic antifungal therapy for this episode of invasive candidiasis, including recurrence of the same *Candida* infection within 2 weeks of completing systemic antifungal therapy.
- Infant with a concomitant medical condition, whose participation, in the opinion of the Investigator and/or medical advisor, may have created an unacceptable additional risk.
- Infant previously enrolled in this study.
- Infant who was co-infected with a non-*Candida* fungal organism
- Infant whose positive yeast cultures were solely from an indwelling bladder catheter **(unless obtained at the time the indwelling catheter was placed)** or sputum

Number of Subjects (Planned, Enrolled and Analyzed):

Although 225 infants were planned to be randomized to receive either micafungin or CAB, the study was terminated early due to challenges with enrollment. Thus, only 30 subjects were treated (20 with micafungin and 10 with CAB) and evaluated, which is below the fully powered sample size.

For this circumstance, the statistical inference based on non-inferiority hypothesis test described was not applicable. Thus, there was no intention to conduct statistical comparisons and inferences for this study. Where indicated, some key efficacy endpoints were descriptively summarized by treatment group, with 95% exact confident intervals for their point estimates. Infants with isolated proven candiduria were limited to no more than 20% of the total subjects enrolled.

The full analysis set (**FAS)** was defined as all randomized infants who were administered any amount of study drug. Infants were assigned to the treatment arm based on randomization regardless of actual treatment received.

In the event that an infant was randomized without receiving any study drug, they were excluded from FAS.

FAS was the primary analysis set for efficacy analyses and included all 30 evaluable subjects.

- Treatments

All infants randomized to micafungin received 10 mg/kg per day. All infants randomized to CAB received 1 mg/kg per day.

Study drug therapy was administered for a minimum of 21 days to a maximum of 28 days for infants without end-organ dissemination. Infants with end-organ dissemination may have received a maximum of 42 days of study drug therapy

CHMP assessment:
The administered dose of micafungin of **10 mg/kg** used in this study does not correspond with the proven dose. According to the SmPC the recommended dose for infant for the treatment of candidiasis is as follows:

Use in children (including neonates) and adolescents < 16 years of age

	Body weight > 40 kg	Body weight ≤ 40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*

*If the patient's response is inadequate, e.g. persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients weighing ≤ 40 kg.

- Outcomes/endpoints

Efficacy

The primary endpoint for the study was fungal free survival at one week after the last dose of study drug.

Mycological Response

Mycological response was assessed during screening, at one week (± 1 day) after the last dose of study drug and at the end of study visit (ESV). It was recommended that a minimum of 0.5 mL of blood was drawn for culture.

Mycological response assessments were based on the following definitions:

- **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. If culture result did not show fungal growth within 72 h of collection, for purposes of determining eradication, the culture may have been considered negative.

- **Persistence**: Continued isolation or histological documentation from a normally sterile site. Cultures from blood, urine and CSF should have been obtained as described below. All other procedures, including histology, cytology, and non-culture based diagnostic procedures, were performed and documented as clinically appropriate to assess the status of the fungal infection.

- If baseline CSF culture was positive for *Candida*, a repeat lumbar puncture should have been completed every 4 to 7 days until a negative CSF culture was documented.

- If the baseline urine culture was positive for *Candida*, a repeat urine fungal culture was obtained every 48 h until 2 negative urine cultures separated by at least 24 h were documented. These repeat samples for culture may have been taken via bag specimen.

- If the baseline blood culture was positive for *Candida*, a repeat blood fungal culture was obtained every 48 h until 2 negative blood cultures separated by at least 24 h were documented. For infants who did not have eradication at 1 week following the last dose of study drug, mycological response

was assessed at the 30 day post-treatment ESV, if clinically indicated. All infants who had eradication at the ESV were evaluated for recurrence of the baseline fungal infection throughout the 30 day post-treatment period. Emergence of fungal infections was evaluated throughout the study for all infants.

Clinical Response

Clinical response was assessed during screening, weekly while on study drug therapy (±1 day), at 1 week (±1 day) after the last dose of study drug and at the ESV. Clinical response assessments were based on the following definitions:

- **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.

Assessment of End-organ Dissemination

Following positive cultures from normally sterile sites (i.e. blood, urine or CSF) for *Candida,* end-organ dissemination should have been assessed and evaluated as follows.

Abdominal Ultrasound and/or Computed Tomography

1. Renal ultrasonography consistent with fungal balls (non-shadowing echogenic focus) and/or renal parenchymal infiltration (enlarged kidneys with diffusely increased echogenicity).
2. Liver or splenic ultrasonography or computed tomography (CT) consistent with lesions having a uniformly decreased attenuation or which showed a central high attenuation dot or well-defined lucencies.
3. Abdominal imaging consistent with abdominal abscess.

Echocardiogram

Echocardiogram consistent with valvular vegetation or mural thrombus

Head Imaging

Head ultrasound, magnetic resonance imaging (MRI) or CT scan with abnormalities consistent with fungal disease

Ophthalmoscopy

Characteristic ocular lesions were identified by indirect ophthalmoscopy. Lesions consistent with *Candida* endophthalmitis included multiple or single, unilateral or bilateral, yellow-white, elevated lesions with indistinct borders located on the posterior fundus or other characteristic presentation. 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 in the comments section of the eCRF.

- **Stabilization**: Minor improvement or no change in size, number or density of identified lesions.
- **Worsening**: Increase in size or number of identified lesions.

In the neonatal population, antifungal therapy was generally continued for the recommended period of time following the conversion at the assessable culture site(s). Imaging, because of slow resolution of lesions, has not been useful in guiding duration of medical management [Benjamin et al, 1999].

Assessment of Emergent/Recurrent Fungal Infections

If the infant developed a systemic fungal infection during the treatment or post-treatment period, other than the infection recorded at baseline, the infection was recorded in the eCRF.

Emergent fungal infection

- An invasive fungal infection which was detected at any time during the study that was a non-*Candida* organism, or
- An invasive fungal infection which was detected during the treatment or post-treatment period with a *Candida* species identified other than those detected at baseline. If this occurred within 96 h of the first dose of study drug, the infection was considered part of the final diagnosis of enrolling infection and not an emergent infection.

Recurrent fungal infection

A recurrent infection was 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.

Pharmacokinetics:

Population pharmacokinetic methods were used to develop pharmacokinetic models in this subject population using the plasma micafungin and CAB concentration data from this study. An investigation was made of the relationship between model parameters and select covariates, such as

demographic factors (e.g., weight) and laboratory parameters' values. An analysis was made of the relationship between drug exposure and efficacy and/or safety response. The relationship between plasma and CSF micafungin concentrations and the relationship between plasma and CSF CAB concentrations was examined. Details will be described in a population pharmacokinetic analysis plan. Plasma and CSF micafungin and CAB concentration data were listed.

Safety:

Clinical safety data (including treatment-emergent adverse events and clinical laboratory evaluations) were summarized using descriptive statistics or frequency distributions, as appropriate, for the Safety Analysis Set. Hepatic events, renal events, hemolytic events, histamine-release/allergic-type reactions, injection site reactions and events infusion-related reactions were assessed as events of interest.

- Statistical Methods

For continuous variables, descriptive statistics included the number of subjects (n), mean, SD, median, minimum and maximum. When needed, the use of other percentiles (e.g.10%, 25%, 75% and 90%) were mentioned in the relevant section.

Summaries based on FAS, modified FAS (MFAS) and per protocol set (PPS) (e.g. disposition, baseline and efficacy data) were presented by planned treatment group, unless specifically stated otherwise. Safety analysis and other summaries based on safety analysis set (SAF) were presented by actual treatment received.

The point estimates for fungal free survival and its exact 95% CI were presented by treatment. FAS was the primary efficacy analysis population.

All secondary efficacy endpoints except the time to event variables were presented descriptively by treatment group. The point estimate and its exact 95% confidence interval were presented by treatment group for overall emergent fungal infection, positive clinical response at the end of treatment and one week post the treatment, and eradication at the end of treatment and 1 week post end of treatment.

The summary of clinical response was presented as positive and non-positive responses. The positive response was further categorized as complete and partial response; while non-positive responses will be further categorized as stabilization, progression, and missing.

The summary of mycological response data were presented as eradication and noneradication.

Non-eradication was further subcategorized as persistence and missing. K-M curves by treatment group for time to positive clinical response and time to eradication was generated.

Model parameters such as clearance and volume of distribution used the pharmacokinetic analysis set (PKAS) analysis set.

All analysis of safety will be presented by treatment group for SAF, unless specified otherwise.

Results

- Recruitment/ Number analysed

In total, 31 subjects were screened of which 30 were randomized [Table 1]. One subject, a 33-day old white female, was identified as a screening failure for not meeting the inclusion/exclusion criteria.

Table 1 Subject Disposition and Analysis Sets

Analysis Set	Micafungin(n = 20)	CAB (n = 10)	Total (n = 30)
Randomized	20 (100.0%)	10 (10.0%)	30 (100.0%)
Safety analysis set†	20 (100.0%)	10 (10.0%)	30 (100.0%)
Full Analysis Set‡	20 (100.0%)	10 (10.0%)	30 (100.0%)
Modified Full Analysis Set§	16 (80.0%)	8 (80.0%)	24 (80.0%)
Per Protocol Set¶	8 (40.0%)	3 (30.0%)	11 (36.7%)
Pharmacokinetic Analysis Set††	12 (60.0%)	0	12 (40.0%)

CAB: conventional amphotericin B (amphotericin B deoxycholate)

† All randomized subjects who were administered any amount of study drug. Subjects were assigned to the treatment arm based on actual treatment received.

‡ All randomized subjects that were administered any amount of study drug. Subjects were assigned to the treatment arm based on randomization.

§ A subset of the Full Analysis Set who have confirmed invasive candidiasis or candidemia at baseline.

¶ All randomized, confirmed invasive candidiasis or candidemia at baseline subjects with at least 5 doses of study drug and no major protocol deviations.

†† All subjects receiving 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.

- Baseline data

Demographic and baseline characteristics of all evaluable sets (FAS, SAF, MFAS and PPS) were generally comparable. Demographic and baseline characteristics of FAS are presented in [Table 2].

Table 2 Summary of Demographics and Baseline Characteristics for Subjects in the Full Analysis Set

Parameter Category/ Statistics	Micafungin (n = 20)	CAB (n = 10)	Total (n = 30)
Sex, n (%)			
Male	8 (40.0)	6 (60.0)	14 (46.7)
Female	12 (60.0)	4 (40.0)	16 (53.3)
Race, n (%)			
White	18 (90.0)	9 (90.0)	27 (90.0)
Black or African American	0	1 (10.0)	1 (3.3)
Asian	1 (5.0)	0	1 (3.3)
Other	1 (5.0)	0	1 (3.3)
Ethnicity, n (%)			
Hispanic or Latino	3 (15.0)	3 (30.0)	6 (20.0)
Not Hispanic or Latino	4 (20.0)	3 (30.0)	7 (23.3)
Missing	13 (65.0)	4 (40.0)	17 (56.7)
Age, Group			
≤ 4 weeks	15 (75.0)	10 (100.0)	25 (83.3)
More than 4 weeks to 4 Months	5 (25.0)	0	5 (16.7)
Gestational Age			
< 27 weeks	3 (15.0)	2 (20.0)	5 (16.7)
≥ 27 weeks	17 (85.)	8 (80.0)	25 (83.3)
Region			
North America/Europe	15 (75.0)	9 (90.0)	24 (80.0)
Latin America/Mexico	4 (20.0)	1 (10.0)	5 (16.7)
Other	1 (5.0)	0	1 (3.3)
Age (Days)			
Mean (SD)	30.2 (27.99)	16.9 (5.13)	25.7 (23.70)
Median Min-	17.5	15.5	17.0
Max	9-117	12-26	9-117
Birth Weight (g)			
Mean (SD)	1807.3 (879.03)	2171.4 (1008.79)	1928.6 (923.34)
Median	1605.5	2462.5	1952.5
Min - Max	650-3100	630-3300	630-3300

CAB: conventional amphotericin B (amphotericin B deoxycholate)
All randomized infants who are administered any amount of study drug. (Full Analysis Set)

- Efficacy results

Fungal Free Survival One Week Post Study Drug

Primary analysis was conducted using FAS**.** The primary endpoint of fungal free survival at 1 week following the last dose of study drug as assessed by the DRP was the primary endpoint achieved by 12 (60.0%) and 7 (70.0%) subjects in micafungin and CAB treatment arms, respectively [Table 3].

Table 3 Fungal Free Survival (DRP) One Week After the Last Dose of Study Drug Full Analysis Set

Category/Statistic	Micafungin (n = 20)	CAB (n = 10)
Success	12 (60.0%)	7 (70.0%)
95% CI	(36.1, 80.9)	(34.8, 93.3)
Failure	8 (40.0%)	3 (30.0%)

CAB: conventional amphotericin B (amphotericin B deoxycholate); DRP: Data Review Panel

Secondary Efficacy Endpoints

Secondary endpoints assessed in this study included time to mycological clearance of invasive candidiasis, fungal free survival and status of follow-up imaging and exams (improved, stable, worse) in infants with end-organ dissemination as well as clinical (complete, partial, stabilization, progression) and mycological responses at end of study drug therapy and one week after last dose of study drug, overall incidence of emergent and recurrent fungal infections through the end of study and time to positive clinical response (complete or partial).

The Investigator's assessment of fungal free survival among micafungin-treated subjects was in agreement with that of the **DRP** (Data Review Panel).

Per DRP, 11 (61.1%) micafungin-treated infants that experienced clinical signs and symptoms at baseline achieved a positive (either complete or partial) response at end of study drug therapy and one week after the last dose of study drug. Of the 7 (38.9%) micafungin-treated subjects with who did not have a positive response, 1 (5.6%) was stable at each of these evaluable timepoints, and 3 (16.7%) subjects progressed at end of study drug therapy and 1 (5.6%) subject progressed one week after the last dose of study drug. Details for subjects who did not have a positive response were missing for 3 (16.7%) micafungin-treated subjects at end of study drug therapy and for 5 (27.8%) subjects a week after the last dose of study drug.

Of the subjects treated with CAB, 7 (70.0%) subjects who had baseline clinical signs and symptoms achieved a positive (complete) response at end of study drug therapy and one week after the last dose of study drug while 1 (10.0%) was stable and 2 (20.0%) subjects progressed at each of these timepoints per DRP.

Of note, Investigator's assessment of clinical response was similar to that of the DRP.

Eleven (55.0%) and 8 (80.0%) of micafungin- and CAB-treated subjects, respectively achieved eradication at end of study drug therapy and 1 week after the last dose of study drug. Of the 9 (45.0%) micafungin-treated subjects at both timepoints with mycological failure, infection persisted in 2 (10.0%) and was not assessed in 7 (35.0%) individuals. For CAB-treated subjects with mycological failure, all exhibited persistence at both time points.

A total of 7 micafungin-treated subjects, but no CAB-treated subjects, were assessed by the DRC as "not assessed" one week after the last dose. Of these subjects, 3 subjects (57020004, 57020008, 90010028) had one post-baseline negative blood culture, but a follow-up blood culture to verify eradication was not obtained, for 2 other subjects (30030005, 11020016), no post baseline samples were obtained, and for 2 more subjects (36060013, 36060021), blood culture samples continued to be positive. Of note, Subjects 57020004 and 36060013 showed a complete clinical response, and Subjects 90010028 and 36060021 showed progression of clinical sign and symptoms one week after last dose.

The Investigator's assessments were generally similar to those of the DRP.

Recurrent infections were not noted by the Investigator or the DRP (either through the end of study, within one week of EOT or after one week of EOT) in the micafungin-treated infants. Recurrent fungal infection was noted by the DRP and the Investigator in 1 CAB-treated infant (Subject 10220015) through end of study and after the one week post-end of treatment visit. *C. glabrata* was identified as the infection-causing species with the site of recurrent infection in this subject being localized to the urinary tract. The CAB minimum inhibitory concentration (MIC) value against *C. glabrata* organism at screening by Clinical and Laboratory Standards Institute and European Committee on Antimicrobial

Susceptibility Testing methods was 1 μg/mL and 0.25 μg/mL, respectively. One week post end treatment, this subject was alive with no alternative antifungal therapy for treatment. The infection was eradicated one week after the last dose of study drug but was recurrent at end of study.

Per DRP, the 25th percentile of time to mycological clearance among the infants in both treatment groups was 3.0 days.

Per DRP, fungal free survival in infants with end-organ dissemination was assessed in 7 and 3 subjects on micafungin and CAB, respectively. Of these, 3 (42.9%) micafungin-treated subjects and 1(33.3%) CAB-treated subject achieved fungal free survival at both end of study drug therapy and 1 week after the last dose of study drug. Of note, status of success or failure at end of study drug therapy was missing for 3 (42.9%) subjects on micafungin.

Of the micafungin-treated subjects with end-organ assessments, improvement was noted in 4 (57.1%) subjects, with an additional 1 (14.3%) subject each either being stable, worse or not assessed at follow-up per DRP. In contrast, 1 (33.3%) CAB-treated subject with end-organ assessment was noted as having improved and 2 (66.7%) subjects worsened.

Fungal isolates collected from both treatment groups were tested for susceptibility with various antifungal compounds and details can be found in. For micafungin-treated subjects, MIC values for 23 baseline isolates met the susceptible criteria (according to CLSI criteria) for all isolates from subjects in this treatment group. For the CAB-treated subjects, all of the 13 baseline isolates tested were below the epidemiological cut-off values for CAB as described by Pfaller and colleagues [Pfaller et al, 2012]. No clinical breakpoints have been established for CAB and any *Candida* species.

Time to positive clinical response (complete or partial) based on DRP assessment was not evaluated due to insufficient data.

- Safety results

Overall, 18 (90.0%) and 9 (90.0%) micafungin- and CAB-treated infants, respectively, experienced at least a single treatment-emergent adverse event (TEAE). The proportion of micafungin- and CAB-treated subjects experiencing individual AEs were similar [Table 4].

The majority of TEAEs noted in this study in either treatment arm were considered to be study drug-related by the Investigator.

Table 4 Incidence of Treatment-Emergent Adverse Events

MedDRA v12.0 System Organ Class Preferred Term	**Micafungin N = 20 n**	**CAB N = 10 n**
Overall	**18 (90.0)**	**9 (90.0)**
Blood and Lymphatic System Disorders	**10 (50.0)**	**6 (60.0)**
Anemia	9 (45.0)	3 (30.0)
Thrombocytopenia	2 (10.0)	3 (30.0)
Neutropenia	3 (15.0)	0
Anaemia neonatal	1 (5.0)	1 (10.0)
Eosinophilia	0	1 (10.0)
Leukocytosis	0	1 (10.0)
Infections and Infestations	**11 (55.0)**	**3 (30.0)**
Sepsis	1 (5.0)	1 (10.0)
Sepsis neonatal	0	2 (20.0)

Septic Shock	2 (10.0)	0
Staphylococcal infection	2 (10.0)	0
Urinary tract infection bacterial	2 (10.0)	0
Bacterial sepsis	1 (5.0)	0
Endocarditis	1 (5.0)	0
Neonatal infection	1 (5.0)	0
Pneumonia	1 (5.0)	0
Staphylococcal sepsis	1 (5.0)	0
General disorders and Administration Site Conditions	**3**	**5 (50.0)**
Pyrexia	1 (5.0)	2 (20.0)
Hypothermia	1 (5.0)	1 (10.0)
Infusion related reaction	0	1 (10.0)
Infusion site extravasation	0	1 (10.0)
Infusion site rash	1 (5.0)	0
Investigations	**5**	**3 (30.0)**
Aspartate aminotransferase increased	1 (5.0)	1 (10.0)
Liver function test abnormal	2 (10.0)	0
Activated partial thromboplastin time prolonged	0	1 (10.0)
Alanine aminotransferase increased	1 (5.0)	0
Antithrombin III decreased	0	1 (10.0)
Bacteria blood identified	1 (5.0)	0
Blood bilirubin abnormal	1 (5.0)	0
Blood bilirubin increased	1 (5.0)	0
Blood urea increased	1 (5.0)	0
C-reactive protein increased	0	1 (10.0)
γ-glutamyltransferase increased	0	1 (10.0)
Hepatic enzyme abnormal	1 (5.0)	0
Hepatic enzyme increased	0	1 (10.0)
Neutrophil count increased	0	1 (10.0)
Oxygen consumption increased	0	1 (10.0)
Serum ferritin increased	0	1 (10.0)
Vascular Disorders	**3**	**3 (30.0)**
Hypertension	1 (5.0)	1 (10.0)
Cardiovascular insufficiency	1 (5.0)	0
Hypotension	0	1 (10.0)
Phlebitis	1 (5.0)	0
Thrombophlebitis	0	1 (10.0)
Metabolism and Nutrition Disorders	**1 (5.0)**	**2 (20.0)**
Hyperglycaemia	0	1 (10.0)
Hyperphosphataemia	0	1 (10.0)
Hypoalbuminaemia	1 (5.0)	0
Hypochloraemia	0	1 (10.0)
Hyponatraemia	0	1 (10.0)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**3 (30.0)**
Atelectasis	0	1 (10.0)
Hypercapnia	0	1 (10.0)
Obstructive airways disorder	0	1 (10.0)
Skin and Subcutaneous Tissue Disorders	**1 (5.0)**	**2 (20.0)**
Drug eruption	0	2 (20.0)
Dermatitis	1 (5.0)	0
Gastrointestinal Disorders	**1 (5.0)**	**1 (10.0)**
Intestinal perforation	0	1 (10.0)
Vomiting	1 (5.0)	0
Hepatobiliary Disorders	**1 (5.0)**	**1 (10.0)**
Hepatic function abnormal	1 (5.)	0

Hyperbilirubinaemia	0	1 (10.0)
Injury, Poisoning and Procedural Complications	**1 (5.0)**	**1 (10.0)**
Femur fracture	0	1 (10.0)
Medical device complication	1 (5.0)	0
Post procedural haemorrhage	1 (5.0)	0
Nervous System Disorders	**1 (5.0)**	**1 (10.0)**
Intraventricular haemorrhage	1 (5.0)	1 (10.0)
Hydrocephalus	1 (5.0)	0
Renal and Urinary Disorders	**1 (5.0)**	**1 (10.0)**
Oliguria	0	1 (10.0)
Renal failure acute	1 (5.0)	0
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (10.0)**
Osteopenia	0	1 (10.0)
Psychiatric Disorders	**0**	**1 (10.0)**
Agitation	0	1 (10.0)
Reproductive System and Breast Disorders	**0**	**1 (10.0)**
Galactorrhoea	0	1 (10.0)

CAB: conventional amphotericin B (amphotericin B deoxycholate) Number and percentage of subjects (%) are shown.

Within a SOC, subjects may have experienced more than 1 adverse event.

Sorting order: descending frequency for test drug total group by SOC and by PT. In the case of ties, an alphabetical order was applied.

Overall, 12 (60.0%) of micafungin-treated subjects and 7 (70.0%) of CAB-treated subjects experienced at least a single SAE [Table 5]. For one subject with concurrent sepsis (Subject 36060017), elevated LDH was observed concurrently with an event of anemia, potentially indicating a hemolytic nature of the event. The overall rate of individual SAEs among the CAB-treated subjects was comparable to that among the micafungin treated infants. All events of anemia in all subjects and treatment groups resolved. In the micafungin treatment group, anemia was the most common SAE noted experienced by 4 (20.0%) infants; the remaining reported SAEs in this treatment group were experienced by no more than 2 (10.0%) subjects each.

One subject on CAB (10160007) and 3 subjects (36060021, 36060017, 90010028) on micafungin died while on study. Of note, none of the events leading to death were considered to be study-drug related by the Investigator. Of the micafungin-treated subjects who succumbed to death, 1 subject each experienced underlying gastrointestinal necrosis (confirmed on day 31), cardiovascular insufficiency on study day 3 and septic shock on study day 3. Neither cardiovascular insufficiency nor septic shock was considered to be as drug-related TEAEs leading to death by the Investigator.

In total, 9 (45.0%) and 6 (60.0%) micafungin- and CAB-treated subjects discontinued treatment. Five (25.0%) and 3 (30.0%) subjects on micafungin and CAB, respectively, permanently discontinued study drug due to a TEAE. The majority of events among micafungin-treated subjects were considered to be probably related to study drug exposure by the Investigator. None of the events leading to discontinuation among CAB-treated subjects were considered to be study-drug related. No important differences in the proportion of micafungin-treated infants and CAB-treated infants experiencing increases in liver enzyme abnormalities or increases in creatinine were observed.

Table 5 Summary of Serious Treatment-Emergent Adverse Events

MedDRA (v. 12.0) Primary System Organ Class Preferred Term	Number of Subjects (%) Micafungin n = 20	CAB n = 10
Overall	12 (60.0)	7 (70.0)
Infections and Infestations	**4 (20.0)**	**3 (30.0)**
Sepsis	1 (5.0)	1 (10.0)
Sepsis neonatal	0	2 (20.0)
Septic shock	2 (10.0)	0
Bacterial sepsis	1 (5.0)	0
Blood and Lymphatic System Disorders	**4 (20.0)**	**1 (10.0)**
Anaemia	4 (20.0)	1 (10.0)
Vascular Disorders	**1 (5.0)**	**2 (20.0)**
Cardiovascular insufficiency	1 (5.0)	0
Hypertension	0	1 (10.0)
Hypotension	0	1 (10.0)
Investigations	**2 (10.0)**	**0**
Alanine aminotransferase increased	1 (5.0)	0
Aspartate aminotransferase increased	1 (5.0)	0
Blood bilirubin increased	1 (5.0)	0
Liver function test abnormal	1 (5.0)	0
Renal and Urinary Disorders	**1 (5.0)**	**1 (10.0)**
Oliguria	0	1 (10.0)
Renal failure acute	1 (5.0)	0
Gastrointestinal Disorders	**0**	**1 (10.0)**
Intestinal perforation	0	1 (10.0)
General Disorders and Administration Site Conditions	**0**	**1 (10.0)**
Hypothermia	0	1 (10.0)
Nervous System Disorders	**1 (5.0)**	**0**
Hydrocephalus	1 (5.0)	0
Intraventricular haemorrhage	1 (5.0)	0
Respiratory, thoracic and mediastinal disorders	**0**	**1 (10.0)**
Obstructive airways disorder	0	1 (10.0)

CAB: conventional amphotericin B (amphotericin B deoxycholate)
Within a SOC, subjects may experience more than one adverse event.
Sorting Order: Descending frequency for test drug total group by SOC and by PT. In the case of ties, alphabetical order was applied.

Discussion on clinical aspects

The MAH discusses the clinical aspects of this submission and concludes:

The original sample size for this study was 225 infants; however, this study was terminated early due to enrollment challenges. Only 30 subjects were enrolled and received study drug. Therefore, no inferential statistical testing was carried out, and all interpretations of results should be done with caution. No meaningful differences between treatment groups for demographic and baseline characteristics were observed. Seventy-five (75%) micafungin-treated and 100% CAB-treated subjects were less than or equal to 4 weeks of age. Of note, more micafungin-treated infants than CAB-treated infants were infected with C. parapsilosis.

Twelve out of 20 micafungin-treated infants (60%, CI [36, 81]) and 7 out of 10 CAB-treated subjects (70% CI [35, 93]) responded to treatment, as assessed by fungal-free survival at 1 week after the EOT by the DRP. These response rates were confirmed in the MFAS set as well as in the Investigator-assessed analyses. While the point estimates for the percentages of infants responding to treatment

were similar in the micafungin and CAB groups, the confidence intervals were wide due to the small sample size in each arm.

The results observed for the primary endpoint are corroborated by the clinical response rate. Eleven out of 18 micafungin-treated subjects (61% CI [36, 83]) and 7 out of 10 CAB-treated infants (70% CI [35, 93]) showed a clinical response at the EOT and one week thereafter. These numbers were similar regardless of DRP or Investigator assessment. Of note, within the PPS, all infants enrolled in this study with clinical signs and symptoms at baseline achieved a complete clinical response as assessed by the DRP.

Fewer micafungin-treated infants (11/20, 55% CI [32, 77]) than CAB-treated infants (8/10, 80% CI [44.4, 97.5]) achieved a mycological response. It should be noted however, that 7 out of 9 micafungin-treated infants with mycological failure were actually due to mycological response not assessed while all CAB-treated infants with mycological failure exhibited persistence. Of the 7 not assessed in the micafungin arm, 3 of them appeared to have eradicated but were lacking a confirmatory culture.

Among those infants with mycological eradication outcome at the EOT, one infant in the CAB treatment group experienced a recurrent infection. There were no recurrent fungal infections in the micafungin treatment group. One infant in the micafungin treatment group experienced an emergent fungal infection during the treatment period vs none in the CAB-treated group.

Efficacy in the treatment of invasive candidiasis and candidemia was observed in both the micafungin and CAB treatment groups regardless of fungal species, infection site, age, gender, race, gestational age, or geographic region.

A similar proportion of micafungin-treated infants and CAB-treated infants experienced an AE. No differences between groups were observed when individual adverse events were compared. In addition, no differences between groups were observed when SAEs and AEs leading to withdrawal were compared. No differences between groups were observed for AEs of special interest, and no infant experienced an event of hemolytic anemia.

Three infants in the micafungin-treatment group and 1 in the CAB-treatment group died. All deaths were attributable to complications of prematurity or concurrent medical conditions.

No differences between the micafungin- and CAB-treatment groups were observed in the shift analyses of safety labs. Differences in the proportion of micafungin-treated infants and CAB-treated infants experiencing increases in liver enzyme abnormalities or increases in creatinine were not clinically relevant due to concomitant conditions and medications known to affect liver enzyme elevations.

Increases from baseline in serum creatinine were generally similar between groups. No important changes in vital signs were observed.

CHMP overall conclusion and recommendation

Overall conclusion

The CHMP agrees with the overall conclusion by the MAH.

However, although the study was well- designed (no obviously deficiencies could be identified) it should be noted that the number of evaluable patients was too low for an outcome of validated data on efficacy and safety at a dosage of 10 mg/kg for the treatment of neonatal candidiasis. So, the benefit risk ratio is unpredictable.

Recommendation
In our point of view, the authorized application of micafungin should not be changed.

☒ **The PAM is Fulfilled – No regulatory action required.**

However, although P46-038 has now been fulfilled with this submitted MAH's Follow-up information, the comment by **a Member state** should be taken into consideration (*please see below*).

There were the following Member State comments on the Preliminary AR:

MS (Co-Rapp): The MS agrees with the Rapporteur and has no further comments to make.

MS2: The MS agrees with the Rapporteur that the current study does not allow for conclusions regarding the comparative safety of Micafungin vs. Amphotericin B.
However, several publications have pointed towards a higher clearance in premature infants as well as in neonates (See below), and suggest that the current dose recommendations of 2 mg/kg/day are insufficient for children < 4 months of age or for premature infants, in particular if the CNS is involved. The present ESCMID clinical guidelines recommend a dose of 4-10 mg/kg/day – which is higher than currently approved in the SmPC. Considering the concerns of the optimal dose in this age group , irrespective of the present study that failed due to insufficient recruitment, we are of the opinion that further discussion is needed on the appropriateness of the current dose recommendation for infants <4 months in the treatment of neonatal candidiasis.

References

Benjamin DK Jr, Smith PB, Arrieta A, et al. Safety and pharmacokinetics of repeat-dose micafungin in young infants. Clin Pharmacol Ther 2010;87:93–9.
Heresi GP, Gerstmann DR, Reed MD, et al. The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. Pediatr Infect Dis J 2006;25:1110–5. PubMed
Hope, WW. D. Mickiene, V Petraitis, et al. The pharmacokinetics and pharmacodynamics of micafungin in experimental hematogenous candida meningoencephalitis: implications for echinocandin therapy in neonates J Infect Dis, 197 (2008), pp. 163–171
Hope, WW. PB. Smith, A Arrieta, et al. Population pharmacokinetics of micafungin in neonates and young infants Antimicrob Agents Chemother, 54 (2010), pp. 2633–2637
Lawrence C. Ku & P. Brian Smith; Dosing in neonates: special considerations in physiology and trial design; Pediatric Research(2015) 77,2–9doi:10.1038/pr.2014.143
Smith PB, Walsh TJ, Hope W, et al. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. Pediatr Infect Dis J 2009;28:412–5. PubMed
Yanni SB, Smith PB, Benjamin DK Jr, Augustijns PF, Thakker DR, Annaert PP. Higher clearance of micafungin in neonates compared with adults: role of age-dependent micafungin serum binding. Biopharm Drug Dispos 2011;32:222–32.

MS3: As already stated in our comment for procedure II 026 (PGR update) 3rd RSI in July 2015, we would like to take the opportunity of this procedure to reiterate the sensitive issue of dose in premature and neonates.

Indeed, off label use with higher dose level than currently recommended is reported. However, it cannot be denied that such an off label use translates the concerns at the scientific community level that the currently recommended dose might be sub-optimal in those very young children.
This has triggered the present study which could not be conclusive given the limited enrolment. Moreover, this has triggered dedicated investigations within the scientific community with a European institutional multicenter study recently validated through a VHP procedure with higher doses of micafungin than currently approved (10 mg/kg after a loading dose).

Although this study cannot be conclusive the level of response with a 10 mg/kg to some extent further echoes the concern that the lower dose as currently recommended could be suboptimal. Moreover, the safety data with this higher dose do not raise particular concern, notably liver toxicity.

Overall, it is very concerning to consider that very young children could be exposed to sub-optimal dose (given the life threatening nature of the disease). **We consider that the applicant should be requested to further substantiate the dose in premature and neonates by an updated review of the literature and dedicated PK investigations. A post authorisation measure should be set to this purpose.**

CHMP's comment:
We support the opinion of the MS2 and MS3 that the appropriate dosing for infants < 4 months for the treatment of neonatal candidiasis should be discussed.
A respective review has been requested as outcome of the variation EMEA/H/C/000734/II/26 on the RMP finalised in July 2015 and it has been agreed with EMA and Rapporteur to extend the submission of this review by the end of 2015. In this context the MAH has explained within the cover letter for P46-038:

"Astellas is evaluating all neonatal data including the 2303 study results, and the conclusions will be presented separately later this year, applying appropriate submission procedures."

The MAH is therefore reminded to submit the requested review as an outcome of EMEA/H/C/000734/II/26 by the end of 2015 including also a discussion on the adequacy of the actual recommended dose of 2 mg/kg to max 4 mg/kg for the treatment of candidiasis in children <4 months (including neonates and premature infants) in comparison to a dose of > 4 mg/kg (to 10 mg/kg). For this review the pharmacokinetics (incl. metabolism) of micafungin in this age group, the efficacy and in particular the safety should be considered.

Additional clarifications requested

Regarding the need for an optimal dose for children < 4 months (incl. neonates and premature) further clarification on this issue is required and has been already requested as outcome of EMEA/H/C/000734/II/26.
Thus, the MAH is reminded to submit the requested review as outcome of EMEA/H/C/000734/II/26 by the end of 2015 including a discussion on the adequacy of the actual recommended dose of 2 mg/kg to max 4 mg/kg for the treatment of candidiasis in children <4 months (including neonates and premature infants) in comparison to a dose of > 4 mg/kg (to 10 mg/kg). For this review the pharmacokinetics (incl. metabolism) of micafungin in this age group, the efficacy and in particular the safety should be considered.

Annex 1: Line listing of all the studies included in the development program

Clinical studies

Product Name: **Mycamine for Injection** Active substance: **Micafungin**

Study title	Study number	Date of completion	Date of submission of final study report
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	9463-CL-2303	23.02.2013	15.12.2014