15 November 2018
EMA/869774/2018
Human Medicines Evaluation Division

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

Cancidas

caspofungin

Procedure no: EMEA/H/C/000379/P46/063

Note

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

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Table of contents

1. Introduction

On 22 august 2018, the MAH submitted a completed paediatric study for Cancidas, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "Protocol P064 clinical study: a Multicentre, Double- Blind, Randomized, Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Amphotericin B Deoxycholate in the Treatment of Invasive Candidiasis in Neonates and Infants Less Than 3 Months of Age" is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Powder for concentrate for solution for infusion 50 and 70 mg

Cancidas was intravenously administered as caspofungin acetate (50mg/vial)

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- P064 clinical study: a Multicentre, Double- Blind, Randomized, Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Amphotericin B Deoxycholate in the Treatment of Invasive Candidiasis in Neonates and Infants Less Than 3 Months of Age

2.3.2. Clinical study

P064 clinical study: a Multicentre, Double- Blind, Randomized, Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Amphotericin B Deoxycholate in the Treatment of Invasive Candidiasis in Neonates and Infants Less Than 3 Months of Age

Description

This was a multicentre, double-blind, randomized, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin versus amphotericin B deoxycholate in the treatment of neonatal and infant invasive candidiasis. Neonates and infants less than 3 months of age with documented (culture-confirmed) invasive Candida infection (ICI) within 96 hours prior to study entry were to be randomized in a 2:1 ratio to receive either intravenous caspofungin 2 mg/kg (per body weight) once daily infused over 2 hours or intravenous amphotericin B deoxycholate 1 mg/kg (per body weight) once daily infused over 2 hours. In an effort to strive for adequate representation of participants from different weight groups (reflective of participant gestational age) in both intervention groups, randomization was stratified into 3 weight categories (based on weight at study entry): <1000

grams, 1000 to 1500 grams, and >1500 grams. The study was terminated early due to operational infeasibility prior to enrolling the projected sample size.

Methods

Objective(s)

Primary objective

To compare caspofungin to amphotericin B deoxycholate with respect to the efficacy endpoint of fungal-free survival at the 2-week posttherapy follow-up visit (ie, the proportion of participants who survived through the 2-week posttherapy follow-up period and had documented microbiological eradication of Candida sp. from follow-up cultures collected after the initiation of study therapy).

Secondary objectives

Efficacy:

To assess in neonates and infants who are treated with caspofungin or amphotericin B deoxycholate for documented invasive candidiasis, fungal-free survival at the end of study therapy (ie, the proportion of patients who survived through the end of study therapy visit period and had documented microbiological eradication of Candida sp. from follow-up cultures collected after the initiation of study therapy).

Safety:

To assess the safety in neonates and infants who are treated with caspofungin or amphotericin B deoxycholate for documented invasive candidiasis.

Exploratory objectives

To assess in neonates and infants who are treated with caspofungin or amphotericin B deoxycholate for documented invasive candidiasis:

1. The proportion of participants in each treatment group with evidence of Candida meningoencephalitis at study entry who had fungal-free survival at the 2-week posttherapy follow-up visit.
2. The proportion of participants in each treatment group with the development of complicated candidiasis while on study therapy or during the 8-week posttherapy follow-up period. (NOTE: The definition of complicated candidiasis includes the development of at least one of the following on or after Day 5 of study therapy: [a] valvular vegetation or mural thrombus on echocardiogram, [b] meningitis documented by the presence of Candida in CSF culture or a CSF WBC count >25 cells/mm3 with no other organism identified, [c] evidence of abdominal abscess, or [d] documented endophthalmitis).
3. The efficacy profile relative to caspofungin-treated participants with invasive candidiasis in the prior pediatric documented infection study (Protocol 043, children and adolescents [3 months to 17 years]) and prior adult studies (Protocols 014 and 801).

Study design

This was a multicentre, double-blind, randomized, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin versus amphotericin B deoxycholate in the treatment of neonatal invasive candidiasis. Approximately 90 neonates and infants less than 3 months of age with

documented (culture-confirmed) ICI within 96 hours prior to study entry were to be randomized in a 2:1 ratio to receive either intravenous caspofungin 2 mg/kg (per body weight) once daily infused over 2 hours or intravenous amphotericin B deoxycholate 1 mg/kg (per body weight) once daily infused over 2 hours. The study was terminated early due to operational infeasibility prior to enrolling the projected sample size.

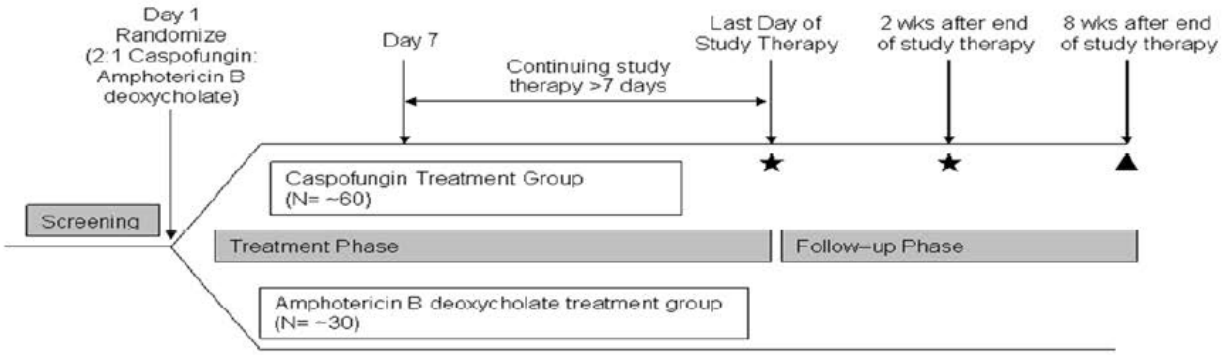
The duration of study therapy with caspofungin or amphotericin B deoxycholate was variable and dependent on a variety of factors, including the rapidity of a participant's clinical and microbiological response, the participant's general medical condition, and the underlying site of Candida infection. In general, patients were to be treated with study therapy for a minimum of 14 days following the time of documented negative cultures from the site of infection and improvement of any clinical signs and symptoms of invasive candidiasis. The maximum duration of study therapy permitted was 90 days. If warranted, permission to extend the duration of therapy could be requested.

Participants were monitored for adverse experiences while on study therapy and during the 2-week posttherapy follow-up period. Selected laboratory safety tests were performed from blood collected at screening, on Day 4 (or Day 3 or Day 5) and Day 7 of study therapy, twice weekly thereafter while on study therapy, on the last day of study therapy, and at the 2-week posttherapy follow-up visit. A physical examination was performed at prestudy, twice weekly throughout the study therapy period (including Days 4 and 7), on the last day of study therapy, and at each of the 2 posttherapy follow-up visits.

A detailed description and evaluation of the Candida infection was performed at screening, daily while on study therapy, on the last day study therapy, and at the 2- and 8-week posttherapy follow-up visits. Resolution or progression of the Candida infection was to be documented by assessment of signs and symptoms, radiographic studies (when clinically indicated), and follow-up blood cultures or, as appropriate, other follow-up cultures (including urine or CSF). Based on all available data, an efficacy assessment was to be made at the end of study therapy and at the 2-week posttherapy follow-up visit.

Caspofungin pharmacokinetic parameters (C2h [peak] and C24h [trough]) were also determined on Days 4 and 7 of study therapy. Sparse plasma PK samples were obtained from different participants on Days 4 and 7 to minimize the blood volume needed from each participant.

MK-0991 Protocol 064 Trial Design



Note:
1) Timepoints in the figure are applicable to both the caspofungin and amphotericin B deoxycholate treatment groups.
2) Please refer to the Section 1.7 (Study Flow Chart) and Section 3.2.3 for complete descriptions of study procedures.
3) Patients will be monitored for adverse events while on study therapy and through the 2-week posttherapy follow-up visit.
4) Study therapy begins on Day 1 and should not exceed 90 days
★ = The primary efficacy assessment is fungal-free survival at the end of study therapy (secondary timepoint) and 2-week posttherapy follow-up visit (primary timepoint).
▲ = An exploratory efficacy assessment is development of complicated candidiasis at the 8-week posttherapy follow-up visit.

Assessors comments

This was a multicentre, double-blind, randomized, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin versus amphotericin B deoxycholate in the treatment of neonatal invasive candidiasis. Approximately 90 neonates or infants (<3m) with confirmed invasive candidiasis (culture confirmed) were to be randomized (2:1) to either treatment with caspofungin 2mg/kg infused over 2 hours or amphothericin B deoxycholate 1mg/kg infused over 2 hours. Infusion time for caspofungin was different than stated in the SmPC. However this was altered for blinding reasons, which is acceptable. Longer infusion time is sometimes applied to reduce infusion related toxicities. Therefore this could have an influence on the safety evaluation of caspofungin.

Treatment duration was variable, depending on rapidity of response, patients characteristics and on site of infection. In general, patients were to be treated at least 14 days after cultures from site of infection became negative and improvement in clinical signs and symptoms of invasive candidiasis.

The study design is acceptable to meet the primary and secondary objectives. The comparator is, however, not an ideal comparator, since fluconazole or liposomal amphotericin B are used more often and thus considered more as standard-of-care by many sites, despite being recommended in guidelines (including the IDSA guidelines published in 2016).

Study population /Sample size

Inclusion criteria

Neonates and infants who were <3 months (90 days) of age with documented (culture confirmed), invasive Candida infection were eligible to participate in this trial. Documented invasive Candida infection was defined as follows:

- A positive culture for Candida spp. collected from a normally sterile body fluid within 96 hours of study entry OR
- A positive culture for Candida spp. collected within 96 hours of study entry from a newly-placed drain inserted into a normally sterile body site.

Parent (or guardian) understands the study procedures, alternative treatments available, and risks involved with the study and voluntarily agree to the patient's participation by giving written informed consent.

Parent (or guardian) provides written informed consent for the trial.

Exclusion criteria

- Participant is ≥3 months (≥90 days) of age at the time of informed consent.
- Participant has Candida disease limited to the oropharynx, esophagus, or other mucosal or superficial skin surfaces (eg, vagina or other genitalia, colonic tract, skin folds, nail beds, etc.).
- Participant has evidence of infection limited to a positive culture for Candida spp. From the sputum, broncho-alveolar lavage, catheter tip, or previously placed indwelling nonvascular catheters/drains.
- Participant has a prosthetic device (eg, prosthetic heart valve) at a suspected site of Candida infection.
- Participant is actively co-infected with a non-Candida fungal organism.
- Participant has received more than 48 hours of systemic (IV or oral) antifungal treatment since the time the positive Candida index culture was collected as therapy for this episode of invasive candidiasis.
- Participant has failed prior systemic (IV or oral) antifungal therapy for this episode of invasive candidiasis.
- Participant has exclusionary laboratory values obtained within 48 hours of study therapy initiation.
- Participant is not expected to survive at least 5 days.
- Participant has a diagnosis of acute hepatitis or cirrhosis due to any cause.
- Participant is currently participating or has participated in a study with an investigational compound or device.
- Participant has previously participated in this study.
- Participant is scheduled or anticipated to receive rifampin or other systemic (IV or oral) antifungal therapy (ie, an intravenous or oral formulation of the member of the polyene, triazole, or echinocandin class) while on study therapy.
- Participant has known renal insufficiency, which, in the investigator's assessment, has the potential to worsen as a result of subsequent study therapy with amphotericin B deoxycholate.
- Participant or the participant's mother has a history of allergy, hypersensitivity, or any serious reaction to caspofungin or another member of the echinocandin class (eg, micafungin, anidulafungin, or aminocandin).

- Participant or the participant's mother has a history of allergy, hypersensitivity, or any serious reaction to amphotericin B deoxycholate or other members of the polyene class (eg, amphotericin B lipid complex, liposomal amphotericin B, or amphotericin B colloidal dispersion).
- Participant has a severe congenital disorder known to lower immune response.

Sample size

The study will enroll approximately 60 patients in the caspofungin treatment group and 30 patients in the amphotericin B deoxycholate treatment group, to achieve 80% power (2-sided, α=0.05) to demonstrate the primary efficacy hypothesis that caspofungin is superior to amphotericin B deoxycholate with regard to the proportion of patients with fungal-free survival at the 2-week posttherapy follow-up visit. The minimum criterion for success is that the lower bound of the 95% CI for the difference between the 2 treatment groups (caspofungin minus amphotericin B deoxycholate) in the primary efficacy endpoint is >0.

The sample size is based on an underlying response rate of 50% for the amphotericin B deoxycholate treatment group from the recently published comparative study in 32 neonates and infants with invasive candidiasis where a favorable response was observed in 86.7% of caspofungin-treated patients and 41.7% of amphotericin B deoxycholatetreated patients. The study is designed to have 80% power to demonstrate the superiority of caspofungin over amphotericin B deoxycholate at an overall two-sided, 5% alpha-level, if the underlying treatment difference in fungal-free survival at the 2-week posttherapy visit is ~30 percentage points (or larger).

Assessors comments

Inclusion and exclusion criteria are acceptable, as well as sample size.

Treatments

Caspofungin was administered at 2 mg/kg once daily (with no loading dose). Amphotericin B deoxycholate was administered at 1 mg/kg once daily.

Initial dosing with the study medications was based on the participant's actual body weight (in kg) at the time of study entry. The participant was weighed at least weekly during the treatment period. The study intervention dose (mg) was adjusted as the participant's weight increased to maintain the mg/kg dose of the assigned treatment throughout the study treatment period.

Caspofungin and amphotericin B deoxycholate were both reconstituted/prepared by an unblinded study pharmacist and administered intravenously over approximately 2 hours. The caspofungin prescribing information indicates that the dose should be administered over 1 hour; however, in this trial, a 2-hour infusion duration was used to maintain study blind. As these 2 products differ in color, opaque masking was used over the infusion materials to ensure adequate blinding of the treatment group.

Outcomes/endpoints

Efficacy endpoints are summarized below.

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Proportion of patients with fungal-free survival through the 2-week posttherapy period	P	Miettinen and Nurminen method	FAS	A patient with missing data will be considered a failure.
Proportion of patients with fungal-free survival through the 2-week posttherapy period	S	Miettinen and Nurminen method	PP	Observed data
Secondary				
Proportion of patients reporting fungal-free survival at the end of study therapy	P	Miettinen and Nurminen method	FAS	A patient with missing data will be considered a failure.
Proportion of patients reporting fungal-free survival at the end of study therapy	S	Miettinen and Nurminen method	PP	Observed data
Exploratory #1				
Proportion of patients with fungal-free survival at the 2-week posttherapy follow-up visit in the subset of patients with *Candida* meningoencephalitis at study entry	P	Descriptive	FAS	A patient with missing data will be considered a failure.
Exploratory #2				
Proportion of patients with complicated candidiasis through the 8-week posttherapy follow-up visit	P	Descriptive	FAS	Observed data
[a] P=Primary approach; S=Secondary approach.				

All safety tabulations will use an all-patients-as-treated (APaT) population, which includes all patients who receive at least one dose of study therapy. There are no safety parameters that rise to the level of formal statistical testing in this study (i.e., no Tier 1 events).

Assessors comments

acceptable

Statistical Methods

The primary hypothesis will be evaluated by comparing the caspofungin treatment group to the amphotericin B deoxycholate treatment group with respect to the proportion of patients with fungal-free survival at the 2-week posttherapy follow-up visit.

All efficacy evaluations will use a full analysis set (FAS) patient population, which includes those patients who receive at least one dose of study therapy and have a documented (culture-confirmed) diagnosis of invasive candidiasis (see Inclusion Criteria). All patients, irrespective of body weight at study entry, will be grouped together for the primary evaluation. Subgroup evaluation based on the 3 body weight categories at study entry (<1000 grams, 1000-1500 grams, >1500 grams) will also be displayed. Of note, a per-protocol population will also be evaluated for the primary and secondary efficacy endpoints.

The treatment comparisons for the primary and secondary efficacy analyses will be made using the difference in response rates between the 2 treatment groups and its 95% confidence interval. The

confidence interval for the difference in response rates will be calculated using a methodology proposed by Miettinen and Nurminen.

Assessors comments

acceptable

Results

Recruitment/ Number analysed

Due to the decision to terminate the study early, only 51 of the projected 90 participants were randomized into this study. Overall, 34 participants were randomized to the caspofungin group, and 17 participants randomized to the amphotericin B deoxycholate group. A total of 49 participants received study medication, as 1 randomized participant in the caspofungin treatment group died prior to dosing, and 1 randomized participant in the amphotericin B deoxycholate treatment group discontinued the study prior to dosing due to physician's decision. An additional 2 participants in the caspofungin treatment group did not have documented (culture-confirmed) invasive Candida infections at study entry. Therefore, the ASaT population included 49 participants and the FAS population included 47 participants.

Disposition of Subjects

	Caspofungin 2 mg/kg		Amphotericin B deoxycholate 1 mg/kg		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					10	
All Subjects as Randomized	34		17		51	
Trial Disposition Status						
Completed	28	(82.4)	13	(76.5)	41	(80.4)
Discontinued	6	(17.6)	4	(23.5)	10	(19.6)
Adverse Event	1	(2.9)	0	(0.0)	1	(2.0)
Death	3	(8.8)	3	(17.6)	6	(11.8)
Physician Decision	1	(2.9)	1	(5.9)	2	(3.9)
Technical Problems	1	(2.9)	0	(0.0)	1	(2.0)
Study Medication Disposition Status						
Started	33		16		49	
Completed	22	(66.7)	13	(81.3)	35	(71.4)
Discontinued	11	(33.3)	3	(18.8)	14	(28.6)
Adverse Event	4	(12.1)	0	(0.0)	4	(8.2)
Death	1	(3.0)	1	(6.3)	2	(4.1)
Lack Of Efficacy	1	(3.0)	0	(0.0)	1	(2.0)
Non-Compliance With Study Drug	1	(3.0)	0	(0.0)	1	(2.0)
Other	2	(6.1)	0	(0.0)	2	(4.1)
Physician Decision	2	(6.1)	2	(12.5)	4	(8.2)
Each subject is counted once for Trial Disposition, Subject Study Medication Disposition based on the latest corresponding disposition record.						

Source: [P064MK0991: adam-adsl]

Assessors comments

Due to early study termination only 51 of the projected 90 participants were randomized. 34 were randomized to receive caspofungin, 17 to the amphotericin B deoxycholate group. 2 participants never received medication, 1 because of early death prior to receiving study treatment (caspofungin) and 1 discontinued prior to dosing due to physician's decision. 2 patients did not have documented (culture-confirmed) invasive candida infection.

Eighty percent of randomized patients completed the study and 71% completed the study intervention regimen. Most common reason for early study discontinuation in both groups was death. Participants discontinued study treatment early was higher in amphotericin B deoxycholate group. Most common reason for study intervention discontinuation among caspofungin treatment was an AE.

One patient was unblinded by site personnel to clinical manage the participant, after receiving an overdose of study therapy on 5 occasions due to a dosage miscalculation. No AEs were reported associated with overdose. The participant discontinued study therapy.

Baseline data

The participant population included critically-ill infants and neonates with culture-confirmed invasive candidiasis. Overall, mean gestational age was 32.4 weeks . At trial enrolment median age was 22.0 days, and mean weight was 2042.9 grams. Similar proportions of participants received prior antifungal therapy in each intervention group.

The most common pre-treatment manifestation of invasive candidiasis was candidemia, seen in 32 (68.1%) of the 47 participants in the FAS.

Of the 34 participants from whom baseline isolates were available for central laboratory testing, 30 participants (88%) had an infection with Candida albicans only; 1 participant (3%) had both Candida albicans and Candida glabrata identified at baseline; and 1 participant (3%) had an infection with Candida glabrata only. Additionally, there was 1 participant (3%) with Candida intermedia, and 1 participant (3%) with Candida tropicalis. All isolates were obtained from blood or urine. There were 4 participants who had CSF sampling performed at screening, all of which were negative.

Table 10-3
Subject Characteristics
Full Analysis Set Population

	Caspofungin 2 mg/kg		Amphotericin B deoxycholate 1 mg/kg		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	31		16		47	
Gender						
Male	18	(58.1)	7	(43.8)	25	(53.2)
Female	13	(41.9)	9	(56.3)	22	(46.8)
Age (Days)						
0 - 27 28 - 55 56- 83 ≥ 84	PPD		PPD		PPD	
Mean SD Median Range	30.0 19.6 PPD		30.6 22.3 PPD		30.2 20.3 PPD	
Race						
American Indian or Alaska Native Black or African American Multi-Racial White	PPD		PPD		PPD	
Ethnicity						
Hispanic Or Latino Not Hispanic Or Latino Not Reported Unknown	PPD		PPD		PPD	
Baseline Weight (g)						
<1000 g	4	(12.9)	3	(18.8)	7	(14.9)
1000 to 1500 g	9	(29.0)	4	(25.0)	13	(27.7)
>1500 g	18	(58.1)	9	(56.3)	27	(57.4)
Mean SD Median Range	1982.1 980.6 PPD		2160.9 1513.8 PPD		2042.9 1175.5 PPD	
Gestation Age (Weeks)						
Mean SD Median Range	32.521 5.163 PPD		32.080 4.399 PPD		32.371 4.873 PPD	
Birth Weight (g)						
<1000 g	7	(22.6)	3	(18.8)	10	(21.3)

	Caspofungin 2 mg/kg		Amphotericin B deoxycholate 1 mg/kg		Total	
	n	(%)	n	(%)	n	(%)
1000 to 1500 g	11	(35.5)	6	(37.5)	17	(36.2)
>1500 g	13	(41.9)	7	(43.8)	20	(42.6)
Mean	1803.8		1836.3		1814.9	
SD	937.9		1177.1		1012.8	
Median	PPD		PPD		PPD	
Range						
Country						
Brazil	PPD		PPD		PPD	
Colombia						
Mexico						
South Africa						
Turkey						
Prestudy Systemic Antifungal Prophylaxis						
Antifungal prophylax	24	(77.4)	13	(81.3)	37	(78.7)
No antifungal prophylaxis	7	(22.6)	3	(18.8)	10	(21.3)

Source: [P064MK0991: adam-adsl]

Assessors comments

The groups were generally well balanced for baseline characteristics: age, gestational age, baseline weight, birth weight and antifungal prophylaxis.

Clinical pharmacology

In study P064, caspofungin pharmacokinetics in plasma in neonates and infants (<3 months of age) were assessed following 4 or 7 days of daily dosing with 2 mg/kg caspofungin administered by intravenous infusion over 2 hours. Sparse plasma PK samples were obtained from different participants on Days 4 and 7 to minimize the blood volume collected from each participant as described in the protocol [Ref. 5.3.5.1: P064MK0991: 16.1.1]. CSF samples for caspofungin assay were to be collected in this study whenever possible. Only one CSF sample was obtained and was not assayed since it would not provide meaningful information.

Geometric mean peak plasma concentrations (at the end of the 2-hour infusion) of caspofungin were 8.58 µg/mg (n=12) and 5.99 µg/mL (n=11) after 4 and 7 days of dosing, respectively and geometric mean trough plasma concentration (~24 hours after start of infusion) were 2.93 µg/mL (n=13) and 3.12 µg/mL (n=12) after 4 and 7 days of dosing, respectively. Caspofungin peak and trough plasma concentrations were comparable after 4 and 7 days of dosing supporting that steady state is achieved within 4 days [Ref. 5.3.5.1: P064MK0991: 11.2].

In a previous study in neonates and infants (<3 months of age), geometric mean peak and trough plasma concentrations following 4 days of dosing with 25 mg/m2 caspofungin administered by intravenous infusion over 1 hour were 10.48 µg/mL (n=12) and 2.96 µg/mL (n=11) [Ref. 5.3.3.2: P058: 11]. Caspofungin pharmacokinetic data from study P064 are not directly comparable to this or other previous studies since caspofungin was infused over 2 hours in study P064 to maintain the blinding versus a 1-hour infusion used in previous studies and included in the prescribing information. Nevertheless, the similarity in trough concentration, in particular, between the two studies in neonates and infants suggests caspofungin exposure was comparable.

Assessors comments

In the context of a paediatric study in neonates and infants (<3 months of age), pharmacokinetic data may be relevant for identification of sub-groups in which the exposure differs from the overall study population to a clinically relevant extent. These two groups present the largest pharmacokinetic challenges because rapid developmental changes in absorption, distribution, metabolism and excretion may occur. However, due to the small sample size enrolled in study P064, due to the fact that PK analysis is neither a primary objective nor a secondary objective in this study and due to the fact the time of infusion used (2 hours) is different from the previous studies and from the time recommended in the labelling, PK input is limited. Nevertheless, some relevant information regarding the pharmacokinetic characteristics can be gathered, especially that caspofungin peak and trough plasma concentrations were comparable after 4 and 7 days of dosing supporting that steady state is achieved within 4 days. Descriptive statistics were calculated for peak, trough and intermediate caspofungin plasma concentrations on Days 4 and 7 and a comparable Ctrough is observed compared to a previous study in neonates and infants. The methodology and the analytical methods are deemed adequate for the intended PK purpose.

The current dosing recommendations in the paediatric population given under 4.2 of the SmPC correspond to the administration of a slow intravenous infusion over approximately 1 hour and not a 2-hours infusion. In this context, the new limited PK data do not warrant a revision to the current approved information in sections 4.2 and 5.2.

Efficacy results

In the FAS population, the proportion of participants with fungal-free survival at 2 weeks posttherapy in the caspofungin treatment group (71.0%) was similar to that seen in the amphotericin B deoxycholate treatment group (68.8%). The adjusted fungal-free survival difference between the 2 treatment groups (caspofungin minus amphotericin B deoxycholate) and the 95% CI based on Miettinen & Nurminen method stratified by weight category was -0.9 (95% CI -24.3 to 27.7). Comparable results were also noted in the Per-Protocol population

Table 2.5: 1

Proportion of Subjects with Fungal-Free Survival at the 2-week Post Therapy
Full Analysis Set Population

Endpoint	Caspofungin 2 mg/kg (N=31) [1] m/n (%) (95% CI)	Amphotericin B deoxycholate 1 mg/kg (N=16) [2] m/n (%) (95% CI)	Difference [1] - [2] % (95% CI)
Fungal-free survival at the 2-week post therapy	22/31 (71.0) (52.0 , 85.8)	11/16 (68.8) (41.3 , 89.0)	-0.9 (-24.3, 27.7)

N=Number of subjects in each treatment group.

m/n = Number of subjects with fungal-free survival /number of subjects in the analysis.

Missing data were imputed as failure if death or rescue medication was taken; Otherwise, missing data were imputed with LOCF method.

95% exact CI for the proportion was calculated in each treatment group. 95% CI for difference between two treatment groups was calculated based on Miettinen & Nurminen method stratified by stratum (Weight category based on weight at study entry) with Cochran Mantel-Haenszel's weights.

Source: [P064MK0991: adam-adsl; admb]

No formal subgroup analyses were planned or performed. Descriptive statistics, such as counts and percentages by gender, race, and weight stratification categories (<1000g, 1000-1500g, >1500g), and use of prestudy systemic (oral or IV) antifungal prophylaxis, are presented below:

Proportion of Subjects with Fungal-Free Survival at the 2-Week Post Therapy by Various Subgroups
Full Analysis Set Population

Subgroup	Caspofungin 2 mg/kg (N=31) m/n (%)	Amphotericin B deoxycholate 1 mg/kg (N=16) m/n (%)
Weight Stratification Category		
<1000g	0/4 (0.0)	2/3 (66.7)
1000-1500g	7/9 (77.8)	4/4 (100.0)
>1500g	15/18 (83.3)	5/9 (55.6)
Gender		
Male	11/18 (61.1)	5/7 (71.4)
Female	11/13 (84.6)	6/9 (66.7)
Race		
American Indian or Alaska Native	PPD	PPD
Black or African American		
Multi-Racial		
White		
Use of prestudy systemic (oral or IV) antifungal prohylaxis		
Antifungal prophylax	16/24 (66.7)	8/13 (61.5)
No antifungal prophylaxis	6/7 (85.7)	3/3 (100.0)

N=Number of subjects in each treatment group.
m/n = Number of subjects with fungal-free survival /number of subjects in the analysis.
Missing data were imputed as failure if death or rescue medication was taken; Otherwise, missing data were imputed with LOCF method.

Source: [P064MK0991: adam-adsl; admb]

Table 11-3
Proportion of Subjects with a Fungal Free Survival Response at the 2-week Post Therapy by Baseline Pathogen from Central Laboratory
Full Analysis Set Population

Pathogen	Caspofungin 2 mg/kg (N=31) m/n (%)	Amphotericin B deoxycholate 1 mg/kg (N=16) m/n (%)
Candida albicans	16/22 (72.7)	5/9 (55.6)
Candida glabrata	1/1 (100.0)	1/1 (100.0)
Candida intermedia	0/1 (0.0)	0/0
Candida tropicalis	1/1 (100.0)	0/0

N = Number of subjects in the analysis population.
m/n = Number of subject with fungal free survival response /number of subjects with this pathogen in baseline
Missing fungal free survival Response were imputed as failure if death or rescue medication was taken; Otherwise, missing data were imputed with LOCF method.
One subject had both *Candida albicans* and *Candida glabrata* identified at baseline.

Source: [P064MK0991: adam-adsl; admb]

Secondary efficacy endpoints

The proportion of participants achieving fungal-free survival at the end of study therapy was similar among the caspofungin group (71.0%) and the amphotericin B deoxycholate group (75.0%) in the FAS population.

Proportion of Subjects with Fungal-Free Survival at the end of study therapy
Full Analysis Set Population

Endpoint	Caspofungin 2 mg/kg (N=31) [1] m/n (%) (95% CI)	Amphotericin B deoxycholate 1 mg/kg (N=16) [2] m/n (%) (95% CI)	Difference [1] - [2] % (95% CI)
Fungal-free survival at the end of study therapy	22/31 (71.0) (52.0 , 85.8)	12/16 (75.0) (47.6 , 92.7)	-6.3 (-30.2, 22.6)

N=Number of subjects in each treatment group.
m/n = Number of subjects with fungal-free survival /number of subjects in the analysis.
Missing data were imputed as failure if death or rescue medication was taken; Otherwise, missing data were imputed with LOCF method.
95% exact CI for the proportion was calculated in each treatment group. 95% CI for difference between two treatment groups was calculated based on Miettinen & Nurminen method stratified by stratum (Weight category based on weight at study entry) with Cochran Mantel-Haenszel's weights.

Source: [P064MK0991: adam-adsl; admb]

Comparable results were also noted in the Per-Protocol population.

Proportion of Subjects with Fungal-Free Survival at the end of study therapy
Per Protocol Population

Endpoint	Caspofungin 2 mg/kg (N=23) [1] m/n (%) (95% CI)	Amphotericin B deoxycholate 1 mg/kg (N=12) [2] m/n (%) (95% CI)	Difference [1] - [2] % (95% CI)
Fungal-free survival at the end of study therapy	19/23 (82.6) (61.2 , 95.0)	11/12 (91.7) (61.5 , 99.8)	-9.5 (-34.0, 20.4)

N=Number of subjects in each treatment group.
m/n = Number of subjects with fungal-free survival /number of subjects in the analysis.
Missing data were imputed as failure if death or rescue medication was taken; Otherwise, missing data were imputed with LOCF method.
95% exact CI for the proportion was calculated in each treatment group. 95% CI for difference between two treatment groups was calculated based on Miettinen & Nurminen method stratified by stratum (Weight category based on weight at study entry) with Cochran Mantel-Haenszel's weights.

Source: [P064MK0991: adam-adsl; admb]

Assessors comments

Efficacy results are comparable between caspofungin and amphotericin B deoxycholate, for both the FAS and PP populations. No formal subgroup analysis was performed. Descriptive statistics were presented.

Of the 34 participants from whom baseline isolates were available for central laboratory testing, 1 participant (3%) had both Candida albicans and Candida glabrata identified at baseline; 30 participants (88%) had an infection with Candida albicans only; 1 participant (3%) had an infection with Candida glabrata only. Additionally, there was 1 participant (3%) with Candida intermedia, and 1 participant (3%) with Candida tropicalis. All isolates were obtained from blood or urine. There were 4 participants who had cerebrospinal fluid sampling performed at screening, all of which were negative.

The small sample size limits the conclusions that can be drawn, however in patients with C albicans there was a higher proportion of patients with fungal-free survival at 2 weeks posttherapy.

Efficacy results at end of study are comparable between groups both in the FAS and PP populations.

Clinical response was comparable between both groups at all time points in both the FAS and PP population.

Safety results

The safety and tolerability of caspofungin in infants and neonates < 3 months of age was monitored by clinical assessment of AEs and by repeated measurements of hematology and blood chemistry, and vital signs. All safety analyses were based on the ASaT population, which included 49 randomized participants who received at least 1 dose of study intervention.

Overall extent of exposure

The mean duration of exposure was similar in the caspofungin group (16.8 days) and the amphotericin B deoxycholate group (17.8 days). The majority of participants in both intervention groups received study intervention for 15 to 21 days.

Summary of adverse events

As expected in this critically ill patient population, the incidence of AEs was high in both intervention groups. Although the small sample size limits the conclusions that can be drawn, the proportion of participants who experienced a SAE was higher in the amphotericin B deoxycholate group compared with the caspofungin group. No SAEs were considered to be related to study intervention. Overall, few subjects discontinued due to an AE and few AEs were considered related to study intervention by the investigator.

Analysis of Adverse Event Summary
Treatment Period and First 14 Follow-Up Days
All Subjects as Treated Population

	Caspofungin 2 mg/kg [1]		Amphotericin B deoxycholate 1 mg/kg [2]		Difference [1] - [2]
	m	n (%)	m	n (%)	% Estimate (95% CI)†
Subjects in population	33		16		
with one or more adverse events	28	(84.8)	16	(100.0)	-15.2 (-31.1, 5.5)
with no adverse event	5	(15.2)	0	(0.0)	15.2 (-5.5, 31.1)
with drug-related‡ adverse events	2	(6.1)	2	(12.5)	-6.4 (-31.1, 10.2)
with non-serious adverse events	28	(84.8)	15	(93.8)	-8.9 (-26.5, 15.2)
with serious adverse events	6	(18.2)	7	(43.8)	-25.6 (-51.9, 1.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0.0 (-19.7, 10.6)
who died	2	(6.1)	2	(12.5)	-6.4 (-31.1, 10.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-19.7, 10.6)
discontinued drug due to an adverse event	4	(12.1)	1	(6.3)	5.9 (-17.9, 22.8)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-19.7, 10.6)
discontinued drug due to a serious adverse event	2	(6.1)	1	(6.3)	-0.2 (-23.3, 14.9)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-19.7, 10.6)

† Based on Miettinen & Nurminen method.
‡ Determined by the investigator to be related to the drug.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Source: [P064MK0991: adam-adsl; adae]

Common adverse events

The most frequently reported individual AE terms by participants in the caspofungin group included anemia 10 (30.3%), pyrexia 6 (18.2%), and sepsis 3 (9.1%). In the amphotericin B deoxycholate group, the most frequently reported AEs included anemia 8 (50.0%), sepsis 4 (25.0%), pyrexia 3 (18.8%), and aspartate aminotransferase increased 3 (18.8%).

Subjects With Adverse Events
(Incidence ≥ 10% in One or More Treatment Groups)
Treatment Period and First 14 Follow-Up Days
All Subjects as Treated Population

	Caspofungin 2 mg/kg		Amphotericin B deoxycholate 1 mg/kg	
	n	(%)	n	(%)
Subjects in population	33		16	
with one or more adverse events	28	(84.8)	16	(100.0)
with no adverse events	5	(15.2)	0	(0.0)
Blood and lymphatic system disorders	**10**	**(30.3)**	**8**	**(50.0)**
Anaemia	10	(30.3)	8	(50.0)
Cardiac disorders	**2**	**(6.1)**	**4**	**(25.0)**
Tachycardia	2	(6.1)	2	(12.5)
Gastrointestinal disorders	**11**	**(33.3)**	**5**	**(31.3)**
Abdominal distension	1	(3.0)	2	(12.5)
General disorders and administration site conditions	**7**	**(21.2)**	**3**	**(18.8)**
Pyrexia	6	(18.2)	3	(18.8)
Hepatobiliary disorders	**4**	**(12.1)**	**3**	**(18.8)**
Infections and infestations	**14**	**(42.4)**	**10**	**(62.5)**
Sepsis	3	(9.1)	4	(25.0)
Injury, poisoning and procedural complications	**4**	**(12.1)**	**2**	**(12.5)**
Investigations	**1**	**(3.0)**	**4**	**(25.0)**
Alanine aminotransferase increased	0	(0.0)	2	(12.5)
Aspartate aminotransferase increased	0	(0.0)	3	(18.8)
Blood bilirubin increased	0	(0.0)	2	(12.5)
Metabolism and nutrition disorders	**6**	**(18.2)**	**4**	**(25.0)**
Hypoglycaemia	2	(6.1)	2	(12.5)
Respiratory, thoracic and mediastinal disorders	**5**	**(15.2)**	**3**	**(18.8)**
Skin and subcutaneous tissue disorders	**2**	**(6.1)**	**2**	**(12.5)**

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Source: [P064MK0991: adam-adsl; adae]

Deaths

There were 4 participants with reported AEs that resulted in death, including 2 (6.1%) in caspofungin group and 2 (12.5%) in amphotericin B deoxycholate group while receiving study intervention and through the 2-week posttherapy follow-up visit.

In the caspofungin group, the AEs resulting in death included septic shock (event onset study Day 1) and necrotizing enterocolitis neonatal (event onset study Day 28). In the amphotericin B deoxycholate

group, suture rupture (event onset study Day 16) and cardiac arrest/ procedural pneumothorax (event onset study Day 4) were the AEs that resulted in death.

An additional participant in the amphotericin B deoxycholate group experienced an AE resulting in death (pulmonary hemorrhage, event onset Day 56) during the 8-week posttherapy follow-up period.

These events were not considered by the investigator to be related to study intervention, and were mainly related to the participant's underlying condition.

Serious adverse events

Thirteen participants reported a SAE (including those participants who reported AEs resulting in death) while receiving study intervention and through the 2-week posttherapy follow-up visit. Although the small sample size limits the conclusions that can be drawn, a higher proportion of SAEs was observed in the amphotericin B deoxycholate group compared with the caspofungin group [Table 2.5: 4] [Ref. 5.3.5.1: P064MK0991: 12.2.1.2].

All SAEs were considered unrelated to trial intervention by the investigator and there was no clustering of SAEs during conduct of the study either chronologically or by site. All SAEs were attributable to, and consistent with, the critically ill population in this study.

Subjects With Serious Adverse Events
(Incidence > 0% in One or More Treatment Groups)
Treatment Period and First 14 Follow-Up Days
All Subjects as Treated Population

	Caspofungin 2 mg/kg		Amphotericin B deoxycholate 1 mg/kg	
	n	(%)	n	(%)
Subjects in population	33		16	
with one or more serious adverse events	6	(18.2)	7	(43.8)
with no serious adverse events	27	(81.8)	9	(56.3)
Cardiac disorders	**0**	**(0.0)**	**1**	**(6.3)**
Cardiac arrest	0	(0.0)	1	(6.3)
Gastrointestinal disorders	**2**	**(6.1)**	**0**	**(0.0)**
Necrotising colitis	1	(3.0)	0	(0.0)
Necrotising enterocolitis neonatal	1	(3.0)	0	(0.0)
Infections and infestations	**3**	**(9.1)**	**4**	**(25.0)**
Bacterial sepsis	0	(0.0)	1	(6.3)
Device related sepsis	0	(0.0)	1	(6.3)
Endocarditis	1	(3.0)	0	(0.0)
Escherichia sepsis	1	(3.0)	0	(0.0)
Fungal infection	0	(0.0)	1	(6.3)
Meningitis bacterial	0	(0.0)	1	(6.3)
Pneumonia escherichia	0	(0.0)	1	(6.3)
Septic shock	1	(3.0)	0	(0.0)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**2**	**(12.5)**
Anastomotic complication	0	(0.0)	1	(6.3)
Procedural pneumothorax	0	(0.0)	1	(6.3)
Suture rupture	0	(0.0)	1	(6.3)
Respiratory, thoracic and mediastinal disorders	**1**	**(3.0)**	**1**	**(6.3)**
Apnoea	1	(3.0)	0	(0.0)
Dyspnoea	0	(0.0)	1	(6.3)
Vascular disorders	**1**	**(3.0)**	**0**	**(0.0)**
Superior vena cava syndrome	1	(3.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Source: [P064MK0991: adam-adsl; adae]

Drug-related Adverse Events

Overall, 4 participants (2 [6.1%] in the caspofungin group and 2 [12.5%] in the amphotericin B deoxycholate group) reported study intervention-related AEs while receiving study intervention and through the 2-week posttherapy follow-up visit [Table 2.5: 5] [Ref. 5.3.5.1: P064MK0991: 12.1.3.1].

In the caspofungin group, events considered related to study intervention included 1 participant who reported a mild, NSAE of infusion site oedema and 1 participant who reported a moderate, NSAE of jaundice cholestatic. The latter event represented a worsening of a pre-existing condition (medical history of jaundice cholestatic and cholelithiasis). In both cases, no action was taken with regard to study intervention, and the events resolved.

In the amphotericin B deoxycholate group, 1 participant experienced a study intervention related AE of anaemia on Day 3, which represented a worsening of a pre-existing condition. No action was taken with regard to study intervention in response to this AE, which resolved. Another participant in the amphotericin B deoxycholate group experienced a study intervention related AEs of blood lactate dehydrogenase increased (onset Day 5) and metabolic alkalosis (onset Day 8). This participant had ongoing congestive cardiac failure and Escherichia coli infection, and the treating physician decided to stop study intervention after Day 8.

Subjects With Drug-Related Adverse Events
(Incidence > 0% in One or More Treatment Groups)
Treatment Period and First 14 Follow-Up Days
All Subjects as Treated Population

	Caspofungin 2 mg/kg		Amphotericin B deoxycholate 1 mg/kg	
	n	(%)	n	(%)
Subjects in population	33		16	
with one or more drug-related adverse events	2	(6.1)	2	(12.5)
with no drug-related adverse events	31	(93.9)	14	(87.5)
Blood and lymphatic system disorders	**0**	**(0.0)**	**1**	**(6.3)**
Anaemia	0	(0.0)	1	(6.3)
General disorders and administration site conditions	**1**	**(3.0)**	**0**	**(0.0)**
Infusion site oedema	1	(3.0)	0	(0.0)
Hepatobiliary disorders	**1**	**(3.0)**	**0**	**(0.0)**
Jaundice cholestatic	1	(3.0)	0	(0.0)
Investigations	**0**	**(0.0)**	**1**	**(6.3)**
Blood lactate dehydrogenase increased	0	(0.0)	1	(6.3)
Metabolism and nutrition disorders	**0**	**(0.0)**	**1**	**(6.3)**
Metabolic alkalosis	0	(0.0)	1	(6.3)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Adverse Events leading to intervention discontinuation

Discontinuation of study intervention occurred in 4 (12.1%) participants in the caspofungin group and 1 (6.3%) participant in the amphotericin B deoxycholate group. These AEs were not considered by the investigator to be related to study intervention. Specifically, in the caspofungin group, the AEs that led to discontinuation included cholestasis, endocarditis, accidental overdose, and superior vena cava syndrome. The event of accidental overdose was not associated with other AEs. In the amphotericin B deoxycholate group, 1 participant discontinued study intervention due to cardiac arrest/procedural pneumothorax.

Overdose

During the course of the trial, 2 participants in the caspofungin group reported an accidental overdose. In both cases, no AEs associated with the overdose were reported. One participant experienced an overdose during a single infusion. The remaining participant received multiple (5) infusions with an incorrect dosage.

Clinical laboratory evaluations

No clinically meaningful findings were noted in mean change from baseline in chemistry and hematology laboratory tests. Creatinine laboratory shifts were similar between the caspofungin group and the amphotericin B deoxycholate group.

Vital sign assessment

The vital sign assessments were comparable across the caspofungin and amphotericin B deoxycholate intervention groups and no clinically meaningful findings were noted.

Safety summary:

As expected in this critically ill patient population, the incidence of AEs was high in both intervention groups. All SAEs, including those with a fatal outcome, were consistent with this seriously ill population and none were considered related to study intervention by the investigator. Few subjects discontinued due to an AE and few AEs were considered related to study intervention by the investigator. Two participants reported an overdose during the course of the trial, neither of which resulted in the report of an associated AE. No clinically meaningful laboratory or vital sign findings were noted.

Assessors comments

Adverse events incidence was high in both groups, which was expected in this critically ill population.

Most common reported AEs in the caspofungin group were anemia (30%), pyrexia (18%) and sepsis (9%).

2 AEs were considered related to caspofungin, namely an infusion site oedema which was considered mild in intensity, resolved after 2 days and did not result in treatment discontinuation, and jaundice (cholestatic) which was moderate in intensity, resolved spontaneously and did not lead to discontinuation. The patient who experienced the jaundice later discontinued study intervention due to an SAE of superior vena cava syndrome.

4 patients reported AEs that resulted in death, 2 in the caspofungin group (septic shock and necrotizing enterocolitis neonatal) and 2 in the amphotericin B deoxycholate group (suture rupture and cardiac arrest/procedural pneumothorax). All deaths were considered unrelated to study intervention and mainly related to patients underlying condition.

18.2% of the caspofungin group experienced severe adverse events, versus 43.8% in the amphotericin B deoxycholate group. All SAEs were considered unrelated to trial intervention.

5 patients reported AEs resulting in discontinuation of study intervention, all considered unrelated to study interventions.

2 patients reported an accidental overdose with caspofungin, which did not lead to adverse events in both cases.

A higher proportion of participants in the amphotericin B deoxycholate group met the PDLC criteria of ALT > 2.5 × baseline and AST > 2.5 × baseline compared to the caspofungin group. Creatinine laboratory shifts were similar between the treatment groups.

Overall, incidence rate of AEs was high in both groups, as expected. No new adverse events were seen then already known and described in the SmPC. Appropriate warnings for liver function disturbances are already described in the SmPC

Impact on benefit/risk balance

In this study of caspofungin compared to amphotericin B deoxycholate in neonates and infants < 3 months of age, the proportion of participants with fungal-free survival at 2 weeks posttherapy and at the end of therapy in the caspofungin treatment group was similar to that seen in the amphotericin B deoxycholate treatment group. Additionally, caspofungin 2 mg/kg was generally well-tolerated in neonates and infants < 3 months of age with invasive candidiasis and no new or unique safety issues were identified.

Previous evidence supporting the safety and efficacy of caspofungin in neonatal invasive candidiasis has been published in the medical literature, with the most compelling evidence coming from a prospective study from Saudi Arabia. Also, data from several published case reports and case series have also contributed to a growing acceptance of caspofungin use in preterm neonates with invasive candidiasis. In multiple reports, caspofungin therapy was started as salvage therapy in VLBW preterm neonates only after initial therapy with conventional antifungals (amphotericin B deoxycholate, fluconazole, with or without flucytosine) had failed, due either to pathogen resistance or to intolerance of the initial therapy. Other anecdotes reported clearance of shunt associated Candida albicans meningitis with, and intractable candidemia in 23- and 24-week preterm neonates. In each published report of caspofungin use in neonatal invasive candidiasis, there have been no unexpected or drug-related SAEs.

Due to the small sample size (n=49) enrolled and treated in the P064 study, the data are insufficient to provide a conclusion regarding the comparative efficacy and safety of caspofungin and amphotericin B deoxycholate in neonates and infants <3 months of age with invasive candidiasis. Further, no new PK information meaningfully supplementing that already summarized in product labeling was obtained. With the limited sample size, and inconclusive findings, no changes to the caspofungin prescribing information are proposed and no changes to the current treatment guidelines for neonatal invasive candidiasis are expected.

The results of this study do not alter the benefit/risk profile of caspofungin. At this time, no additional studies are planned for caspofungin in the pediatric patient population.

Assessors comments

The MAH concludes that due to the small sample size no formal conclusion regarding the comparative efficacy and safety of caspofungin and amphotericin B deoxycholate in neonates and infants <3m of age could be made. The study terminated enrolment before the target number of participants was randomized. Multiple reasons were mentioned by the MAH: the critical ill study population, other standard of care (liposomal amphotericin instead of amphotericin B deoxycholate), already available caspofungin data in this population (which demonstrates its value) and, perhaps the most important reason, the changing epidemiology of invasive candidiasis in neonatology due to use of fluconazole prophylaxis, earlier empiric antifungal treatment and decreased use of broad-spectrum antibiotics especially in the low birth-weight population.

Because of these challenges, resulting in a small sample size, this study was not powered to evaluate statistically significant differences in safety and efficacy parameters between caspofungin and amphotericin B deoxycholate intervention groups. No changes in prescribing information is warranted.

However, according to the SmPC guideline, available data outside of the authorised pediatric indication should be presented and cross-referenced to section 4.2. Therefore the MAH is asked to update section 5.1 with efficacy data of the P064 study. The inclusion in section 5.1 could read as follows:

In a double-blind, randomized (2:1) comparator-controlled study safety, tolerability and efficacy of caspofungin (2mg/kg/d intravenously, infused over 2 hours) vs amphothericin B deoxycholate (1mg/kg/d) was evaluated in neonates and infants less than 3 months of age with (culture-confirmed) invasive candidiasis. Due to poor enrolment, the study was terminated early and only 51 patients were randomized. The proportion of patients with fungal-free survival at 2 weeks posttherapy in the caspofungin treatment group (71.0%) was similar to that seen in the amphotericin B deoxycholate treatment group (68.8%). Based on this study, no posology recommendations for neonates and infants can be made.

The MAH should therefor submit a variation or provide a justification for not doing so.

3. Rapporteur's overall conclusion and recommendation

The MAH concluded that this study was not powered to evaluate statistically significant differences in safety and efficacy parameters between caspofungin and amphotericin B deoxycholate intervention groups. No changes in prescribing information is warranted.

However, according to the SmPC guideline, available data outside of the authorised pediatric indication should be presented and cross-referenced to section 4.2. Therefore the MAH is asked to update section 5.1 with efficacy data of the P064 study. The inclusion in section 5.1 could read as follows:

In a double-blind, randomized (2:1) comparator-controlled study safety, tolerability and efficacy of caspofungin (2mg/kg/d intravenously, infused over 2 hours) vs amphothericin B deoxycholate (1mg/kg/d) was evaluated in neonates and infants less than 3 months of age with (culture-confirmed) invasive candidiasis. Due to poor enrolment, the study was terminated early and only 51 patients were randomized. The proportion of patients with fungal-free survival at 2 weeks posttherapy in the caspofungin treatment group (71.0%) was similar to that seen in the amphotericin B deoxycholate treatment group (68.8%). Based on this study, no posology recommendations for neonates and infants can be made.

☒ Fulfilled:

In view of the available data regarding the safety and efficacy of caspofungin in neonates and infants less than 3 months of age the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.