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Human Medicines Evaluation 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/P46/040

Note

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

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1. Introduction

On the 9th of January 2019 the MAH submitted a completed paediatric study for Mycamine, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study 9463-CL-6001 is a multicenter uncontrolled study on the pharmacokinetic profile of high-dose micafungin (8 mg/kg) in neonatal and young infant patients until 180 days of age suffering from systemic candidiasis. This study has been performed to gain more insight into the micafungin dose for neonatal and young infant patients.

The Marketing Authorisation of Mycamine in the EU already includes a full paediatric indication, including neonates. The authorized recommended dosing in children younger than 4 months of age is 4 to 10mg/kg body weight. Dosing for patients weighing less than 40 kg is 2 mg/kg/day.

This study was initiated and completed by the Ospedale Pediatrico Bambino Gesu investigators, and Astellas assumed sponsorship after the study had enrolled all but 1 patient. The transfer of sponsorship was approved by the Italian Medicines Agency on 05 Dec 2017. The completion date of this study was 10 April 2018, which was defined as the date for the receipt of the last informed consent form after the patients were re-consented due to the transfer of Sponsorship. Astellas was unable to access the patient data until the last consent was obtained. This led to a delay in the verification and data preparation. The lengthy Sponsorship transfer and data review processes led to longer than typical timelines for completion of the clinical study report, and further to a delay of the submission of this study beyond the 6 months post completion date, which is required as per Article 46 of the Paediatric Regulation (EC) No 1901/2006.

Assessor's comment

The completion date of this study was 10 April 2018, therefore the due date of the article 46 submission was 09 October 2018. However the MAH submitted the data on the 9th of January 2019. The delay was due to the lengthy sponsorship transfer, and therefore difficulties in accessing patient data. The rational for the delay of submission is acceptable.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study 9463-CL-6001 is a stand-alone study.

Micafungin (FK463, Mycamine®) is a member of the echinocandin class of antifungal agents. Micafungin non-competitively inhibits the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall that is not present in mammalian cells. Micafungin exhibits fungicidal activity against most Candida species and prominently inhibits actively growing hyphae of Aspergillus species.

Mycamine was first approved for marketing in Japan on 08 Oct 2002. Mycamine was later approved in the US on 16 Mar 2005 and subsequently approved in the EU on 25 Apr 2008.

The clinical pharmacology (pharmacodynamics and pharmacokinetics), efficacy and safety aspects of micafungin in adults and children have been well established and are described in the Summary of Product Characteristics (SmPC). Mycamine is administered via intravenous infusion, with the dosage based on both the indication, body weight and age of the patient, as described in the SmPC.

Mycamine has been authorized as powder for solution for infusion in the strengths of 50 mg and 100 mg via a Centralized Procedure and is indicated in the EU for:

Adults, adolescents ≥ 16 years of age and elderly:

- Treatment of invasive candidiasis.

● Treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate.

● Prophylaxis of Candida infection in patients undergoing allogeneic hematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells /µL) for 10 or more days.

Children (including neonates) and adolescents < 16 years of age:

● Treatment of invasive candidiasis.

● Prophylaxis of Candida infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/µL) for 10 or more days.

The decision to use Mycamine should take into account a potential risk for the development of liver tumors (see section 4.4 SmPC). Mycamine should therefore only be used if other antifungals are not appropriate.

Consideration should be given to official/national guidance on the appropriate use of antifungal agents.

The following paediatric dosing is included in the SmPC:

Use in children ≥ 4 months of age up to adolescents < 16 years of age

Indication		
	Body weight > 40 kg	Body weight ≤ 40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Prophylaxis of Candida infection	50 mg/day	1 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.

Use in children (including neonates) < 4 months of age

Indication	
Treatment of invasive candidiasis	4 -10 mg/kg/day*
Prophylaxis of Candida infection	2 mg/kg/day

*Micafungin dosed at 4 mg/kg in children less than 4 months approximates drug exposures achieved in adults receiving 100 mg/day for the treatment of invasive candidiasis. If central nervous system (CNS) infection is suspected, a higher dosage (e.g. 10 mg/kg) should be used due to the dose-dependent penetration of micafungin into the CNS (see section 5.2 of the SmPC).

Treatment duration
Invasive candidiasis: The treatment duration of Candida infection should be a minimum of 14 days. The antifungal treatment should continue for at least one week after two sequential negative blood cultures have been obtained and after resolution of clinical signs and symptoms of infection.

Assessor's comment
Mycamine is an already authorised product in the EU for adults as well as for the paediatric population. The scope of this centralised procedure is to submit data in pharmacokinetics in order to get more information about the higher dosing which is required in neonates and young infants. Of note, patients up to 6 months were eligible and patients up to 8 months were actually recruited into this study.

2.2. Information on the pharmaceutical formulation used in the study

Mycamine has been authorised as a powder for solution for infusion in the strengths of 50 mg and 100 mg. The formulation used in the study is the same as the one which is currently marketed in the EU.

Assessor's comment:

The formulation used in the study is already authorised and marketed in the EU which is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

Systemic candidiasis is associated with significant infant morbidity and mortality. The crude rates of mortality vary from 30% to 60% [Saiman et al, 2000; Lee et al, 1998]. Frequently, infants who survive, have neuromotor developmental disorders, chronic lung disease and severe retinopathy of prematurity [Friedman et al, 2000].

Commonly used antifungals in neonates have been amphotericin B deoxycholate, liposomal amphotericin B and fluconazole. However, the renal and bone marrow toxicity of amphotericin B, a relative degree of uncertainty in the optimal dosage, and the resistance of some Candida species limits the therapeutic use of these agents in infants.

The echinocandins (such as micafungin) are becoming more frequently used in the treatment of systemic candidiasis in newborns and infants. The echinocandins block the synthesis of the fungal cell wall by inhibiting the enzyme beta-1,3-glucan synthase, causing the cell to lyse. The mechanism of action explains their characteristics of high specificity, even against resistant species of Candida. In addition, the echinocandins seem to markedly reduce the activity of yeasts in the biofilm of vascular catheters, both newly formed (12 h) and more mature (5 days).

Newborn infants in general, and especially very low birth-weight neonates, seem to require higher doses of micafungin (from 7 to 15 mg/kg/day) than do adults (2 mg/kg/day) because of greater drug clearance, the mechanism of which is unknown [Yanni et al, 2011]. The high risk of early neurological localization of Candida in preterm infants requires an adequate dosage of antifungals, to ensure the quick passage across the blood-brain barrier.

2.3.2. Clinical study

Study 9463-CL-6001

Description

Study 9463-CL-6001 is a multicenter uncontrolled study on the pharmacokinetic profile of high-dose micafungin (8 mg/kg) in neonatal and young infant patients until 180 days of age suffering from systemic candidiasis.

Methods

Objective

The primary objective was to study the pharmacokinetic profile of micafungin administered at a dose of 8 mg/kg per day to neonatal and young infant patients until 180 days of age (calculated starting from gestational age corrected at 37 weeks) suffering from systemic candidiasis.

The secondary objectives were

- To evaluate the proportion of success and of failure of micafungin therapy with micafungin among treated patients.
- To identify a conversion factor to relate plasma levels of micafungin into capillary and venous blood, measured through blood samples from the heel and from a peripheral vein, collected simultaneously.
- To evaluate the safety of micafungin in neonatal and young infant patients.

Study design:

This was a prospective multicenter, open-label, uncontrolled clinical study for the determination of plasma levels of micafungin at high dose in neonatal and young infant patients affected by systemic candidiasis.

Enrolled patients were hospitalised and treated for a minimum of 14 days with a 1h intravenous infusion of micafungin at 8 mg/kg per day according to therapeutic need until demonstration of success or failure of therapy, or until occurrence of death.

All clinical evaluations and laboratory tests were performed before the start of treatment (visit 1, day 1) and at visits 2 (day 3), 3 (day 10), 4 (day 14 ± 2 days), and 5 (the end of trial participation). Results were recorded for in vitro susceptibility testing performed at the investigative site to determine the minimum inhibitory concentration (MIC) for micafungin to each Candida organism grown from normally sterile body sites where systemic candidiasis or candidemia was diagnosed at baseline and those organisms collected during the study that demonstrated persistent candidiasis or candidemia.

Study population /Sample size:

In this study, at least 30 patients up until 180 days of age (calculated starting from gestational age corrected at 37 weeks) affected by systemic candidiasis were planned to be enrolled. Among these patients, ≥ 4 patients affected by Candida meningitis and/or hydrocephalus due to Candida infection and/or bearing external ventricular derivation were to be included.

In summary, 35 neonates and young infants up to 180 days of age (calculated starting from gestational age corrected at 37 weeks) affected by systemic candidiasis and with a survival expectation of ≥ 3 days were enrolled.

Patients were excluded if they had acute (ammonium > 200 µg/dL) or chronic hepatopathy, or if they had a known allergy or hypersensitivity to echinocandins or any of the excipients present in the formulation of micafungin.

Assessor's comment
According to the inclusion criteria specified in protocol v.3.0 (under which the majority of patients was enrolled, 32/35), at least 4 patients affected by Candida meningitis and/or hydrocephalus due

to Candida infection and/or bearing external ventricular derivation were to be included in the study population. No such patients can be identified in the clinical study report. The MAH is asked to confirm whether any such patients were enrolled and to submit any available data regarding these patients. If no such patients were enrolled, the MAH is asked to clarify the reasons for no enrolment.

Treatments:

All patients received micafungin 8 mg/kg per day via intravenous infusion for 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 with or without external ventricular drainage, negative results (absence of Candida growth) from at least 2 consecutive CSF cultures associated with resolution of clinical and laboratory symptoms.

● Addition or switch to another antifungal agent or dosage change of micafungin due to demonstration of therapy failure. Interruption of micafungin therapy due to resolution of the infection was not considered a therapy failure.

Assessor's comment:

The dose of 8 mg/kg per day is in line with section 4.2 of the SmPC. However, the MAH is asked to clarify whether the antifungal treatment was continued for at least one week after two sequential negative blood cultures had been obtained and after resolution of clinical signs and symptoms of infection.

Outcomes/endpoints:

The primary pharmacokinetic endpoints were quantification of micafungin levels in blood (before infusion and 1, 3 and 8 hours afterwards) on 1 of the treatment days (between the third and tenth day of dosing, inclusive) and quantification of micafungin levels in the cerebrospinal fluid.

The secondary pharmacokinetic endpoint aimed to identify a conversion factor between the levels of drug in capillary and venous blood.

The secondary efficacy endpoint was the treatment response at the end of treatment (EOT). The other efficacy endpoints of interest were fungal-free survival at EOT and at end of trial, crude rate of all-cause mortality through the end of trial, mycological response at EOT and end of trial, time to mycological clearance of candidiasis and/or Candida meningitis and overall incidence of emergent and recurrent fungal infections through the end of trial.

The safety endpoints were adverse events (AEs), physical examination results, vital sign assessments and 12-lead electrocardiogram (ECG) evaluations.

Statistical Methods:

No formal sample size was calculated. The planned sample size was 30 patients.

The **safety analysis set** (SAF) consisted of all enrolled patients (intention to treat [ITT]) who had received ≥ 1 administration of study drug. The SAF was used for summaries of demographic and baseline characteristics and all safety related variables.

The **full analysis set** (FAS) consisted of patients in the SAF from whom the blood draws for the analyses of pharmacokinetics were collected, without any major protocol violation. The FAS was used for analyses of pharmacokinetics.

The **modified FAS (mFAS)** was defined as patients in the SAF who had been affected by systemic candidiasis and/or Candida infection at baseline. The mFAS was used for summaries and analysis of efficacy data, as well as selected demographic and baseline characteristics

For continuous variables, descriptive statistics included the number of patients (n), mean, SD, median, minimum and maximum. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of patients with no missing data (i.e., added up to 100%). All statistical comparisons were based on the point estimate and its 2-sided 95% exact confidence interval (CI), unless stated otherwise.

A summary of changes from planned analyses is presented in [Study 9463-CL-6001, Section 5.5.4].

Results

Recruitment/ Number analysed:

Overall, 35 patients were enrolled and included into the SAF. Only 21 patients ultimately were included into the mFAS. Out of 35 patients enrolled, 20 (57.1%) completed study treatment (≥ 14 days of study drug therapy) and 33 (94.3%) completed the study. Overall, 15 patients (42.9%) prematurely discontinued study treatment (lack of efficacy in 4 [26.7%] cases, lack of confirmation of fungal infection in 4 [26.7%] cases, death in 3 [20%] cases and other in 4 [26.7%] cases). Two patients (5.7%) prematurely discontinued the study, 1 due to death and 1 due to clinical worsening in the absence of detectable Candida.

Protocol Deviations

Compliance with study procedures was reviewed by Astellas upon assumption of sponsorship. Protocol deviations were noted for 24 (68.6%) micafungin-treated patients.

Deviations of receiving the wrong treatment or an incorrect dose were the most common deviations observed (17 patients, 48.6%), followed by study entry without satisfying entry criteria (7 patients, 20.0%) and development of withdrawal criteria during the study without patient withdrawal (4 patients, 11.4%). These protocol deviations did not impact patients' safety nor did they affect overall study results or conclusions.

Assessor´s comment:

The MAH is asked to discuss the high number of the protocol deviations in patients who entered the study including the application of the wrong dose in approx. 50% of the population and the impact on the interpretability of the study results. In addition, it is not clear why the patients fulfilling withdrawal criteria had not been withdrawn. The statement that protocol deviations did not impact patients' safety or overall study results or conclusions is not supported as the validity of the study is questioned. The MAH is strongly asked to justify the validity of the study results.

In addition, individual patients with protocol deviations should be listed, broken down by study centre.

Baseline data:

Summary of Demographics and Baseline Characteristics

Parameter Category / Statistics	**Micafungin (n = 35) n (%)**
Sex, n (%)	
Male	20 (57.1)
Female	15 (42.9)
Race, n (%)	
Caucasian	32 (91.4)
Black	2 (5.7)
Other†	1 (2.9)
Age, months	
n	35
Mean (SD)	2.53 (2.11)
Median	1.90
Min - Max	0.3 – 8.1
Age Group	
0 to ≤ 4 weeks	8 (22.9)
> 4 weeks to ≤ 4 months	20 (57.1)
> 4 months to ≤ 6 months	3 (8.6)
> 6 months to < 2 years	4 (11.4)
Gestational Age Group	
< 27 weeks	14 (40.0)
≥ 27 weeks	21 (60.0)
Birth Weight, kg	
n	35
Mean (SD)	1.26 (0.74)
Median	1.00
Min – Max	0.4 – 3.1

Table 8 Candidiasis Infection-Related Baseline Characteristics

Parameter Category/Statistic	**Number of Patients with Baseline Organism (%)**					
	C. albicans	*C. glabrata*	*C. krusei*	*C. lusitaniae*	*C. parapsilosis*	*C. tropicalis*
Overall	11 (31.4)	1 (2.9)	1 (2.9)	1 (2.9)	6 (17.1)	1 (2.9)
Site of Infection						
Blood	10 (28.6)	1 (2.9)	0	1 (2.9)	4 (11.4)	0
Lung	0	0	1 (2.9)	0	1 (2.9)	0
Skin	0	0	0	0	1 (2.9)	0
Urinary tract	1 (2.9)	0	0	0	1 (2.9)	1 (2.9)
Systemic Candidiasis Diagnosis						
Proven	11 (31.4)	1 (2.9)	0	1 (2.9)	6 (17.1)	1 (2.9)
Probable	0	0	1 (2.9)	0	0	0

Safety analysis set: all enrolled patients who had received at least 1 dose of study drug.

Source: End-of-Text Table 12.1.6.1

Assessor´s comment:

35 patients were enrolled in the study. There is a large difference between the SAF (n=35) and the mFAS (n=21) although only four patients are reported to not have had confirmation of a fungal infection. The MAH is asked to clarify.

Of note, seven children older than 4 months (up to 8 months old) were included into the study without further information on the dose used. Daily dosing in both SAF and mFAS was between 6-8 mg/kg. The MAH should clarify and discuss the appropriateness of the dose in children above 4 months.

Demographic and baseline characteristics of the mFAS were generally comparable to those of the SAF.

All patients with a baseline Candida organism were diagnosed with proven systemic candidiasis, except for 1 (2.9%) patient with baseline *C. krusei* who was diagnosed with probable systemic candidiasis. The most common Candida organisms isolated at baseline were *C. albicans* (11 patients, 31.4%) and *C. parapsilosis* (6 patients, 17.1%); *C. glabrata, C. krusei, C. lusitaniae* and *C. tropicalis* were diagnosed in 1 patient (2.9%) each. A total of 94.3% of patients had a central venous catheter in place at baseline, of which 69.7% were removed at some time during the study.

Treatment

In the SAF, the median duration of micafungin therapy was 14 days (range from 4 to 25 days). The mean (SD) daily dose was 7.9296 (0.6163) mg/kg.

Efficacy results:

For the secondary efficacy endpoint, treatment response at EOT, the percentage of success with micafungin therapy was 80.0% (16/20; 95% CI: 56.34%, 94.27%) among the 20 patients in the SAF who completed ≥ 14 days of study drug therapy [Table 1].

Among all 35 patients in the SAF (including 15 patients treated with micafungin for < 14 days), the percentage of success with micafungin therapy was 45.7% (16/35; 95% CI: 28.83%, 63.35%).

In the mFAS, the percentage of success with micafungin therapy was 86.7% (13/15; 95% CI: 59.54%, 98.34%) among the 15 patients who completed ≥ 14 days of study drug therapy and was 61.9% (13/21; 95% CI: 38.44%, 81.89%) among all patients.

Table 1 Treatment Response at End of Treatment

Patient Cohort **Treatment Response Category**	**Micafungin** **(n = 35)** **n (%)**
Completed ≥ 14 days of study drug therapy	20
Success	16 (80.0)
95% 2-sided exact confidence interval	(56.34, 94.27)
Failure	4 (20.0)
All Patients	35
Success	16 (45.7)
95% 2-sided exact confidence interval	(28.83, 63.35)
Failure	4 (11.4)
Did not complete	15 (42.9)

Safety analysis set: all enrolled patients who had received ≥ 1 dose of study drug.
Source: Study 9463-CL-6001, End-of-Text Table 12.3.1.1

Analysis of the treatment response by number of infections and certainty of diagnosis (i.e. proven/probable vs suspected) showed that the percentage of success with micafungin therapy at EOT was higher for proven/probable infections than for suspected infections [Table 2]. The percentage of success was 75.0% (95% CI: 50.90%, 91.34%) among 20 proven/probable infections and was 60.0% (95% CI: 14.66%, 94.73%) among 5 suspected infections.

Table 2 Treatment Response by Certainty of Diagnosis

Certainty of Diagnosis Category/Statistic	Micafungin n (%)
Overall	
Number of patients	20
Number of infections	25
Success	18 (72.0)
95% 2-sided exact confidence interval	(50.61, 87.93)
Failure	7 (28.0)
Proven/Probable	
Number of patients	15
Number of infections	20
Success	15 (75.0)
95% 2-sided exact confidence interval	(50.90, 91.34)
Failure	5 (25.0)
Suspected	
Number of patients	5
Number of infections	5
Success	3 (60.0)
95% 2-sided exact confidence interval	(14.66, 94.73)
Failure	2 (40.0)

Safety analysis set: all enrolled patients who had received ≥ 1 dose of study drug. For each diagnosis, percentages were taken from the number of infections with that diagnosis. Only patients who completed ≥ 14 days of study drug therapy were evaluable for treatment response.

Source: Study 9463-CL-6001, End-of-Text Table 12.3.6.1

Other Efficacy Endpoints of Interest

Fungal free survival was defined as alive by the time of assessment (EOT or end of trial), having cleared the fungal infection (mycological eradication on or before the assessment timepoint) and not requiring additional alternative systemic antifungal therapy for treatment after stopping micafungin. Patients who had received at least 1 dose of study drug and who had a proven or probable systemic candidiasis and/or Candida infection at baseline (mFAS) were evaluated for fungal-free survival. Patients who survived but were missing an assessment for fungal eradication were included as not attaining fungal free survival.

In the mFAS, fungal free survival at EOT and end of trial was achieved by 13 (61.9%) and 18 (85.7%) micafungin-treated patients, respectively [Table 3]. Of the 8 failures at EOT, 6 had continuing infections and 2 were not assessed. At end of trial there were 3 failures (1 patient each): death, lack of eradication, and lack of assessment.

Table 3 Fungal Free Survival at End of Treatment and at End of Trial

Parameter Category/Statistic	Micafungin (n = 21) n (%)
Fungal Free Survival at End of Treatment†	
Success	13 (61.9)
95% 2-sided exact confidence interval	(38.44, 81.89)
Failure	8 (38.1)
Did not have mycological eradication	6
Not assessed	2
Fungal Free Survival at End of Trial	
Success	18 (85.7)
95% 2-sided exact confidence interval	(63.66, 96.95)
Failure	3 (14.3)
Death	1
Did not have mycological eradication	1
Not assessed	1

Modified full analysis set: all enrolled patients who had received ⩾ 1 dose of study drug and who had a proven or probable systemic candidiasis and/or Candida infection at baseline.

† Fungal free survival was defined as alive by the time of assessment (EOT or end of trial), having cleared the fungal infection (mycological eradication on or before the assessment timepoint) and not requiring additional alternative systemic antifungal therapy for treatment after stopping micafungin.

Source: Study 9463-CL-6001, End-of-Text Table 12.3.2.2

In the SAF, the crude rate of all-cause mortality through end of trial was 14.3%

(5/35 patients) (95% CI: 4.81%, 30.26%). In the mFAS it was 9.5% (2/21 patients) (95% CI: 1.17%, 30.38%).

At EOT, in the mFAS, 61.9% (13/21; 95% CI: 38.44%, 81.89%) of micafungin-treated patients achieved eradication. Of the 38.1% (8) of patients with proven/probable infection who had mycological failure at EOT, infection persisted in 75.0% (6) and was not assessed in 25.0% (2) of patients. At end of trial, the percentage of micafungin-treated patients that experienced eradication increased to 90.5% (19/21; 95% CI: 69.62%, 98.83%), including 5 (26.3%) patients with continued eradication (i.e., eradication at EOT that continued until end of trial). Of the 2 (9.5%) patients with mycological failure at end of trial, infection persisted in 1 (50.0%) and was not assessed in 1 (50.0%) patient.

In the SAF, at EOT 42.9% (15/35; 95% CI: 26.32%, 60.65%) of micafungin-treated patients achieved eradication, with more patients with proven/probable infection (56.5% [13/23]) than with suspected infections (16.7% [2/12]) achieving eradication at EOT. At end of trial, the percentage of micafungin-treated patients that experienced eradication increased to 62.9% (22/35), with more patients with proven/probable infection (87.0% [20/23]) than with suspected infections (16.7% [2/12]) achieving eradication at end of trial. The 2 patients with suspected infections that were reported by the investigator to have persistence were based on continued positive antigen detection (Candida mannan assay positive).

In the SAF, emergent fungal infections were noted through end of trial in 1 (2.9%) micafungin-treated patient, which occurred during the treatment period. The emergent fungal infection occurred in a patient who was enrolled with a *C. albicans* candidemia who during treatment had 1 positive stool culture with *C. parapsilosis*. It was categorized as an emergent infection. The primary candidemia did resolve on therapy with micafungin. No recurrent fungal infections were noted through end of trial.

At baseline, the MIC ranged from 0.008 to 0.015 µg/mL for C. albicans (n = 10), from 1 to 2 µg/mL for *C. parapsilosis* (n = 4) and was 0.06 µg/mL for *C. lusitaniae* (n = 1). No postbaseline MIC value was higher than the baseline value.

Assessor´s comment:

The clinical study recruited only 35 patients of whom only 20 patients completed the treatment of 14 days of study drug. The low number of patients and the high number of protocol deviations do not allow firm conclusions with respect to the overall efficacy. The success rate of the treatment with respect to the secondary efficacy endpoints depends largely on the selected population (SAF, FAS, mFAS). The MAH states that the efficacy and safety observed are in line with previous experience. In light of the small number of patients and the large number of protocol deviations, hardly any meaningful comparisons to previous study results can be made at this point.

The percentage of patients achieving mycological eradication at the end of trial was higher than achieving eradication at the end of treatment. 5 patients had been successfully eradicated after treatment until the end of trial. The applicant is asked to clarify the actual duration of treatment in those patients who had been treated for more than 14 days until eradication. Additionally, it should be clarified in how far these patients experienced drug related mild, moderate, severe or life threatening adverse events.

The MAH is requested to clarify if patients who discontinued due to lack of efficacy were included in the efficacy analysis.

Pharmacokinetic Results

A comparison of plasma micafungin levels from capillary and venous sampling at those times is shown in [Table 4]. Over the time points sampled, venous plasma levels of micafungin were slightly higher than capillary levels. Capillary levels ranged on average from 6.179 to 19.196 µg/mL and venous levels from 6.431 to 22.390 µg/mL (predose and end of infusion, respectively). Cerebrospinal fluid data from only 1 patient are available.

Table 4 Summary of Capillary and Venous Plasma Concentrations of Micafungin (µg/mL)

Time Point Category/Statistic	**Capillary (n = 8)**	**Venous (n = 8)**
Predose (n)	(8)	(8)
Mean (SD)	6.179 (2.864)	6.431 (2.841)
Min - Max	1.71-10.50	2.85 - 11.50
Median	6.315	5.960
Q1 - Q3	4.160 - 8.135	4.450 - 8.140
1 hour postdose (end of infusion, n)	(8)	(7)
Mean (SD)	19.196 (5.659)	22.390 (4.972)
Min - Max	11.40 - 30.70	14.20 - 30.90
Median	18.530	21.400
Q1 - Q3	16.070 - 21.135	21.140 - 23.990
3 hours postdose (n)	(8)	(7)
Mean (SD)	16.935 (4.075)	19.000 (3.945)
Min - Max	11.00 - 22.28	13.60 - 24.60
Median	16.805	19.140
Q1 - Q3	13.700 - 20.595	15.000 - 22.850
8 hours postdose (n)	(8)	(7)

Mean (SD)	11.834 (2.433)	12.994 (2.765)
Min - Max	7.80 - 15.30	10.40 - 18.40
Median	11.535	11.940
Q1 - Q3	10.830 - 13.420	10.850 - 14.710

Safety analysis set: all enrolled patients who had received ≥ 1 dose of study drug.

Max: maximum; Min: minimum; Q: quartile

Source: Study 9463-CL-6001, End-of-Text-Table 12.4.2

Assessor´s comment:

No report on population PK and PKPD analyses was provided.

In adults, micafungin is dosed at 2mg/kg per day. No information on concentrations reached in adult patients receiving this dose was available.

The MAH stated that according to literature, the dose for neonates and infants that ensures a good distribution into the CNS appears to be at least 8 mg/kg per day based on nonclinical pharmacology and pharmacokinetic bridging studies.

In another reference, a population pharmacokinetic model found that the weight-adjusted clearance was higher in infants than in older paediatric patients. Causes of this finding are supposed to be lower binding to plasma proteins, so that the proportion of free drug is higher in neonates and young infants. Elimination of micafungin is mostly via the faeces (71%) and to a minor extend in the urine (11.6%). Micafungin is metabolized to a small extent to inactive metabolites (most abundant metabolite occurred at 6.5% from parent compound).

According to Benjamin et al., 2018, micafungin at dosages up to 10 mg/kg demonstrated linear pharmacokinetics and favorable tolerability in infants (< 4 months of age), while also providing exposure levels adequate for CNS coverage.

It is difficult to assess the adequacy of the observed concentrations in the young paediatric patients since no target concentration range seems to be defined, PK bridging from adults is not adequate in this case and no PK-PD analyses are available.

In addition, clarifications are required regarding the time frame for blood sampling for PK analyses (pre-dose, and 1, 3, and 8h post-dose on any day of treatment between day 3-10 of the study). Usually, steady state (in adults) is reached after 4 days at which time plasma concentrations for micafungin are 40-60% higher than after a single dose. The MAH is asked to present the number of patients with blood sampling on day 3 and the possible impact on overall PK results, also taking into account those patients that had received prior micafungin-treatment. Moreover, protocol deviations (see other Assessor's comment) were noted for 24 (68.6%) patients, 17 of which received the wrong treatment or the wrong dose. All protocol deviations should be taken into account for PK analyses and analyses excluding these patients should be presented.

In addition, the proposed dosing schedule was defined for the age group below the age of 4 months. In the study, however, 7 subjects did not fit into the original age groups provided by the SAP and so there was a need to expand the age bands. The new ranges were categorized as 0 to ≤ 4 weeks, > 4 weeks to ≤ 4 months, > 4 months to ≤ 6 months, and > 6 months to < 2 years. It is not considered that enough evidence is now available that this dose is also adequate for children older than 4 months since as stated in the product characteristics, weight-adjusted clearance is highest in the age group below 4 months and slowly approaches values similar to adults in older children. Therefore, for children in the age range 4 months up to two years (in which few patients were included

in the presented study) the dose might be too high. The MAH is asked to present the data for children below 4 months of age and ≥ 4 months of age separately.

It was mentioned as a secondary endpoint of the study to identify a conversion factor between the levels of drug in capillary and venous blood. Finally, no calculation of this factor could be found in the documentation. This should be reported and the possibility to use an evaluation of PK samples based on this factor in the clinical routine should be discussed.

The planned report on population PK and PKPD should be made available to the assessors as soon as available.

Safety results:

12 (34.3%) patients were considered serious. Three TEAEs led to death (i.e., death occurred within 72 h of the last dose of study drug), and there were 5 deaths in the study. No TEAE led to withdrawal of study drug.

A summary of frequent TEAEs (≥ 5.0% of patients in any preferred term) is provided for the SAF in [Table 5]. Overall, 31 patients experienced TEAEs. The most common system organ class categories of TEAEs were Infections and infestations (14/35, 40.0%), Investigations (13/35 patients, 37.1%) and General disorders and administration site conditions (7/35, 20.0%). The most common specific TEAEs were gamma-glutamyltransferase increased in 9 patients (25.7%), oedema in 5 patients (14.3%) and bradycardia in 4 patients (11.4%).

Table 5 Frequent (≥ 5% of Patients in any Preferred Term) TEAEs

MedDRA v20.1 **System Organ Class** **Preferred Term**	**Micafungin** **n = 35** **n (%)**
Overall	**31 (88.6)**
Blood and lymphatic system disorders	**6 (17.1)**
Thrombocytopenia	3 (8.6)
Leukopenia	2 (5.7)
Cardiac disorders	**4 (11.4)**
Bradycardia	4 (11.4)
Gastrointestinal disorders	**4 (11.4)**
Diarrhoea	2 (5.7)
General disorders and administration site conditions	**7 (20.0)**
Oedema	5 (14.3)
Hepatobiliary disorders	**5 (14.3)**
Cholestasis	3 (8.6)
Hypertransaminasaemia	2 (5.7)
Infections and infestations	**14 (40.0)**
Septic shock	3 (8.6)
Bacterial sepsis	2 (5.7)
Klebsiella sepsis	2 (5.7)
Sepsis	2 (5.7)
Urinary tract infection bacterial	2 (5.7)
Injury, poisoning and procedural complications	**2 (5.7)**
Wound dehiscence	2 (5.7)
Investigations	**13 (37.1)**

Gamma-glutamyltransferase increased	9 (25.7)
Blood alkaline phosphatase increased	2 (5.7)
Blood bilirubin increased	2 (5.7)
C-reactive protein increased	2 (5.7)
Metabolism and nutrition disorders	**5 (14.3)**
Hyponatraemia	3 (8.6)
Hypokalaemia	2 (5.7)
Respiratory, thoracic and mediastinal disorders	**3 (8.6)**
Respiratory failure	2 (5.7)
Vascular disorders	**5 (14.3)**
Hypotension	3 (8.6)

Safety analysis set: all enrolled patients who had received ≥ 1 dose of study drug. A TEAE was defined as an AE experienced any time during study drug administration through 72 h after the last dose of study drug. Within a system organ class, patients may have reported more than 1 preferred term. AE: adverse event; TEAE: treatment-emergent adverse event. Source: Study 9463-CL-6001, End-of-Text Table 12.6.1.2

Assessor's comment:

The most common TEAEs observed in this study were infections and infestations (40%), investigations (37.1%), general disorders and administration site conditions (20%). Only frequent TEAEs (defined as ≥ 5% of Patients in any Preferred Term) were reported. The MAH is asked to provide TEAEs by the following frequency categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). While most of the presented TEAEs are already labeled in the current SmPC of Mycamine, others are not (e.g. infections and infestations (40%), respiratory failure (5.7%). The MAH is asked to comment. (also see comment on Table 7)

One (2.9%) patient experienced a TEAE (hypertransaminasemia) that was assessed by the investigator as related to study drug. A total of 15 (42.9%) patients experienced TEAEs with relationship to study drug classified by the investigator as "unknown".

The severity of TEAEs was assessed as mild, moderate, severe, life-threatening or death. Overall, 31 patients experienced 86 TEAEs, which were severe in 6 (17.1%) patients, life-threatening in 4 (11.4%) patients, and resulted in death in 3 (8.6%) patients.

There were 5 deaths during the study [Table 6]. No TEAE leading to death was considered related to the administration of study drug. Septic shock was a primary cause of death in most (4/5) of these patients. In the case of the first patient, the serious TEAE of septic shock had an onset on day 3, and death from septic shock on day 5 was accompanied by the moderate TEAE of coagulopathy. The last dose of study drug was on day 4. At baseline, this patient was positive for multidrug resistant *Pseudomonas aeruginosa* in tracheal aspirate and blood.

On day 5 the second patient experienced the serious TEAE of life-threatening septic shock, accompanied by the serious TEAEs of life-threatening hypotension and anuria. The anuria was resolved on day 5, and the hypotension was not resolved at the time of death of septic shock on day 18. The last dose of study drug was on day 10. At baseline, stool culture was positive for *Pseudomonas aeruginosa*, and tracheal aspirates at baseline and day 9 also found multidrug resistant *Pseudomonas aeruginosa*.

In the third patient, the serious TEAE of septic shock had an onset on day 9, accompanied by the serious TEAE of life-threatening ascites. The patient died of septic shock from *Klebsiella pneumonia* extended spectrum beta-lactamases and ascites on day 10; the last dose of study drug was on day 9.

In the fourth patient, the serious TEAEs of septic shock by *Klebsiella pneumonia* and disseminated intravascular coagulation were both noted on day 27, and both TEAEs were considered as the cause of death on day 28. The last dose of study drug was on day 16.

In the fifth patient the serious TEAEs of peritonitis and multiple organ dysfunction syndrome had an onset on day 15, and both were considered the cause of the patient's death on that day. The last dose of study drug was on day 7.

Narratives of these deaths are provided in [Study 9463-CL-6001, Attachment 1].

An additional 2 patients died more than 30 days after their participation in the study; no further details are available.

Table 6 Deaths

Primary Cause of Death MedDRA (v20.1) Preferred Term	Last Dose Day	Day of Death	Relationship to Study Drug
Septic shock	4	5	Not related
Septic shock	10	18	Not related
Ascites	9	10	Not related
Septic shock			
Disseminated intravascular coagulation	16	28	Not related
Septic shock			
Peritonitis	7	15	Not related
Multiple organ dysfunction syndrome			

Safety analysis set: all enrolled patients who had received ≥ 1 dose of study drug.
Source: Study 9463-CL-6001, Appendix 13.2.7.3

Assessor´s comment:

Five deaths occurred during the study. Narratives of patients with deaths were provided. In 3/5 cases, death seems to have occurred within 72 h of the last dose of study drug.

Patient 01006 developed life-threatening ascitis and septic shock on day 9 and died on day 10 due to septic shock from *Klebsiella pneumoniae* extended-spectrum beta-lactamases (ESBL) sepsis. The dose of study drug was not changed in response to the events, but study drug was stopped on day 9 of the study. The MAH is asked to provide the reason for stopping the study drug and whether this was due to TEAEs.

For patient 01005, the date of death and the study day on which death occurred are unclear: 12-sep-2015 is designated d12 and d18 of the study in different parts of the case narrative for this patient. The MAH is asked to submit the correct data to clarify the time window between last dose of study drug and occurrence of death and to confirm the relationship to the study drug. The cause of death was septic shock and hypotension, the latter possibly secondary to septic shock.

Patient 01030 was withdrawn from study drug treatment due to lack of efficacy on day 7 of the study and died on day 15 due to severe respiratory failure, sepsis from *Candida parapsilosis*, peritonitis, pneumothorax, intestinal perforation, premature birth, multiorgan failure, and septic shock.

Patient 01004 developed septic shock on day 3 of the study, received the last dose of study drug on day 4 (after 4 days of treatment), and died on day 5 due to septic shock. The MAH is asked to provide the reasons for discontinuing the study drug.

Patient 01010 received the last dose of study drug on day 16 of the study (16 days of treatment total) and developed disseminated intravascular coagulation and septic shock on day 27. The patient had received treatment for sepsis already prior to study onset and developed neutropenia and leukopenia during the study, which resolved after treatment. The patient died on day 28 due to septic shock by *Klebsiella pneumoniae* and disseminated intravascular coagulation.

It is acknowledged that given the presence of multiple underlying comorbidities, premature complications, multiple non-candida infections (including MDR pathogens), and multiple concomitant medications, an alternate explanation for the observed TEAEs and deaths may be possible.

Nevertheless, some clarifications are required:

1. In all cases, TEAEs leading to death were considered not related to study drug by the MAH although shock, hypotension, hepatic failure, and disseminated intravascular coagulation area labeled as undesirable effects in section 4.8 of the SmPC (in frequency categories “uncommon” and “not known”). The MAH is asked to discuss.
2. The number of TEAEs leading to death should be clarified. It is not understood how the MAH arrives at 3 TEAEs leading to death in this study.
3. In addition, terminal half-life of micafungin ranges from 10-17h in adults. The MAH is asked to justify the adequacy of the time window of 72h in light of average micafungin half-life and elimination in paediatric patients.
4. The MAH is asked to provide the reasons for study drug discontinuation in patients 01006 and 01004 and to confirm whether development of TEAEs led to withdrawal of the study drug.
5. For patient 01005, the MAH is asked to submit the correct date of death in order to clarify the time window between last dose of study drug and occurrence of death. The relationship to the study drug should be confirmed.

Serious TEAEs were experienced by 12 (34.3%) patients [Table 7]. The most common system organ class category was Infections and infestations (8/35, 22.9%). The most common preferred terms were septic shock (3 patients, 8.6%) followed by bradycardia, bacterial sepsis, Klebsiella sepsis and respiratory failure (2 patients each, 5.7%). None of the patients experienced serious TEAEs considered related to study drug.

Table 7 Serious TEAEs

MedDRA v20.1 **System Organ Class** **Preferred Term**	**Micafungin** **n = 35** **n (%)**
Overall	**12 (34.3)**
Blood and Lymphatic System Disorders	**1 (2.9)**
Neutropenia	1 (2.9)
Cardiac Disorders	**2 (5.7)**
Bradycardia	2 (5.7)
Gastrointestinal Disorders	**1 (2.9)**

Ascites	1 (2.9)
Infections and Infestations	**8 (22.9)**
Septic shock	3 (8.6)
Bacterial sepsis	2 (5.7)
Klebsiella sepsis	2 (5.7)
Candida sepsis	1 (2.9)
Renal and urinary disorders	**2 (5.7)**
Acute kidney injury	1 (2.9)
Anuria	1 (2.9)
Respiratory, Thoracic and Mediastinal Disorders	**3 (8.6)**
Respiratory failure	2 (5.7)
Pulmonary hypertension	1 (2.9)
Vascular Disorders	**1 (2.9)**
Hypotension	1 (2.9)

Safety analysis set: all enrolled patients who had received ≥ 1 dose of study drug. A TEAE was defined as an AE experienced any time during study drug administration through 72 h after the last dose of study drug. Within a system organ class, patients may have reported more than 1 preferred term.

AE: adverse event; TEAE: treatment-emergent adverse event.
Source: Study 9463-CL-6001, End-of-Text Table 12.6.1.6

Assessor's comment:

According to the MAH, no patient experienced serious TEAEs related to the study drug. However, ADRs such as hypotension, neutropenia, acute renal failure, and investigations are labeled in the Mycamine SmPC section 4.8 under paediatric population. Likewise, hypotension, shock and hepatic failure are labeled for adults with frequencies uncommon or not known. Therefore, the statement that no patient experienced serious TEAEs related to study drug is not entirely supported. In addition, infections and infestations were the most common serious TEAE (Table 5, Table 7) and are not labeled in the current SmPC of Mycamine. Also respiratory, thoracic and mediastinal disorders were observed TEAEs and are not already labeled. The MAH is asked to comment. (also see comment on Table 5)

No TEAEs leading to permanent discontinuation of study drug were reported.

TEAEs of special interest included any that were potentially infusion-related reactions, as defined by medical review using the criteria of Siena et al [2010]. Three patients had TEAEs of special interest, all being TEAEs of hypotension. In the case of the first patient, serious TEAE of hypotension on day 5 was accompanied by anuria and of septic shock. The patient died on day 18 of septic shock (see above), and the hypotension was not considered resolved at that time. In the second patient, the TEAE of hypotension was reported on day 2. The event was continuous and of moderate severity. The patient recovered, and the event was considered resolved on day 6. In the third patient, the TEAE of hypotension was also reported on day 2. The event was intermittent and of moderate severity. The patient recovered, and the event was considered resolved on day 7. Narratives of these patients are provided in [Study 9463-CL-6001, Attachment 1].

In general, mean changes in haematology, biochemistry and urinalysis parameters were small and not clinically relevant. Liver enzymes and total bilirubin values for the majority of patients tended to be within the normal laboratory ranges during the study. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) was elevated beyond 3 x upper limit of normal (ULN) in 22.6% (7/31) patients. Values of ALT and/or AST > 3 x ULN and total bilirubin > 2 x ULN in the same sample were

observed in 14.3% (5/35) patients. Values of ALT and/or AST > 3 x ULN and alkaline phosphatase (AP) < 2 x ULN and total bilirubin > 2 x ULN in the same sample were observed in 8.8% (3/34) patients. Narratives of these patients are provided in [Study 9463-CL-6001, Attachment 1].

In general, mean changes over time in vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) were small and not clinically relevant. In the 6 patients with both baseline and post-baseline ECG assessments, ECG assessments remained unchanged after treatment with micafungin.

Assessor's comment:

Elevations in ALT, AST, and AP are in line with labeled undesirable effects for Mycamine in sections 4.4 and 4.8 of the SmPC. Paediatric patients below 1 year of age experienced about two times more often an increase in ALT, AST and AP than older paediatric patients.

2.3.3. Discussion on clinical aspects

This study was submitted by the MAH and aimed at providing more information about the PK and PK/PD profile of a dose range of 8 mg/kg body weight in premature neonates, neonates and infants with systemic candidiasis or candida mengingitis. No information on CNS involvement was found.

In the actual study, patients up to 8 months were included and received micafungin at the dose of 8 mg/kg/day which is only authorised for children less than 4 months. No discussion was found on the adequacy of dose in children beyond 4 months and the population PK report is missing.

No firm conclusion on the secondary efficacy endpoints can be made in view of the low number of patients and the strong difference between the SAF and mFAS populations. A high number of protocol deviations are reported including application of the wrong dose in 48.6% of the SAF.

Therfore, more information is needed in order to assess the study results and confirm the MAH's conclusion that the data support the previous findings on dosing, safety and efficacy in the targeted age group.

3. Initial recommendation

Further information is needed in order to make conclusions on pharmacokinetic profile, efficacy and safety in neonates and young infants.

Based on the data submitted, the MAH should provide description of the additional clarifications requested as part of this procedure. (See: section "Additional clarification requested")

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. According to the inclusion criteria specified in protocol v.3.0 (under which the majority of patients was enrolled, 32/35), at least 4 patients affected by Candida meningitis and/or hydrocephalus due to Candida infection and/or bearing external ventricular derivation were to be included in the study population. No such patients can be identified in the clinical study report. The MAH is asked to confirm whether any such patients were enrolled and to submit

any available data regarding these patients. If no such patients were enrolled, the MAH is asked to clarify the reasons for no enrolment.

2. The dose of 8 mg/kg per day is in line with section 4.2 of the SmPC. However, the MAH is asked to clarify whether the antifungal treatment was continued for at least one week after two sequential negative blood cultures had been obtained and after resolution of clinical signs and symptoms of infection.

3. Protocol deviations:

    a. The MAH is asked to discuss the high number of the protocol deviations in patients who entered the study including the application of the wrong dose in approx. 50% of the population and the impact on the interpretability of the study results. The statement that protocol deviations did not impact patients' safety or overall study results or conclusions is not supported as the validity of the study is questioned. The MAH is asked to justify the validity of the study results.

    b. The MAH should clarify the protocol deviations in patients who entered the study other than those who developed withdrawal criteria. In addition, it is not clear why the patients fulfilling withdrawal criteria had not been withdrawn. The MAH is asked to clarify.

    c. Individual patients with protocol deviations should be listed, broken down by study centre.

4. 35 patients were enrolled in the study. There is a large difference between the SAF (n=35) and the mFAS (n=21) although only four patients are reported to not have had confirmation of a fungal infection. The MAH is asked to clarify.

5. The percentage of patients achieving mycological eradication at the end of trial was higher than achieving eradication at the end of treatment. 5 patients had been successfully eradicated after treatment until the end of trial.

    a. The MAH is asked to clarify the actual duration of treatment in those patients who had been treated for more than 14 days until eradication.

    b. Additionally, it should be clarified in how far these patients experienced drug related mild, moderate, severe or life threatening adverse events.

6. The MAH is requested to clarify if patients who discontinued due to lack of efficacy were included in the efficacy analysis.

7. The planned report on paediatric population PK and PKPD is missing and should be submitted.

8. The target concentration ranges in adults and in infants below the age of 4 months should be stated and justified.

9. Clarifications are required regarding the time frame for blood sampling for PK analyses (pre-dose, and 1, 3, and 8h post-dose on any day of treatment between day 3-10 of the study). Usually, steady state (in adults) is reached after 4 days at which time plasma concentrations for micafungin are 40-60% higher than after a single dose. The MAH is asked to present the number of patients with blood sampling on day 3 and the possible impact on overall PK results, also taking into account those patients that had received prior micafungin-treatment. Moreover, protocol deviations (see other Assessor's comment) were noted for 24 (68.6%) patients, 17 of which received the wrong treatment or the wrong dose. All protocol deviations should be taken into account for PK analyses and analyses excluding these patients should be presented.

10. It should be stated for which age range the dosing schedule of 8mg/kg per day is considered, since in this study infants older than 4 months were included and treated with this dose, which might be too high in children above 4 months. The MAH is asked to present the data for children below 4 months of age and ≥ 4 months of age separately.

11. According to the secondary endpoint of the study to identify a conversion factor between the levels of drug in capillary and venous blood, this facto should be reported and the possibility to use an evaluation of PK samples based on this factor in the clinical routine should be discussed.

12. The most common TEAEs observed in this study were infections and infestations (40%), investigations (37.1%), general disorders and administration site conditions (20%). Only frequent TEAEs (defined as ≥ 5% of Patients in any Preferred Term) were reported. The MAH is asked to provide TEAEs by the following frequency categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). While most of the presented TEAEs are already labeled in the current SmPC of Mycamine, others are not (e.g. infections and infestations (40%), respiratory failure (5.7%). The MAH is asked to comment. (also see comment on Table 7)

13. Regarding TEAEs leading to death:

    a. In all cases, TEAEs leading to death were considered not related to study drug by the MAH although shock, hypotension, hepatic failure, and disseminated intravascular coagulation area labeled as undesirable effects in section 4.8 of the SmPC (in frequency categories “uncommon” and “not known”). The MAH is asked to discuss.

    b. The number of TEAEs leading to death should be clarified. It is not understood how the MAH arrives at 3 TEAEs leading to death in this study.

    c. In addition, terminal half-life of micafungin ranges from 10-17h in adults. The MAH is asked to justify the adequacy of the time window of 72h in light of average micafungin half-life and elimination in paediatric patients.

    d. The MAH is asked to provide the reasons for study drug discontinuation in patients 01006 and 01004 and to confirm whether development of TEAEs led to withdrawal of the study drug.

    e. For patient 01005, the MAH is asked to submit the correct date of death in order to clarify the time window between last dose of study drug and occurrence of death. The relationship to the study drug should be confirmed.

14. According to the MAH, no patient experienced serious TEAEs related to the study drug. However, ADRs such as hypotension, neutropenia, acute renal failure, and investigations are labeled in the Mycamine SmPC section 4.8 under paediatric population. Likewise, hypotension, shock and hepatic failure are labeled for adults with frequencies uncommon or not known. Therefore, the statement that no patient experienced serious TEAEs related to study drug is not entirely supported. In addition, infections and infestations were the most common serious TEAE (Table 5, Table 7) and are not labeled in the current SmPC of Mycamine. Also respiratory, thoracic and mediastinal disorders included TEAEs not already labeled. The MAH is asked to comment. (also see comment on Table 5)

The timetable is a 30 day response timetable with clock stop.

Assessment of the MAH's responses to Request for supplementary information

Question 1

According to the inclusion criteria specified in protocol v.3.0 (under which the majority of patients was enrolled, 32/35), at least 4 patients affected by Candida meningitis and/or hydrocephalus due to Candida infection and/or bearing external ventricular derivation were to be included in the study population. No such patients can be identified in the clinical study report. The MAH is asked to confirm whether any such patients were enrolled and to submit any available data regarding these patients. If no such patients were enrolled, the MAH is asked to clarify the reasons for no enrolment.

Summary of the MAH's response

Inclusion criteria number 2 states the following:

"Neonates affected by Candida meningitis and/or hydrocephalus due to Candida infection, and/or bearing external ventricular derivation, until enrollment of at least 4 subjects with these characteristics."

In accordance with the protocol, the investigator screened patients in an attempt to enrol patients under all criteria, including inclusion criteria number 2. Due to the rareness of the disease, only a limited number of patients were available that met the majority of the inclusion criteria. In this study, the investigator was unable to identify 4 patients who met inclusion criteria number 2. Upon transfer of the study sponsorship to Astellas, the protocol was modified to clarify that the study enrollment would end when the target total number of patients was reached.

One patient (Patient 01029) was diagnosed with invasive candidiasis in multiple organs (cerebrospinal fluid/blood/lung/heart). Fungal infection was proven based on enzyme-linked immunosorbent assay (ELISA) positive for Candida mannan antigen (level of mannan antigen $\geq$ 125 pg/mL). In addition, the ELISA yielded positive results for blood, meninges and lung samples. Furthermore, polymerase chain reaction assessment was performed on cerebrospinal fluid and was positive for Candida albicans. An echocardiographic assessment of the heart showed probable infection with an organism not identified. Further details are provided in the efficacy narratives.

Assessor's comment

The MAH confirmed that given the rarity of the disease no patients affected by *Candida meningitis* and/or hydrocephalus due to Candida infection and/or bearing external ventricular derivation were identified.

Question resolved.

Question 2

The dose of 8 mg/kg per day is in line with section 4.2 of the SmPC. However, the MAH is asked to clarify whether the antifungal treatment was continued for at least one week after two sequential negative blood cultures had been obtained and after resolution of clinical signs and symptoms of infection.

Summary of the MAH's response

The protocol defined treatment duration for this study is as follows:

From a minimum of 14 days until one of the following conditions:

- *obtainment of negative results (absence of Candida growth) from at least two consecutive blood cultures and/or resolution of clinical and laboratory symptoms and reduction of mannan antigen blood level (< 125 pg/mL);*
- *obtainment of negative results (absence of Candida growth) from at least two consecutive cultures of cerebrospinal fluid associated with resolution of clinical and laboratory symptoms in case of meningitis, hydrocephalous and external ventricular derivation;*
- *interruption (including addition or switch to another antifungal agent or dosage change of micafungin) due to demonstration of therapy failure.*

Based on this criteria, patients were required to receive at least 14 days of treatment but did not require a predefined treatment duration after obtaining negative results. Efficacy narratives are provided for all patients.

Assessor's comment

The MAH has clarified the treatment duration.

Question resolved.

Question 3

Protocol deviations:

a. The MAH is asked to discuss the high number of the protocol deviations in patients who entered the study including the application of the wrong dose in approx. 50% of the population and the impact on the interpretability of the study results. The statement that protocol deviations did not impact patients' safety or overall study results or conclusions is not supported as the validity of the study is questioned. The MAH is asked to justify the validity of the study results.

b. The MAH should clarify the protocol deviations in patients who entered the study other than those who developed withdrawal criteria. In addition, it is not clear why the patients fulfilling withdrawal criteria had not been withdrawn. The MAH is asked to clarify.

c. Individual patients with protocol deviations should be listed, broken down by study centre.

Summary of the MAH's response

a. Deviations coded to Protocol Deviation (PD) 3 (received wrong treatment or incorrect dose) were the most common deviations observed (17 patients, 48.6%). In 10 of these patients, dosages were not adjusted by staff due to fluctuations in weight caused by edema or other causes, due to the local neonatal intensive care unit protocol. The mean daily dose was 7.9296 mg/kg (standard deviation: 0.6163), which suggests that there is little deviation from the target 8.0 mg/kg daily dose. Details regarding the actual weight adjusted doses received by patients can be found in the population/pharmacokinetic report [Attachment 2, Appendix 4], which further support the similarity of doses and exposures for the patients in this study.

b. In 5 patients, the PD3 listings were assigned due to medication errors. The next most common deviations were PD1, study entry without satisfying entry criteria (7 patients, 20.0%) and PD2, development of withdrawal criteria during the study without patient withdrawal (4 patients, 11.4%). The decision to withdraw patients from the study for these criteria was left to the discretion of the investigator as to whether the benefits of continuing therapy outweighed the reasons for withdrawal.

c. Protocol deviations are provided for all patients in the previously submitted Clinical Study Report for Study 9463-CL-6001 (Appendix 13.2.2.4 [Attachment 3]). The study was conducted at 2 contracted sites in Italy, The independent ethics committee of site 02 did not approve the transfer of sponsorship from Ospedale Pediatrico Bambino Gesù to Astellas; therefore, the Clinical Study Report did not report on the 1 patient enrolled at the second site.

Assessor's comment

The MAH has clarified the high number of protocol deviations. Dosages were not adjusted by staff due to fluctuations in weight caused by edema or other causes, due to the local neonatal intensive care unit protocol. Development of withdrawal criteria during the study without patient withdrawal was left to the discretion of the investigator based on whether the benefits of continuing the treatment outweighed the reasons for withdrawal. Individual patient listings with protocol deviations by study centre were provided.

Question resolved.

Question 4

35 patients were enrolled in the study. There is a large difference between the SAF (n=35) and the mFAS (n=21) although only four patients are reported to not have had confirmation of a fungal infection. The MAH is asked to clarify.

Summary of the MAH's response

The protocol was prepared by the principal investigator based on the site's standard of care for the diagnosis and treatment of neonates and young infants. The criteria established in the protocol for the diagnosis of infection did not include all of the criteria commonly used in studies intended for registration of antifungal agents (e.g., European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) diagnostic criteria, 2008). In addition, the protocol as written, did not define the criteria for proven, probable and suspected infection. However, the variable was included in the electronic case report form (CRF) and assigned by the investigator based on the principles laid out by the EORTC/MSG diagnostic criteria, i.e., proven infection required a positive culture for Candida species from a normally sterile body site. Of note, the study permitted the enrollment of patients with suspected infection and these patients were included in the safety analysis set (N=35) but not in the modified full analysis set (mFAS, N=21). Upon assuming sponsorship of the study, Astellas utilized the following robust definition for the mFAS population consistent with the methodology currently used in registration studies:

> *Patients who had received at least 1 dose of study drug and who had been affected by (i.e., a diagnosis of proven or probable) systemic candidiasis and/or Candida infection at baseline (mFAS).*

The application of the more robust diagnostic criteria, utilized by Astellas to define the mFAS population (which excluded patients with suspected fungal infection), resulted in 14 patients from the safety analysis set being excluded from the mFAS.

Assessor's comment

The MAH has clarified the reasons for the large difference in patients between the safety analysis set (N=35) and the modified full analysis set (mFAS, N=21). Upon assuming sponsorship of the study, the MAH has utilized an updated definition for the mFAS population consistent with the methodology currently used in registration studies. Although the change of definitions of analysis sets was applied post-study, the ***issue is not further pursued***.

Question 5

The percentage of patients achieving mycological eradication at the end of trial was higher than achieving eradication at the end of treatment. 5 patients had been successfully eradicated after treatment until the end of trial.

a. The MAH is asked to clarify the actual duration of treatment in those patients who had been treated for more than 14 days until eradication.

b. Additionally, it should be clarified in how far these patients experienced drug related mild, moderate, severe or life threatening adverse events.

Summary of the MAH's response

a. Patient profiles [Attachment 4] and efficacy narratives [Attachment 1] are provided for each of the following 5 patients that had been successfully eradicated after treatment until the end of study visit. The 5 patients are: 01017, 01024, 01027, 01034 and 01035. These patients all discontinued treatment on day 14 or earlier [Table 1].

Table 1 Patients that had been Successfully Eradicated after Treatment until the End of the Study Visit

Patient Number	Duration of Treatment (Days)
01017	8
01024	8
01027	9
01034	14
01035	14

Source: Patient profiles [Attachment 4].

A list which identifies the outcome for all patients and includes a column to identify which patients received at least 14 days of treatment is located in Appendix 13.2.1.2.2 [Attachment 5] of the previously submitted Clinical Study Report for Study 9463-CL-6001.

b. The patient profiles are provided [Attachment 4], which list the adverse events reported by these patients, including time of onset and end date of the event. Additionally, safety narratives are provided for Patients 01024, 01034 and 01035 in the previously submitted Clinical Study Report for Study 9463-CL-6001.

Assessor's comment

Actual treatment duration in patients and adverse events reported in these patients have been clarified.

Question resolved.

Question 6

The MAH is requested to clarify if patients who discontinued due to lack of efficacy were included in the efficacy analysis.

Summary of the MAH's response

There were 4 patients that discontinued due to a lack of efficacy: Patients 01017, 01024, 01027 and 01030. All 4 patients were included in the efficacy analysis; efficacy narratives are provided for these patients in [Attachment 1].

Assessor's comment

The MAH has clarified the number of patients that discontinued due to lack of efficacy and confirmed their inclusion in the analysis.

Question resolved.

Question 7

The planned report on paediatric population PK and PKPD is missing and should be submitted.

Summary of the MAH's response

The population/pharmacokinetic report is provided with this response [Attachment 2]. The report references the methodology used for the population/pharmacokinetic report of prior studies [Attachment 6].

Assessor's comment

The report contains summarized information on the developed models.

Question resolved.

Question 8

The target concentration ranges in adults and in infants below the age of 4 months should be stated and justified.

Summary of the MAH's response

The safety and efficacy of the treatment of invasive candidiasis in adults and children above the age of 4 months has been established previously. The posology is reflected in the current Summary of Product Characteristics (SmPC [Attachment 7]). The posology for neonates and young infants < 4 months of age was determined on the basis of the different pathogenesis of invasive candidiasis in this population, which required a different approach to estimate the target exposure than was applied for adults. The target exposure in neonates and young infants are derived from the nonclinical model of hematogenous Candida meningoencephalitis in rabbits (Hope et al, 2010 [Attachment 8]; Hope et al, 2008 [Attachment 9]).

Assessor's comment

The basis for the target concentration ranges in infants below the age of 4 months were clarified. In addition, the population PKPD report provided the information that the lower bound of the target exposure was estimated from the efficacious exposure needed to achieve the near-maximum effect in reducing fungal burden in the cerebrum and cerebellum in the rabbit model considering the higher rate of CNS involvement in neonatal candidiasis 10, 11. The upper bound was from the smallest exposure where treatment-related abnormalities were found in a 4-week study in newborn rats (Study GLR-05-0859, IND 55322 serial 317). Therefore, exposure (AUCss) ranges of 166.5 – 580 µg·hr/mL were targeted.

Question resolved.

Question 9

Clarifications are required regarding the time frame for blood sampling for PK analyses (pre-dose, and 1, 3, and 8h post-dose on any day of treatment between day 3-10 of the study). Usually, steady state (in adults) is reached after 4 days at which time plasma concentrations for micafungin are 40-60% higher than after a single dose. The MAH is asked to present the number of patients with blood sampling on day 3 and the possible impact on overall PK results, also taking into account those patients that had received prior micafungin-treatment. Moreover, protocol deviations (see other Assessor's comment) were noted for 24 (68.6%) patients, 17 of which received the wrong treatment or the wrong dose. All protocol deviations should be taken into account for PK analyses and analyses excluding these patients should be presented.

Summary of the MAH's response

Twelve patients had pharmacokinetic samples withdrawn on or before day 3 in Study 9463-CL-6001. Regardless of day of sampling, data was analyzed using the population/pharmacokinetic approach where individual doses and patient characteristics are taken into account. Empirical Baye's estimates were used from the population/pharmacokinetic model to make assumptions at steady state. Modelling details regarding pharmacokinetic parameters can be found in the population/pharmacokinetic report, [Attachment 2, Appendix 4].

Assessor's comment

Twelve of 34 evaluable patients had PK samples drawn on or before day 3. The potential impact on PK parameters was not discussed. But since the population approach was used, the analyses are considered acceptable with respect to this issue since the time of dosing will be taken into account in the data evaluation. In addition, young children are reported to show higher clearance, so steady state might occur earlier.

Out of the patients with protocol deviations (24 patients (68.6%), 17 received the wrong treatment or the wrong dose (see also Q3). However, protocol deviations seem to not have been taken into account for PK analyses and analyses excluding these patients are not presented. No information related to this issue is found in the PopPKPD report.

Not further pursued.

Question 10

It should be stated for which age range the dosing schedule of 8mg/kg per day is considered, since in this study infants older than 4 months were included and treated with this dose, which might be too high in children above 4 months. The MAH is asked to present the data for children below 4 months of age and ≥ 4 months of age separately.

Summary of the MAH's response

The population/pharmacokinetic report provides results for neonates and young infants less than 4 months of age who received ≥ 8 mg/kg per day. There is a significant overlap in exposure values between 10 mg/kg and 8 mg/kg doses. This study was not intended to support a modification of the SmPC posology. However, the approved posology in the SmPC for this population is further supported by the information from the population/pharmacokinetic analyses and the results of Study 9463-CL-6001. Consistent with the SmPC, a dose of 10 mg/kg continues to be recommended for treatment of neonatal candidiasis in order to maximize the proportion of infants who would be expected to achieve the efficacious exposure (> 166.5 µg·hr/mL). More details can be found in the population/pharmacokinetic report [Attachment 2].

Assessor's comment

Since the dose recommendation for children above 4 months remains at 2 mg/kg/day (up to 4 mg/kg/day, the issue is ***not further pursued***.

Question 11

According to the secondary endpoint of the study to identify a conversion factor between the levels of drug in capillary and venous blood, this facto should be reported and the possibility to use an evaluation of PK samples based on this factor in the clinical routine should be discussed.

Summary of the MAH's response

The analysis from this study to support this endpoint has been published and is thoroughly described in the publication by [Auriti et al, 2018] "Validation of Heel Stick Microsampling to Optimize Micafungin Doses in Neonates and Young Infants" [Attachment 10]. The results describe the similarity in plasma concentrations and exposures when drawn either via capillary or venous blood sampling.

Assessor's comment

The response is given in the article.

Issue resolved.

Question 12

The most common TEAEs observed in this study were infections and infestations (40%), investigations (37.1%), general disorders and administration site conditions (20%). Only frequent TEAEs (defined as ≥ 5% of Patients in any Preferred Term) were reported. The MAH is asked to provide TEAEs by the following frequency categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). While most of the presented TEAEs are already labeled in the current SmPC of Mycamine, others are not (e.g. infections

and infestations (40%), respiratory failure (5.7%). The MAH is asked to comment. (also see comment on Table 7)

Summary of the MAH's response

[Table 2] provides a summary of treatment-emergent adverse events (TEAEs) observed in this study, ordered by frequency. Based on 35 patients in the safety analysis set, any TEAE experienced by 4 or more patients is categorized as very common (≥ 1/10) and TEAEs experienced by 1, 2 or 3 patients are common (≥ 1/100 to < 1/10). Because of the size of this study, no uncommon, rare, or very rare events were observed.

Table 2 Treatment-emergent Adverse Events by Frequency (Safety Analysis Set)

Preferred Term MedDRA v20.1	Micafungin (N = 35)
Very common (≥ 1/10)	
Gamma-glutamyltransferase increased	9 (25.7%)
Oedema	5 (14.3%)
Bradycardia	4 (11.4%)
Common (≥ 1/100 to < 1/10)	
Thrombocytopenia	3 (8.6%)
Cholestasis	3 (8.6%)
Septic shock	3 (8.6%)
Hyponatraemia	3 (8.6%)
Hypotension	3 (8.6%)
Leukopenia	2 (5.7%)
Diarrhoea	2 (5.7%)
Hypertransaminasaemia	2 (5.7%)
Sepsis	2 (5.7%)
Bacterial sepsis	2 (5.7%)
Urinary tract infection bacterial	2 (5.7%)
Klebsiella sepsis	2 (5.7%)
Wound dehiscence	2 (5.7%)
Blood bilirubin increased	2 (5.7%)
C-reactive protein increased	2 (5.7%)
Blood alkaline phosphatase increased	2 (5.7%)
Table continued on next page	

Preferred Term MedDRA v20.1	Micafungin (N = 35)
Common (≥ 1/100 to < 1/10) *(continued)*	
Hypokalaemia	2 (5.7%)
Respiratory failure	2 (5.7%)
Coagulopathy	1 (2.9%)
Leukocytosis	1 (2.9%)
Neutropenia	1 (2.9%)
Ascites	1 (2.9%)
Rectal haemorrhage	1 (2.9%)
Drug withdrawal syndrome neonatal	1 (2.9%)
Pyrexia	1 (2.9%)
Hyperbilirubinaemia	1 (2.9%)
Pneumonia	1 (2.9%)
Pneumonia staphylococcal	1 (2.9%)
Candida sepsis	1 (2.9%)
Escherichia infection	1 (2.9%)
Aspartate aminotransferase abnormal	1 (2.9%)
Inflammatory marker increased	1 (2.9%)
Fluid retention	1 (2.9%)
Hypoalbuminaemia	1 (2.9%)
Cerebral haemorrhage	1 (2.9%)
Anuria	1 (2.9%)
Oliguria	1 (2.9%)
Acute kidney injury	1 (2.9%)
Bronchopulmonary dysplasia	1 (2.9%)
Pulmonary hypertension	1 (2.9%)
Decubitus ulcer	1 (2.9%)
Hypertension	1 (2.9%)
Phlebitis	1 (2.9%)

Safety analysis set: all enrolled patients who had received at least 1 dose of study drug.
Source: Table 12.6.1.2 in the previously submitted Clinical Study Report for Study 9463-CL-6001.

Assessor's comment

A summary of treatment-emergent adverse events (TEAEs) observed in this study, ordered by frequency has been provided. Based on the small sample size no further conclusions can be drawn, the ***issue is not further pursued.***

Question 13

Regarding TEAEs leading to death:

a. In all cases, TEAEs leading to death were considered not related to study drug by the MAH although shock, hypotension, hepatic failure, and disseminated intravascular coagulation area labeled as undesirable effects in section 4.8 of the SmPC (in frequency categories "uncommon" and "not known"). The MAH is asked to discuss.

b. The number of TEAEs leading to death should be clarified. It is not understood how the MAH arrives at 3 TEAEs leading to death in this study.

c. In addition, terminal half-life of micafungin ranges from 10-17h in adults. The MAH is asked to justify the adequacy of the time window of 72h in light of average micafungin half-life and elimination in paediatric patients.

d. The MAH is asked to provide the reasons for study drug discontinuation in patients 01006 and 01004 and to confirm whether development of TEAEs led to withdrawal of the study drug.

e. For patient 01005, the MAH is asked to submit the correct date of death in order to clarify the time window between last dose of study drug and occurrence of death. The relationship to the study drug should be confirmed.

Summary of the MAH's response

a. It should be noted that causal relationship to study drug was assigned by the investigator during the conduct of the study. Astellas reviewed each case and provided a written narrative for each patient in the previously submitted Clinical Study Report for Study 9463-CL-6001. Causality assessed as 'Not Related' is based on the presence of confounding factors or alternative etiologies such as prematurity as explained in the narratives for each individual patient. In these cases, there is no reasonable evidence for causal association of these events with micafungin.

b. Three patients experienced 4 fatal TEAEs [Table 3]. However, Table 4 only shows 3 fatal TEAEs. This nuance is due to an inconsistency between 2 CRFs variables [Table 5]. One of 2 fatal TEAEs for Patient 01006 was marked as life-threatening under the CRF variable, toxicity grade (AETOXGR) used in [Table 4]. However, both TEAEs for Patient 01006 were fatal according to the CRF variable, seriousness criteria for SAE (AESDTH) used in [Table 3].

Table 3 Overview of TEAEs (Safety Analysis Set)

	Micafungin (N = 35)	
	n (%)	Number of Events
Any TEAE	31 (88.6)	86
Drug-related † TEAEs	1 (2.9)	1
TEAE with Unknown Relationship † to Study Drug	15 (42.9)	26
Serious TEAEs ‡	12 (34.3)	18
Drug-related † Serious TEAEs ‡	0	0
Serious TEAEs ‡with Unknown Relationship to Study Drug	3 (8.6)	3
TEAEs Leading to Death	3 (8.6)	4
Drug-related †TEAEs Leading to Death	0	0
TEAE Leading to Death with Unknown Relationship † to Study Drug	0	0
TEAEs Leading to Withdrawal of Treatment	0	0
Drug-Related †TEAE Leading to Withdrawal of Treatment	0	0
TEAE Leading to Withdrawal of Treatment with Unknown Relationship † to Study Drug	0	0
Death § ¶	5 (14.3)	8

Safety analysis set: all enrolled patients who had received at least 1 dose of study drug.

A TEAE was defined as an AE experienced any time during study drug administration through 72 hours after the last dose of study drug. Within a system organ class, patients may have experienced more than one adverse event.

AE: adverse event; TEAE: treatment-emergent adverse event

† A reasonable possibility that the event could have been caused by the study drug as assessed by the investigator. If relationship is missing, then it is considered as drug-related. Causal Relationship case report form options were Related/Not Related/Unknown.

‡ Includes SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.

§ All deaths reported after the first study drug administration.

¶ Two patients were reported to have died outside of the 30-day window; however, no further details are available.

Source: Table 12.6.1.1 in the previously submitted Clinical Study Report for Study 9463-CL-6001.

Table 4 TEAEs by Severity (Safety Analysis Set)

Maximum Severity	Micafungin (N = 35)	
	n (%)	Number of Events
Mild	4 (11.4%)	23
Moderate	14 (40.0%)	41
Severe	6 (17.1%)	11
Life-threatening	4 (11.4%)	8
Death	3 (8.6%)	3
Total	31 (88.6%)	86

Safety analysis set: all enrolled patients who had received at least 1 dose of study drug.

Source: Table 12.6.1.4 in the previously submitted Clinical Study Report for Study 9463-CL-6001.

Table 5 Patients with TEAEs Leading to Death

Patient ID	Case Report Form Variable		
	AESDTH	AETOXGR	AETERM
9463-CL-6001-01004	Y	Death	septic shock
9463-CL-6001-01005	Y	Death	septic shock
9463-CL-6001-01006	Y	Life-threatening	septic shock
	Y	Death	septic shock

AESDTH= seriousness criteria for SAE; AETERM=adverse event; AETOXGR= toxicity grade.

Source: Patient profiles [Attachment 4].

c. In the vast majority of micafungin clinical studies, both paediatric and adult studies, a window of 72 hours was used. This window allows for > 4 half-lives to pass and subsequently a near elimination of micafungin from plasma. After 4 half-lives, the amount of drug remaining is considered to be negligible. Regardless of day of sampling, data was analyzed using the population/pharmacokinetic approach where individual doses and patient characteristics are taken into account. Empirical Baye's estimates were used from the population/pharmacokinetic model to make assumptions at steady state.

d. Both patients (Patients 01004 and 01006) experienced fatal events of septic shock [Table 5]. The fatal events were considered unrelated to study drug by the investigator. The patient narratives in Attachment 1 of the previously submitted Clinical Study Report for Study 9463-CL-6001 provide further details and comments from the sponsor.

e. The event of septic shock for Patient 01005 started on 30 August 2015 (4 days after the start of treatment) and the patient died from this event on 12 September 2015. The relationship of the fatal event of septic shock was considered by the investigator not related to study drug. The patient narratives in Attachment 1 of the previously submitted Clinical Study Report for Study 9463-CL-6001 provide further details and comments from the sponsor.

Assessor's comment

The numbers of TEAEs leading to death and reasons for study drug discontinuation have been clarified. Causality assessment has been confirmed.

Question resolved.

Question 14

According to the MAH, no patient experienced serious TEAEs related to the study drug. However, ADRs such as hypotension, neutropenia, acute renal failure, and investigations are labeled in the Mycamine SmPC section 4.8 under paediatric population. Likewise, hypotension, shock and hepatic failure are labeled for adults with frequencies uncommon or not known. Therefore, the statement that no patient experienced serious TEAEs related to study drug is not entirely supported. In addition, infections and infestations were the most common serious TEAE (Table 5, Table 7) and are not labeled in the current SmPC of Mycamine. Also respiratory, thoracic and mediastinal disorders included TEAEs not already labeled. The MAH is asked to comment. (also see comment on Table 5)

Summary of the MAH's response

The causal relationship of adverse events to study drug is at the sole discretion of the investigator. This assessment is based on the clinical course of the individual patient, and labeled adverse drug

reactions may or may not be taken into account when this assessment is being done. The labeled adverse drug reactions in the SmPC are based on the integrated data from all studies and company causality assessment.

Assessor's comment

Causality assessment was performed by the investigator. Although TEAEs were reported that match those labelled in the product information of mycamine, no TEAE was judged as drug-related by the investigator. Based on the data provided, no further inferences can be made. ***Issue not further pursued.***

5. CHMP overall conclusion and recommendation

Study 9463-CL-6001 was submitted by the MAH and aimed at providing more information about the PK and PK/PD profile of a dose range of 8 mg/kg body weight in premature neonates, neonates and infants with systemic candidiasis or candida mengingitis. No information on CNS involvement was found.

In the actual study, patients up to 8 months were included and received micafungin at the dose of 8 mg/kg/day which is only authorised for children less than 4 months.

No firm conclusion on the secondary efficacy endpoints can be made in view of the low number of patients and the strong difference between the SAF and mFAS populations. A high number of protocol deviations are reported including application of the wrong dose in 48.6% of the SAF. Dosages were not adjusted by staff due to fluctuations in weight caused by edema or other causes, due to the local neonatal intensive care unit protocol. Development of withdrawal criteria during the study without patient withdrawal was left to the discretion of the investigator based on whether the benefits of continuing the treatment outweighed the reasons for withdrawal.

No changes to the product information of Mycamine were applied for within this procedure.

☒ Fulfilled:

No further information is requested.