European Medicines Agency

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ASSESSMENT REPORT
FOR
CANCIDAS

International Nonproprietary Name:
caspofungin

Procedure No. EMEA/H/C/379/II/33

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

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1. Introduction

Caspofungin acetate is a semisynthetic lipopeptide compound of the echinocandin family and represents a new class of antifungal agents (glucan synthesis inhibitors) that inhibits the synthesis of beta (1,3)-D-glucan an integral component of the fungal cell wall. Caspofungin MSD was initially granted a Marketing Authorisation under exceptional circumstances on 24 October 2001.

Currently, the following indications are approved in the EU:

- Treatment of invasive candidiasis in adult patients.
- Treatment of invasive aspergillosis in adult patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.
- Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropenic adult patients.

The approved adult dosage is a single 70 mg loading dose on day 1, followed by 50 mg thereafter. Duration of treatment is not specified and is to be based upon the severity of the patient's underlying disease, recovery from immunosuppression and clinical response.

The incidence of *Candida* and *Aspergillus* infections are increasing in children inflicted with haematological malignancies, congenital immune deficiencies, and other childhood medical conditions that require aggressive immunosuppressive or antibiotic therapy. Childhood leukaemia and lymphoma, as well as the chemotherapies used to treat these oncological diseases, result in prolonged periods of neutropenia, which in turn, increase the risk of serious fungal infections. Furthermore, bloodstream infections with *Candida spp.* are occurring in children who do not suffer from childhood cancers but have similar hospital exposures and risks, including central venous catheters, surgical procedures, broad spectrum antibiotics, total parenteral nutrition, and immunosuppressive therapy.
Candida remains the most common cause of invasive fungal infections (IFI) in children, especially in chronically ill or immunocompromised children and adolescents. Candidemia is seen in all paediatric age groups. Similarly, as in adults, *Aspergillus spp.* remains the predominant cause of filamentous mould infections in the paediatric population. Paediatric patients with invasive aspergillosis have a significant in-hospital mortality (18%).

The current application concerns a Type II variation (EMEA/H/C/379/II/33) to extent the indication to the paediatric population. This variation includes all data to be collected in compliance with the agreed PIP (Decision P/30/2008 dated on 23 May 2008). The PDCO has performed the verification of compliance with the agreed paediatric investigation plan and adopted an opinion on 4 June 2008.

The MAH applied for paediatric usage of caspofungin for the indications currently approved. The paediatric program includes paediatric pharmacokinetic data (neonates to 17 years of age) in conjunction with paediatric safety and efficacy data, from 3 months of age. The rational has been reviewed and approved in the Paediatric Investigation Plan (PIP) for Cancidas, with a positive opinion issued by the PDCO on 18 January 2008.

2. Non-clinical aspects

2.1. Introduction

The MAH submitted 2 non-clinical studies:
- a new '*efficacy, pharmacokinetics and pharmacodynamic study in a juvenile mouse model of central nervous system candidiasis'* and,
- a '*5 week repeat dose toxicity study in juvenile monkeys'*.

As part of the application, the MAH submitted a non-clinical overview/summary pertaining only to these 2 above-mentioned studies. No update of the non-clinical overview or non-clinical summaries as submitted at the time of the initial application was provided. As part of the answer to the RSI adopted in May 2008 (see attachment 3), the MAH only revealed one additional publication on the efficacy of micafungin in neonates using an adult rabbit model of experimental hematogenous Candida meningoencephalitis. During the assessment, the MAH justified the choice of non-clinical studies to support the paediatric indication in accordance with the relevant aspects cited in the Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (EMEA/ CHMP/SWP/169215/2005), by stating that in the case of caspofungin, the non-clinical studies outlined for the paediatric development program were initiated prior to the availability of this Guidance.

2.2. Pharmacology

- ***Description of data submitted***

In vivo study "*Efficacy, pharmacokinetics and pharmacodynamics of caspofungin in a juvenile mouse model of central nervous system candidiasis*"

In the caspofungin development program, a DBA/2 mouse model of disseminated candidiasis was used to predict efficacy in the human patient population. In this model, mice were infected intravenously with *Candida albicans* and the efficacy of caspofungin was measured by reduction of tissue *Candida* burden relative to vehicle-treated controls. Caspofungin treatment resulted in significant reduction in kidney *Candida* burden when caspofungin therapy was delayed by 24 hours after inoculation, ultimately showing that caspofungin is efficacious against an established infection. Caspofungin was also efficacious in reducing *Candida* burden in various organs, including brain, after twice-daily treatment for 2 days beginning immediately after inoculation. This *in vivo* model of candidiasis ultimately proved to be a reliable predictor of clinical efficacy.

However, no preclinical data were previously available to describe the efficacy of caspofungin against an established *Candida* infection in the CNS. To aid in predicting efficacy in the paediatric patient population where dissemination of *Candida* to distant organs, particularly the CNS, is more common, the standard murine disseminated candidiasis model was modified to use juvenile mice to more closely approximate how a *Candida* infection might propagate in paediatric patients.

Therefore, DBA/2N mice were infected intravenously with *C. albicans* MY1055 and the initiation of antifungal therapy was delayed until 30 hours after infectious challenge to determine efficacy against an established CNS infection. Histological and microbiological analysis of kidney and brain samples taken at the initiation of antifungal therapy (30 hours following infectious challenge) showed evidence of marked to severe kidney infection and minimal to mild multifocal encephalitis with little meningitis. Vehicle-treated mice had progression of infection with peak kidney and brain *Candida* burden at Day 5 and 100% mortality by Day 11 after infectious challenge.

The results of this study demonstrate that caspofungin administered by once-daily intraperitoneal injection at doses of 1, 2, 4 or 8 mg/kg/day for 7 days was effective in treating established disseminated candidiasis with CNS involvement in this juvenile mouse model. Caspofungin treatment beginning 30 hours after intravenous *Candida* challenge significantly reduced kidney and brain *Candida* burden in juvenile mice compared to vehicle-treated control mice by both microbiological and histopathological endpoints. Caspofungin treatment also resulted in 100% survival through Day 28 as compared to 100% mortality in vehicle-treated controls by Day 11 after challenge.

The pharmacokinetics of caspofungin showed similar plasma exposure in *Candida* infected and uninfected juvenile mice, while brain exposure was higher in infected animals. The lowest dose of caspofungin in this study, 1 mg/kg/day, corresponded to a Day 7 caspofungin exposure ($AUC_{0\text{-}24\ hr}$) of 35.5 μM/hour in plasma and of 7.84 μM/hour in brain of infected animals. This exposure was sufficient to provide efficacy equivalent to or better than amphotericin B at 1 mg/kg in this model.

- ***Conclusion on Pharmacology***

Caspofungin (1-8 mg/kg/day, i.p., 7 days) shows dose-dependent efficacy against established disseminated candidiasis with CNS involvement in a mouse model (age: 7-11 weeks old). Culture and histology show evidence of disseminated candidiasis with multifocal encephalitis at the start of antifungal therapy 30 hours after infectious challenge. Caspofungin significantly reduces kidney and brain *Candida* burden compared to vehicle-treated control mice by both microbiological and histopathological endpoints at all doses tested. Caspofungin treatment also results in 100% survival through Day 28 as compared to 100% mortality in vehicle-treated controls by Day 11 after challenge.

The pharmacokinetics of caspofungin in the DBA/2 mouse model of disseminated candidiasis show similar plasma exposure in *Candida* infected and uninfected juvenile mice, while brain exposure is higher in infected animals. The lowest dose of caspofungin in this study, 1 mg/kg/day, corresponds to a Day 7 caspofungin exposure (Area Under a Curve, $AUC_{0\text{-}24\ hr}$) of 35.5 μM/hour in plasma and of 7.84 μM/hour in brain of infected animals. This exposure is sufficient to provide equivalent or better efficacy than amphotericin B at 1 mg/kg in this model.

The animals used in this efficacy study were 7-11 weeks old at study initiation. As animals of that age are considered to be at the end of puberty / start of adulthood, this study is not considered to be a juvenile animal study. Moreover, clinical efficacy data are available for the older paediatric age groups. Consequently, the data presented here were not considered relevant in the frame of this extension to the paediatric population.

2.3. Toxicology

- ***Repeat-dose toxicity***

Description of data submitted

"*5-week intravenous toxicity study in infant rhesus monkey* (*Macaca mulatta*) (TT#98-613-0)". This study was already part of the initial application for caspofungin, and was here re-submitted. This study will be named "*juvenile monkey study*" in this assessment report.

The purpose of this study was to determine the potential toxic effects of caspofungin, when administered intravenously to infant rhesus monkeys for approximately 5 weeks. This information was necessary to support the potential use of caspofungin in paediatric patients.

Rhesus monkeys ranging in weight from 0.684 kg to 1.090 kg and in age from 1 month 28 days to 2 months 8 days of age were assigned to the study, which would correspond to a human age of approximately 8 to 9 months. Ten (10) infants (6 males and 4 females) in the low-dose group (2 mg/kg/day) and 10 infants (7 males and 3 females) in the high-dose group (5 mg/kg/day) were administered the lyophilized formulation of caspofungin i.v. via the saphenous veins once daily over an approximate 10-minute dosing period. Similarly, 1 control group of 10 infants (7 males and 3 females) received the vehicle (0.9% saline plus excipients) at a dosing volume of 10 ml/kg according to the same treatment regimen.

The animals were observed twice daily during the treatment period for evidence of adverse physical signs (once in the morning and once approximately 2 hours after treatment). Infant body weights were recorded daily prior to treatment until necropsy on Treatment Day 28. A complete physical examination was performed by a CRPRC veterinarian prior to treatment and during Dosing Week 4.

Blood samples were collected prior to treatment and during Dosing Week 4 prior to necropsy for CBCs (Complete Blood Counts) and clinical chemistry evaluations. For clinical chemistry screens, parameters assessed included chloride, potassium, sodium, calcium, phosphorus, albumin, blood urea nitrogen, glucose, total protein, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatinine, total bilirubin, cholesterol, and triglycerides. Blood samples were collected from 4 of 10 animals in each dose group for determination of plasma caspofungin levels during

Dosing Week 4 prior to treatment and approximately 2, 6, 12, and 24 hours postdosing. Urine was collected from all infants for a urinalysis pre-treatment and during Dosing Week 4.

All animals underwent a complete ophthalmologic examination pre-treatment and prior to necropsy. Direct, indirect, and slit lamp examinations were performed. A complete necropsy was performed on all infants during Dosing Week 4. Organ weights taken at the time of necropsy included brain, pituitary, thymus, thyroid, heart, liver, spleen, adrenals, kidneys, ovaries or testes/epididymis, and prostate. A complete microscopic examination of numerous paraffin-embedded, hematoxylin- and eosin-stained sections from all animals in the control and 5-mg/kg/day groups was performed.

There were no treatment-related findings in any of the animals in either caspofungin treatment group (2 mg/kg/day or 5 mg/kg/day). All body weight changes, CBCs, clinical biochemical assessments, urinalyses, ophthalmologic examinations, and gross and microscopic findings were within normal limits for animals in this age group.

The $AUC_{2\text{-}24hr}$ (µg•hr/ml), C_{max} (µg/ml), and $T_{1/2}$ (hr) for the 2- and (5)-mg/kg/day dose groups were 121.0 ± 4.7 (410.2 ± 42.4), 12.2 ± 0.9 (36.4 ± 2.1), and 8.7 ± 0.4 (9.8 ± 0.5), respectively.

Therefore, no antemortem or postmortem toxicity occurred in infant rhesus monkeys administered caspofungin intravenously daily for approximately 5 weeks at doses that achieved exposures approximately 2.5 to 4.5 greater than that achieved in children administered caspofungin at a maintenance dose of 50 mg/m^2 daily.

Conclusion on repeat-dose toxicity

It should be noted that findings on repeated dose toxicity were provided and assessed as part of the initial application for caspofungin. The conclusions were as follows:

1) The liver was identified as target organ in a repeat dose toxicity studies in monkeys: increases in serum transaminases (accompanied by slight subcapsular necrosis at 5 mg/kg in the 5-week study). A NOEL of 2(1.5) mg/kg was determined in the 14(27)-week study. Transaminase increases correlated with the hepatic level of caspofungin. The 5 mg/kg.day dose producing serum ALT and AST increases was associated with an AUC of 496 µg.h/ml, that is about 2.9-fold the human value at a dose of 70 mg/m^2.

2) Pharmacokinetic studies in monkeys showed increased half-life and systemic exposure levels after repeated dose, with steady-state levels reached in 10 days. Repeat dose toxicity studies in the same species showed that systemic exposure levels approximately doubled from day 1 to 28.

In the above-described *juvenile monkey study*, no relevant toxicological changes were evident at doses up to 5 mg/kg (= high dose levels, = NOEL (No-Observed-Effect Level)). AUC levels reached after 28 days were similar to the levels observed on day 28 in the 5-week repeat dose toxicity study carried out with adult rhesus monkeys. The Cmax levels at the high dose level of 5 mg/kg/day in juvenile monkeys (36.4 µg/ml) was slightly lower than the level in adult monkeys (51.2 µg/ml). Since the pharmacokinetic data obtained in humans are restricted to plasma concentrations, safety margins are based upon Ctime ratios for neonates at 25 mg/m^2 (C_{1hr} = 11.1 µg/ml) and for the older paediatric population at 50 mg/m^2 (C_{1hr} = 15.6-13.5 µg/ml). Consequently, safety margins of 3.3 and 2.3-2.7, for respectively the paediatric population of <3 months and >3 months are reached. Whilst for the <3 months the ratio is appropriate, for the >3 months it should be taken into account that the maximum recommended dose is 70 mg/m^2, and thus lower safety margins are to be expected.

In addition to the *juvenile monkey study*, numerous studies of 5 to 27 weeks duration were conducted in paediatric/adolescent rhesus monkeys (1 to 2 years of age, corresponding to a human age of 4 to 10 years), and rats (starting at approximately 6 weeks of age, and dosing up through 33 weeks of age, corresponding to a human age of approximately 10 years through adulthood) as part of the general toxicity testing of caspofungin provided and assessed in the frame of the initial application for caspofungin.

The age of the monkeys used in the *juvenile monkey study* was 1 month 28 days to 2 months 8 days, which would correspond to a human age of approximately 8 to 9 months. Therefore, these toxicity

studies, altogether, included an appropriate age range for assessment of the toxicologic potential of caspofungin in the targeted paediatric population.

- ***Other toxicity studies***

Immunotoxicity

The potential immunotoxicity of caspofungin was assessed by monitoring of clinical signs, evaluation of hematologic, and serum biochemical parameters, and by gross and microscopic evaluation of tissues (including lymph nodes, spleen, and thymus) from 5- to 27-week studies in rats and monkeys, including the 5-week intravenous toxicity study in infant rhesus monkeys. There was no evidence of immunotoxicity in rats or monkeys administered caspofungin in these studies.

Metabolites

Studies previously submitted were conducted to compare the metabolism of caspofungin in preclinical species (rats, monkeys, rabbits, and mice) and humans indicated that, qualitatively and quantitatively, the metabolic pathways and metabolites of caspofungin in the animal species were similar to the findings in humans.

Impurities

The impurities characterized in the batches used in the preclinical toxicity studies compares well to the proposed specifications of the market formulations. In addition, a significant portion of the preclinical toxicity evaluation program was conducted using the lyophilized formulation containing degradates at levels that equalled or exceeded the specifications established for the 5°C clinical formulation proposed for registration. Further, no toxicity was attributed to the impurities/degradates and the doses of the bulk drug administered in the preclinical toxicity studies provide multiples above the intended clinical dosage.

- ***Ecotoxicity/environmental risk assessment***

No environmental risk assessment was submitted as part of this Type II variation. However, according the Guideline on environmental risk assessment of medicinal products for human use (EMEA/CHMP/ SWP/4447/00), for type II variations, the evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g. a new indication may result in a significant increase in the extent of the use. In the answer to the RSI adopted in May 2008, the MAH submitted an expert declaration that provides a rationale for the absence of an Environmental Risk Assessment stating that this extension of indication is for paediatric use to be administered only in hospital settings. As such, it is applicable to a limited patient population and will not significantly increase the environmental exposure. The declaration stated also that the anticipated paediatric use of Cancidas will not result in a significant incremental environmental exposure of the drug substance. The CHMP considered the justification acceptable.

2.3. Discussion on the non-clinical aspects

The MAH submitted 2 non-clinical studies:
1- A new '*efficacy, pharmacokinetics and pharmacodynamic study in a juvenile mouse model of central nervous system candidiasis'* and,
The animals used in this efficacy study were 7-11 weeks old at study initiation. As animals of that age are considered to be at the end of puberty / start of adulthood, this study is not considered to be a juvenile animal study. Moreover, clinical efficacy data are available for the older paediatric age groups. Consequently, the data presented here were not considered relevant in the frame of this extension to the paediatric population.

2- A '*5 week repeat dose toxicity study in juvenile monkeys'*.

Previously submitted repeat-dose intravenous toxicity studies have shown that the toxicity profile of caspofungin consists of signs of histamine release in rats and rhesus monkeys, irritation at the injection sites in rats and monkeys, and slight elevations in serum transaminase values with or without very slight to slight subcapsular liver necrosis in monkeys.

With regard to toxicity in infant rhesus monkeys, there were no treatment-related findings in any of the animals in either caspofungin treatment group (2 mg/kg/day or 5 mg/kg/day). All body weight changes, CBCs, clinical biochemical assessment, urinalyses, ophthalmologic examinations, and gross and microscopic findings were within normal limits for animals in this age group. No antemortem or postmortem toxicity occurred in infant rhesus monkeys administered caspofungin intravenously daily for approximately 5 weeks at doses that achieved exposures approximately 2.3 to 2.7 greater than that achieved in children >3 months administered caspofungin at a maintenance dose of 50 mg/m^2 daily (not the maximum recommended dose of 70 mg/m^2).

3. Clinical aspects

3.1. Introduction

The clinical development program for caspofungin in paediatric patients submitted with this application consisted of the following 5 clinical studies:

- Pharmacokinetic Study (**Protocol 033**): A Multicenter, Open, Sequential Dose-Escalation Study to Investigate the Safety, Tolerability, and Pharmacokinetics of 2 Separate Doses of Caspofungin in Children & Adolescents 2 to 17 Years of Age With New Onset Fever and Neutropenia
- Pharmacokinetic Study (**Protocol 042**): A Multicenter, Open Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Caspofungin in Children Between the Ages of 3 to 24 Months With New Onset Fever and Neutropenia
- Pharmacokinetic Study (**Protocol 058**): A Multicenter, Sequential-Panel, Open-Label, Noncomparative Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Caspofungin in Neonates and Infants <3 Months of Age
- Safety/Efficacy Study (**Protocol 043**): A Multicenter, Open-Label, Noncomparative Study to Evaluate the Safety and Efficacy of Caspofungin in Pediatric Patients (3 Months to 17 Years of Age) With Documented *Candida* and *Aspergillus* Infections
- Safety/Efficacy Study (**Protocol 044**): A Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Liposomal Amphotericin B for Injection as Empirical Therapy in Pediatric Patients (2 to 17 Years of Age) With Persistent Fever and Neutropenia

3.2. Clinical pharmacology

- ***Background***

Metabolism and excretion of caspofungin is slow and the plasma clearance and plasma concentration-time profile are suggested to be determined rather by the rate of distribution of caspofungin from plasma into tissues. Thus, it is suggested that any factor (such as a concomitant medication) affecting plasma pharmacokinetics most likely exerts its influence on the distribution of caspofungin from plasma into tissues, rather than on the metabolism or excretion. The uptake of caspofungin into hepatocytes and possibly other tissue cells appears to be mediated, at least in part, by an active transport process. Recent *in vitro* investigations suggest that the OATP1B1 (Organic Anion-Transporting Polypeptide) transporter may be involved in the hepatic uptake of caspofungin.

Approximately 75% of radioactivity is recovered in urine and faeces over 27 days after administration of a single dose of radiolabelled caspofungin to healthy adult men. The major metabolic pathways are peptide hydrolysis and *N*-acetylation; however, the major circulating and putative initial metabolite appears to be formed by spontaneous chemical degradation. Caspofungin is a poor substrate for the major cytochrome P450 (CYP) enzymes. There is a low level (3 to 7 pmol/mg protein) of irreversible binding of radioactivity in plasma following single-dose administration of radiolabelled caspofungin and, consequently, total radioactivity in plasma falls below the limit of quantitation at 22.3 weeks following a single dose. Renal clearance of unchanged caspofungin constitutes a minor pathway of elimination (~1.4% of dose).

Following single doses up to 210 mg in adults, caspofungin pharmacokinetics are dose-proportional, and a dominant beta-phase, with half-life of 9 to 11 hours, characterises much of the plasma profile. Caspofungin shows moderate accumulation (~50% for AUC) on once-daily dosing with a modest dose-dependency in the degree of accumulation. Caspofungin at a dose of 100 mg daily achieves an AUC approximately 2.5 times that of the 50 mg daily regimen. Average concentrations at steady-state from a caspofungin 50-mg once daily regimen are above the preclinically defined target concentration of 1 μg/ml.

Modest, but clinically unimportant, elevations in plasma concentrations are seen in women, the elderly, patients with varying degrees of renal insufficiency, and patients with mild hepatic insufficiency. In adult patients with moderate hepatic insufficiency, a caspofungin dose reduction to 35 mg daily maintenance dose provides exposures similar to those obtained in controls receiving the standard regimen.

In vitro studies indicate that drug interactions based on alterations in CYP-mediated metabolism are unlikely to occur. Co-administration of cyclosporin A moderately increases plasma concentrations of caspofungin (~35% for AUC), most likely due to reduced tissue uptake. Rifampin has a slight induction of caspofungin plasma clearance at steady-state (~30% decrease in trough concentrations). Consistent with the rifampin results, population pharmacokinetic screening of caspofungin concentrations in patients suggests that coadministration of other agents known to induce drug metabolism or transporters may reduce caspofungin plasma concentrations. As a result, a dose escalation to 70 mg daily is recommended in adult patients receiving caspofungin concomitantly with inducers of drug clearance, especially if the patient is not responding to the standard 50-mg once-daily dosing regimen.

In concentration/response analyses of adult studies, caspofungin pharmacokinetic values were found not to be significant predictors of overall treatment in patients with invasive candidiasis, invasive aspergillosis, or patients receiving empirical therapy. In adults with mucosal candidiasis, caspofungin pharmacokinetic values were not significant factors for predicting overall treatment outcome, although an exploratory evaluation indicated that $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, and $C_{24\ hr}$ were significant factors for predicting endoscopic (or oropharyngeal exam) response in this dataset, which included patients treated at less than the recommended adult dose for caspofungin (35 mg daily). The lack of correlation between plasma concentrations and treatment outcomes in patients receiving the recommended

50 mg/day dose regimen suggests that the range of concentrations obtained at 50 mg daily falls at the top of the concentration-response curve, where treatment response has, at most, only a modest concentration dependency.

Analyses of the potential for caspofungin pharmacokinetic values to predict clinical adverse events in adult patients indicates that, with the possible exception of nausea, the occurrence of adverse experiences is not increased by higher caspofungin plasma concentrations. The analyses indicate the possibility that the occurrence of nausea could be increased by higher $C_{1\ hr}$, although no statistically significant correlations were obtained. The occurrence of drug-related nausea in all of these patient populations was stated to be infrequent and the severities were generally mild or moderate and not therapy-limiting.

- ***Pharmacokinetics***

- Pharmacokinetic Study (**Protocol 033**): A Multicenter, Open, Sequential Dose-Escalation Study to Investigate the Safety, Tolerability, and Pharmacokinetics of 2 Separate Doses of Caspofungin in Children & Adolescents 2 to 17 Years of Age With New Onset Fever and Neutropenia
- Pharmacokinetic Study (**Protocol 042**): A Multicenter, Open Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Caspofungin in Children Between the Ages of 3 to 24 Months With New Onset Fever and Neutropenia
- Pharmacokinetic Study (**Protocol 058**): A Multicenter, Sequential-Panel, Open-Label, Noncomparative Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Caspofungin in Neonates and Infants <3 Months of Age

  - ***Methods***

<u>*Studies*</u>

Three (3) paediatric pharmacokinetic studies are submitted (Protocols 033, 042, and 058). The objective of these studies was to examine the pharmacokinetics, safety, and tolerability of caspofungin across the entire age range of paediatric patients (0 months through 17 years of age). Ultimately, the intent of these studies was to find a safe dose with sufficient plasma exposures for use in the Phase IIb paediatric safety/efficacy clinical trials (Protocols 043 and 044).

The studies were performed sequentially, so that safety and pharmacokinetic data from the oldest age group (2-17 years of age) became available before the study in the younger age group (3-24 months of age) was initiated. Similarly, preliminary safety and pharmacokinetic data from the study in the 3-24 months old patients were made available prior to the initiation of the pharmacokinetic study in infants and neonates (0-3 months of age).

The two studies Protocols 033 and 042 were performed in immunocompromised children with febrile neutropenia using an "early empirical therapy" approach, wherein antifungal agents are initiated on the first day of confirmed fever and neutropenia, simultaneously with antibiotics for the empirical therapy of bacterial infections. The study Protocols 058 was performed in neonates and infants with suspected or documented invasive candidiasis. As this is a fragile patient population with a serious infection, adequate antifungal therapy other than caspofungin was mandated. Thus, the study design required that caspofungin be administered as combination therapy with an intravenous formulation of amphotericin B. A sequential panel design was also implemented to ensure the safety of a single dose of caspofungin in 6 patients prior to multiple dose administration. It should be noted that $AUC_{0\text{-}24\ hr}$ assessments were not performed in these neonates and infants because the number of blood samples required from an individual patient over a 24-hour period for an $AUC_{0\text{-}24\ hr}$ assessment could not be collected in these very young patients. As a result, the $C_{24\ hr}$ (trough) was predefined as the primary pharmacokinetic parameter in Protocol 058.

The paediatric pharmacokinetic data was compared to adult controls from 2 phase IIa studies Protocol 003 (Pilot *Candida* oesophagitis study), and Protocol 007 (*Candida* oesophagitis PK Study) and a 4321phase IIb study Protocol 004 (Dose-Response oropharyngeal Candidiasis or oesophageal Candidiasis Study). These 3 studies were submitted and assessed as part of the initial application for caspofungin. The subjects in these studies were adult patients with esophageal and/or oropharyngeal

candidiasis who received the standard dose of 50 or 70 mg/day as 1-hr intravenous infusion. For the patients from Protocol 004 and Protocol 007 full pharmacokinetic profiles and AUC values were available, while for the patients from Protocol 003, only $C_{1\ hr}$ and C_{trough} values were available.

Where appropriate, samples were collected from the CSF in patients who received at least 4 days of caspofungin in any of the 5 paediatric studies (Protocols 033, 042, 058, 043, and 044) in an effort to assess for caspofungin CSF concentrations. CSF samples were also collected from an investigator in Costa Rica who treated premature infants and neonates with caspofungin in Costa Rica.

Analysis method

A previously described method utilising solid-phase extraction for analyte isolation, followed by high-performance liquid chromatography (HPLC) with fluorescence detection, was used to assay human plasma samples from the new paediatric studies. In addition to the established plasma assay, an exploratory human CSF assay was developed. This was an HPLC fluorescence analysis employing the same analog internal standard used in the plasma assay. The limit of quantitation (LOQ) for this assay was 10 ng/ml, using 0.25 mL CSF. The range of the assay was 10-250 ng/ml.

Pharmacokinetic parameters and statistical methods

Based on preclinical studies using a murine model of candidiasis, $AUC_{0\text{-}24\ hr}$ has been suggested to be the most predictive parameter of efficacy. The primary pharmacokinetic parameter for the paediatric pharmacokinetic studies was therefore to approximate the plasma exposure and tolerability of the 50 mg once-daily standard dosing regimen in adults.

Pharmacokinetic parameters were calculated using non-compartmental methods. The natural log-transformed parameters were then analysed with mixed effects model with fixed terms for age group, day, and age-by-day interaction, and subject as a random effect. To compare AUC between children and adults, a two-sided 90% confidence interval (CI) for the true arithmetic mean difference was calculated using the appropriate components of variance from the aforementioned model and referencing a t-distribution. These limits were then exponentiated to obtain a CI for the true geometric mean ratio.

The MAH defined a CI of AUC ratio outside 0.7 to 1.5 as being a clinically significant alteration in caspofungin AUC. The lower bound is based on an analysis suggesting reduced efficacy against the *Candida* infection with reductions in caspofungin AUC or trough concentration of greater than 30%. The upper bound is *not* based on an association between an increased risk of a dose-limiting adverse event and increases in AUC but was obtained from the ratio of the mean plasma concentrations at the highest dose studied at the time of the initial filing (70 mg daily) relative to the recommended adult dose for caspofungin (50 mg daily). The caspofungin 70-mg daily regimen has been extensively evaluated in adult patients and healthy subjects and has been generally well tolerated. In addition, the MAH suggests that more recent clinical evaluation of the caspofungin 100 mg daily regimen suggests that this regimen is also well tolerated. The AUC obtained with caspofungin 100 mg daily is ~2.5-fold the AUC obtained at 50 mg daily.

Population PK and PK/PD analysis

A population pharmacokinetic analysis was also performed on all paediatric patients receiving a maintenance dose of caspofungin 50 mg/m^2 daily by combining the pharmacokinetic data from the two pharmacokinetic studies in children and adolescents (Protocols 033 and 042) and the two safety/efficacy studies (Protocols 043 and 044).

The pooled data thus included 102 paediatric patients with the following indications: invasive candidiasis (Protocol 043), invasive aspergillosis (Protocol 043), patients empirically treated for suspected fungal infections in the setting of persistent fever and neutropenia (from Protocol 044), and patients who received caspofungin in the setting of new-onset fever and neutropenia in the pharmacokinetic studies (from Protocols 033 and 042). Patients from the pharmacokinetic study in neonates and infants less than 3 months of age (Protocol 058) were excluded because they received a different dose (25 mg/m2 daily). Similarly, patients who received caspofungin at 1 mg/kg daily and 70 mg/m^2 daily in the first pharmacokinetic study in children and adolescents 2 to 17 years of age

(Protocol 033) were also excluded because of the different dose. All doses were administered as 1-hour, constant-rate, intravenous (IV) infusions.

The objectives of these population pharmacokinetic and PK/PD analyses were to investigate the concentration-effect relationships between caspofungin pharmacokinetics and both treatment outcome and the occurrence of adverse experiences; investigate the effect of patient characteristics on caspofungin pharmacokinetics; screen for unanticipated drug interactions; and characterise caspofungin pharmacokinetics in paediatric patients. The pharmacokinetic data in paediatric patients were obtained using either extensive or sparse sampling schemes. Analyses were conducted using a two-step method. Average individual pharmacokinetic parameters were first determined for each patient, and then statistical models were used to evaluate the relationships between those parameters and various outcome measures or patient covariates. In the concentration/response analysis, each disease indication was analysed separately for the overall treatment outcome.

The analysis was a simple two-stage approach with regression analysis. If non-linear mixed effect modelling had been used instead, possibly more information could have been obtained from the available data, such as effect of age, maturation factor or predictions of steady state.

- ***Results***

<u>Pharmacokinetic Study in 2 to 17 Year Old Patients (Protocol 033)</u>

The study was to enrol 32 evaluable patients including 8 patients in each of 2 age groups (2-11 years and 12-17 years) and at each of 2 doses. Initially, the children received a bodyweight-adjusted dose of 1.0 mg/kg/day caspofungin. However, in a total of 9 patients (2-11 years) receiving this dose, the AUC, C_{24hr} and half-life were significantly reduced (41%, 67%, and 37%, respectively, after the first dose; and 46%, 69%, and 37%, respectively, after multiple doses) compared with historical adult controls receiving 50 mg/day. Additional analyses confirmed that weight-based dosing of caspofungin resulted in substantial variation in plasma concentrations with weight and did not result in optimal dosing for paediatric populations. Thus, the study was amended to instead evaluate body surface area (BSA)-based dosing of caspofungin in paediatric patients. The two dosing regimens tested were 50 mg/m^2/day and 70 mg/m^2/day, respectively, with a maximum daily dose of 70 mg.

The results are given below per age group, 2-11 years and 12-17 years:

- *Children aged 2-11 years*

In this age group, caspofungin at 50 mg/m^2/day administered as 1-hr infusion resulted in a $AUC_{0\text{-}24\ hr}$ after multiple doses that was comparable to that in adults receiving caspofungin at 50 mg/day (see Table 1 below). Similarly, Day 3-14 $AUC_{0\text{-}24\ hr}$ was comparable in children receiving 70 mg/m^2/day and adults receiving 70 mg/day (see Table 2 below). On the first day of caspofungin administration, $AUC_{0\text{-}24\ hr}$ was somewhat higher in children than adults for these comparisons (37% increase for the 50 mg/m^2/day to 50 mg/day comparison and 60% increase for the 70 mg/m^2/day to 70 mg/day comparison). However, the AUC values in children on Day 1 were still less than those seen in adults at steady-state. Additionally, as a result of a shortened half-life, the $C_{1\ hr}$ is higher and the $C_{24\ hr}$ is lower in children relative to adults. Nevertheless, the $C_{1\ hr}$ in these children is comparable to the $C_{1\ hr}$ in adult patients treated with caspofungin at 70 mg/day (i.e., a dose for which there is notable safety experience).

Table 1. Comparison of Caspofungin Pharmacokinetics in Older Children (**Ages 2 to 11 Years**) Receiving Caspofungin **50 mg/m^2** Once Daily to Historical Control Adult Patients Receiving Caspofungin **50 mg** Once Daily

Parameter	Pediatric Patients (Ages 2 to 11 Years)		Historical Adult Controls (Protocols 003, 004 and 007)		GMR (95% CI)† (Pediatric/Adult)	
	N	LSM (95% CI)†	N	LSM (95% CI)†		
Day 1						
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	9	96.40 (79.15, 117.41)	32	70.60 (63.59, 78.38)	1.37	(1.09, 1.71)
$C_{1\ hr}$ (µg/mL)	10	13.99 (11.74, 16.68)	38	7.67 (7.01, 8.40)	1.82	(1.50, 2.22)
$C_{24\ hr}$ (µg/mL)	9	1.09 (0.81, 1.47)	33	1.35 (1.15, 1.57)	0.81	(0.58, 1.13)
β-phase $t_{½}$ (hr)	9	7.63 (1.61)‡	6	11.70 (2.92)‡	--	--
Day 3 to 14 Time-Averaged§						
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	9	115.23 (94.71, 140.19)	38	103.38 (93.97, 113.73)	1.11	(0.90, 1.39)
$C_{1\ hr}$ (µg/mL)	9	15.61 (13.15, 18.52)	38	9.39 (8.64, 10.20)	1.66	(1.37, 2.01)
$C_{24\ hr}$ (µg/mL)	9	1.46 (1.10, 1.93)	60	2.01 (1.80, 2.24)	0.72	(0.54, 0.98)
β-phase $t_{½}$ (hr)	9	8.21 (2.35)‡	5	13.00 (1.91)‡	--	--

N = Number of patients included in the analysis.
† Least Square Means (LSM) and Geometric Mean Ratios (GMR) are reported for $AUC_{(0\text{-}\infty)}$, $C_{1\ hr}$, and $C_{24\ hr}$.
‡ Harmonic means (jackknife SD) are reported for β-phase $t_{½}$.
§ Time-averaged parameters determined as the geometric mean of all values obtained between Day 3 and 14.
The mean square errors (MSEs) for the analysis were 0.0885, 0.0785, 0.2030, 0.0878, 0.0669, 0.1809 on the $\log_e$ scale, for Day 1 $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, $C_{24\ hr}$, Day 3 to 14 $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, $C_{24\ hr}$, respectively.

Table 2. Comparison of Caspofungin Pharmacokinetics in Pediatric Patients (**Ages 2 to 11 Years**) Receiving **70 mg/m^2** Caspofungin Once Daily and Historical Control Adult Patients Receiving **70 mg** Caspofungin Once Daily

Parameter	Pediatric Patients (Ages 2 to 11 Years)		Historical Adult Controls (Protocols 003, 004 and 007)		GMR (95% CI)† (Pediatric/Adult)	
	N	LSM (95% CI)†	N	LSM (95% CI)†		
Day 1						
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	12	154.97 (130.65, 183.82)	29	97.13 (87.03, 108.41)	1.60	(1.30, 1.95)
$C_{1\ hr}$ (µg/mL)	12	19.47 (16.58, 22.85)	37	10.04 (9.17, 11.00)	1.94	(1.61, 2.33)
$C_{24\ hr}$ (µg/mL)	12	2.16 (1.67, 2.80)	29	1.95 (1.65, 2.30)	1.11	(0.82, 1.51)
β-phase $t_{½}$ (hr)	11	8.91 (2.28)‡	6	12.25 (2.84)‡	--	--
Day 3 to 14 Time-Averaged§						
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	9	161.44 (132.70, 196.42)	35	153.65 (139.11, 169.71)	1.05	(0.84, 1.31)
$C_{1\ hr}$ (µg/mL)	10	20.97 (17.83, 24.67)	35	13.32 (12.22, 14.53)	1.57	(1.31, 1.89)
$C_{24\ hr}$ (µg/mL)	9	2.47 (1.87, 3.27)	57	3.33 (2.98, 3.72)	0.74	(0.55, 1.00)
β-phase $t_{½}$ (hr)	7	9.71 (2.03)‡	5	16.46 (7.04)‡	--	--

N = Number of patients included in the analysis.
† Least Square Means (LSM) and Geometric Mean Ratios (GMR) are reported for $AUC_{(0\text{-}\infty)}$, $C_{1\ hr}$, and $C_{24\ hr}$.
‡ Harmonic means (jackknife SD) are reported for β-phase $t_{½}$.
§ Time-averaged parameters determined as the geometric mean of all values obtained between Day 3 and 14.
The mean square errors (MSEs) for the analysis were 0.0885, 0.0785, 0.2030, 0.0878, 0.0669, 0.1809 on the $\log_e$ scale, for Day 1 $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, $C_{24\ hr}$, Day 3 to 14 $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, $C_{24\ hr}$, respectively.

- *Children aged 12-17 years*

In adolescents (ages 12 to 17 years) receiving caspofungin at 50 mg/m^2/day (maximum not to exceed 70 mg daily), the pharmacokinetics of caspofungin were generally comparable to those seen in adults receiving caspofungin at 50 mg/day after both the first and multiple doses were administered (see Table 3 below). However, in this study, all adolescents received doses >50 mg/day, and, in fact, 6 of 8 patients received the maximum dose of 70 mg/day. The caspofungin plasma concentrations in these adolescents were lower than in adults receiving 70 mg/day (see Table 4 below). There were trends in the data in adolescents towards higher $C_{1\ hr}$ and shorter half-life relative to adults consistent with the trends noted in children aged 2 to 11 years, although the differences were of smaller magnitude in the adolescents than in younger children. Thus, adolescents likely require somewhat higher doses (a

dosing regimen of 50 mg/m^2/day with a maximum of 70 mg/day), to obtain pharmacokinetics similar to those obtained in adults receiving caspofungin at 50 mg/day. Because the maximum dose was frequently achieved and the pharmacokinetics were similar to adults, a decision was made not to enrol adolescents at 70 mg/m^2/day.

Table 3. Comparison of Caspofungin Pharmacokinetics in Adolescents (**Ages 12 to 17 Years**) Receiving Caspofungin **50 mg/m^2** Once Daily to Historical Control Adult Patients Receiving Caspofungin **50 mg** Daily

Parameter	Pediatric Patients (Ages 12 to 17 Years) N	Pediatric Patients (Ages 12 to 17 Years) LSM (95% CI)†	Historical Adult Controls (Protocols 003, 004 and 007) N	Historical Adult Controls (Protocols 003, 004 and 007) LSM (95% CI)†	GMR (95% CI)† (Pediatric/Adult)	
Day 1						
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	7	77.58 (62.04, 97.01)	32	70.60 (63.59, 78.38)	1.10	(0.86, 1.41)
$C_{1\ hr}$ (µg/mL)	8	8.95 (7.36, 10.90)	38	7.67 (7.01, 8.40)	1.17	(0.94, 1.45)
$C_{24\ hr}$ (µg/mL)	7	1.26 (0.90, 1.77)	33	1.35 (1.15, 1.57)	0.94	(0.65, 1.36)
β-phase $t_{½}$ (hr)	7	10.51 (2.81)‡	6	11.70 (2.92)‡	--	--
Day 3 to 14 Time-Averaged§						
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	8	117.19 (95.18, 144.28)	38	103.38 (93.97, 113.73)	1.13	(0.90, 1.43)
$C_{1\ hr}$ (µg/mL)	8	12.90 (10.76, 15.46)	38	9.39 (8.64, 10.20)	1.37	(1.13, 1.68)
$C_{24\ hr}$ (µg/mL)	8	2.15 (1.60, 2.90)	60	2.01 (1.80, 2.24)	1.07	(0.78, 1.47)
β-phase $t_{½}$ (hr)	8	11.20 (1.71)‡	5	13.00 (1.91)‡	--	--

N = Number of patients included in the analysis.
† Least Square Means (LSM) and Geometric Mean Ratios (GMR) are reported for $AUC_{(0\text{-}\infty)}$, $C_{1\ hr}$, and $C_{24\ hr}$.
‡ Harmonic means (jackknife SD) are reported for β-phase $t_{½}$.
§ Time-averaged parameters determined as the geometric mean of all values obtained between Day 3 and 14.
The mean square errors (MSEs) for the analysis were 0.0885, 0.0785, 0.2030, 0.0878, 0.0669, 0.1809 on the $\log_e$ scale, for Day 1 $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, $C_{24\ hr}$, Day 3 to 14 $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, $C_{24\ hr}$, respectively.

Table 4 . Exploratory Comparison of Caspofungin Pharmacokinetics in Pediatric Patients (**Ages 12 to 17 Years**) Receiving **50 mg/m^2** Caspofungin Once Daily and Historical Control Adult Patients Receiving **70 mg** Caspofungin Daily

Parameter	Pediatric Patients (Ages 12 to 17 Years) N	Pediatric Patients (Ages 12 to 17 Years) LSM (95% CI)†	Historical Adult Controls (Protocols 003, 004 and 007) N	Historical Adult Controls (Protocols 003, 004 and 007) LSM (95% CI)†	GMR (95% CI)† (Pediatric/Adult)	
Day 1						
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	7	77.58 (62.04, 97.01)	29	97.13 (87.03, 108.41)	0.80	(0.62, 1.02)
$C_{1\ hr}$ (µg/mL)	8	8.95 (7.36, 10.90)	37	10.04 (9.17, 11.00)	0.89	(0.72, 1.11)
$C_{24\ hr}$ (µg/mL)	7	1.26 (0.90, 1.77)	29	1.95 (1.65, 2.30)	0.65	(0.44, 0.94)
β-phase $t_{½}$ (hr)	7	10.51 (2.81)‡	6	12.25 (2.84)‡	--	--
Day 3 to 14 Time-Averaged§						
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	8	117.19 (95.18, 144.28)	35	153.65 (139.11, 169.71)	0.76	(0.61, 0.96)
$C_{1\ hr}$ (µg/mL)	8	12.90 (10.76, 15.46)	35	13.32 (12.22, 14.53)	0.97	(0.79, 1.18)
$C_{24\ hr}$ (µg/mL)	8	2.15 (1.60, 2.90)	57	3.33 (2.98, 3.72)	0.65	(0.47, 0.89)
β-phase $t_{½}$ (hr)	8	11.20 (1.71)‡	5	16.46 (7.04)‡	--	--

N = Number of patients included in the analysis.
† Least Square Means (LSM) and Geometric Mean Ratios (GMR) are reported for $AUC_{(0\text{-}\infty)}$, $C_{1\ hr}$, and $C_{24\ hr}$.
‡ Harmonic means (jackknife SD) are reported for β-phase $t_{½}$.
§ Time-averaged parameters determined as the geometric mean of all values obtained between Day 3 and 14.

The MAH presented scatterplots of individual pharmacokinetic parameters (C_{24h}, C_{1h} and AUC_{0-24h}) versus age at the different doses tested in study Protocol 033 on days 3-14. The scatterplots in the 2-17 years group did not indicate any trends of pharmacokinetic changing with age, although data are sparse.

Although AUC on the first day appeared to be higher in the 2-11 years age group than in adults, the AUC on days 3-14 met the predefined ratio of being within 0.7 to 1.5 times (90% CI) the adult AUC. From a pharmacokinetic point of view, 50 mg/m^2 per day appears to be an appropriate dose for the age group 2-17 years based on average data. The Ctrough ($C_{24\ hr}$) was somewhat lower in the paediatric patients receiving 50 mg/m^2 than in adults receiving 50 mg, but it was still well above the suggested target concentration o 1 μg/ml. However, the data are especially sparse in patients about 2-7 years. Possibly, clearance is largest in this group.

Pharmacokinetic Study in 3 to 24 Month Old Patients (Protocol 042)

This study enrolled a total of 9 patients. It should be noted that the inclusion criteria on age was 3 to 24 months of age, however the age group studied in Protocol 042 was actually 10 to 24 months. All patients enrolled in this study received caspofungin at 50 mg/m^2/day. Full (7-point) plasma samples were collected on Day 1 and Day 4 of caspofungin study therapy. Pharmacokinetic parameters, including $AUC_{0-24\ hr}$, peak ($C_{1\ hr}$), and trough ($C_{24\ hr}$) concentrations and half-life determinations, were evaluated for all patients and compared relative to adult controls with mucosal (oesophageal and/or oropharyngeal) candidiasis receiving 50 mg/day. As in children 2 to 11 years of age (from Protocol 033), the $AUC_{0-24\ hr}$ in these younger children on Day 1 of therapy was increased in comparison to the $AUC_{0-24\ hr}$ in adult patients. However, on Day 4, the $AUC_{0-24\ hr}$ in these young children was similar to the $AUC_{0-24\ hr}$ in the same adult cohort (see Table 5 below). However, as a result of a shortened apparent terminal half-life, the $C_{1\ hr}$ was higher and the $C_{24\ hr}$ was comparable in these young children relative to adults. The $C_{1\ hr}$ achieved in these young children is within the range of clinical experience of safe and well-tolerated caspofungin therapy in adults.
Table 6 further below shows a comparison of the 50 mg/m^2 dose to small children with the 70 mg dose to adults.

The pharmacokinetic results from these young children (3 to 24 months) receiving caspofungin at 50 mg/m^2/day were similar to the results seen in older children (2 to 11 years) that received the same dosing regimen. The shape of the mean concentration-time profiles and the apparent terminal half-life were similar between the two groups. Although slightly higher $AUC_{0-24\ hr}$, $C_{1\ hr}$, and $C_{24\ hr}$ values were found in the younger children, none of these differences were statistically significant (see Table 7 below)

Taken together, these results suggest that the steady-state exposure in young children (3 months to 11 years) receiving caspofungin at 50 mg/m^2 daily is similar to adults receiving the standard caspofungin 50-mg daily dosing regimen. The increase in $C_{1\ hr}$ in these children relative to adults is suggested not to be clinically meaningful. The shorter caspofungin apparent terminal half-life in young children relative to adults is likely due to increased plasma clearance in these young children.

Table 5. Comparison of Caspofungin Pharmacokinetics in Young Children (Ages 3 to 24 Months) Receiving Caspofungin 50 mg/m^2 Once Daily and Historical Control Adult Patients Receiving Caspofungin **50 mg** Once Daily

Parameter	Young Children (Age 3-24 Months) N	Young Children (Age 3-24 Months) LSM (95% CI)[†]	Historical Adult Controls (Protocols 003, 004 and 007) N	Historical Adult Controls (Protocols 003, 004 and 007) LSM (95% CI)[†]	GMR (90% CI)[†] Young Children/Adults
Day 1					
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	7	120.20 (100.93, 143.15)	32	70.60 (65.06, 76.61)	1.70 (1.45, 2.00)
$C_{1\ hr}$ (µg/mL)	9	17.46 (14.75, 20.68)	38	7.67 (7.07, 8.33)	2.28 (1.95, 2.66)
$C_{24\ hr}$ (µg/mL)	7	1.34 (1.03, 1.76)	33	1.35 (1.19, 1.52)	1.00 (0.78, 1.28)
β-phase $t_{1/2}$ (hr)	7	7.79 (2.31)[‡]	6	11.70 (2.92)[‡]	--
Day 4 or 3 to 14 Time Averaged[§]					
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	8	130.29 (107.46, 157.96)	38	103.38 (94.63, 112.93)	1.26 (1.06, 1.50)
$C_{1\ hr}$ (µg/mL)	8	17.21 (14.56, 20.36)	38	9.39 (8.69, 10.14)	1.83 (1.57, 2.14)
$C_{24\ hr}$ (µg/mL)	8	1.64 (1.24, 2.16)	60	2.01 (1.82, 2.22)	0.81 (0.64, 1.04)
β-phase $t_{1/2}$ (hr)	8	8.80 (2.10)[‡]	5	13.00 (1.91)[‡]	--

N = Number of patients included in the analysis.

[†] Least Square Means (LSM) and Geometric Mean Ratios (GMR) are reported for $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, and $C_{24\ hr}$.

[‡] Harmonic means (jackknife SD) are reported for β-phase $t_{1/2}$.

[§] Time-averaged parameters determined as the geometric mean of all values obtained between Day 3 and 14. The Day 4 $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$ and β-phase $t_{1/2}$ for young children were compared to Day 3 to 14 time-averaged $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$ and β-phase $t_{1/2}$ for adult controls. The Day 3 to 14 time-averaged $C_{24\ hr}$ for young children were compared to the Day 3 to 14 time averaged $C_{24\ hr}$ for adult controls.

Table 6. Comparison of Caspofungin Pharmacokinetics in Young Children (Ages 3 to 24 Months) Receiving Caspofungin 50 mg/m^2 Once Daily and Historical Control Adult Patients Receiving Caspofungin **70 mg** Once Daily

Parameter	Young Children (Age 3-24 Months) N	Young Children (Age 3-24 Months) LSM (95% CI)[†]	Historical Adult Controls (Protocols 003, 004 and 007) N	Historical Adult Controls (Protocols 003, 004 and 007) LSM (95% CI)[†]	GMR (90% CI)[†] Young Children/Adults
Day 1					
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	7	120.20 (100.93, 143.15)	29	97.13 (89.14, 105.84)	1.24 (1.05, 1.46)
$C_{1\ hr}$ (µg/mL)	9	17.46 (14.75, 20.68)	37	10.04 (9.24, 10.92)	1.74 (1.49, 2.04)
$C_{24\ hr}$ (µg/mL)	7	1.34 (1.03, 1.76)	29	1.95 (1.71, 2.22)	0.69 (0.54, 0.89)
β-phase $t_{1/2}$ (hr)	7	7.79 (2.31)[‡]	6	12.25 (2.84)[‡]	--
Day 4 or 3 to 14 Time Averaged[§]					
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	8	130.29 (107.46, 157.96)	35	153.65 (140.13, 168.47)	0.85 (0.71, 1.01)
$C_{1\ hr}$ (µg/mL)	8	17.21 (14.56, 20.36)	35	13.32 (12.30, 14.44)	1.29 (1.11, 1.51)
$C_{24\ hr}$ (µg/mL)	8	1.64 (1.24, 2.16)	57	3.33 (3.00, 3.69)	0.49 (0.38, 0.63)
β-phase $t_{1/2}$ (hr)	8	8.80 (2.10)[‡]	5	16.46 (7.04)[‡]	--

N = Number of patients included in the analysis.

[†] Least Square Means (LSM) and Geometric Mean Ratios (GMR) are reported for $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, and $C_{24\ hr}$.

[‡] Harmonic means (jackknife SD) are reported for β-phase $t_{1/2}$.

[§] Time-averaged parameters determined as the geometric mean of all values obtained between Day 3 and 14. The Day 4 $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$ and β-phase $t_{1/2}$ for young children were compared to Day 3 to 14 time-averaged $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$ and β-phase $t_{1/2}$ for adult controls. The Day 3 to 14 time-averaged $C_{24\ hr}$ for young children were compared to the Day 3 to 14 time-averaged $C_{24\ hr}$ for adult controls.

Table 7. Comparison of Caspofungin Pharmacokinetics in Young Children (Ages **3 to 24 Months**) Receiving Caspofungin **50 mg/m^2** Once Daily and Older Children (Ages **2 to 11 Years**) Receiving Caspofungin **50 mg/m^2** Once Daily

Parameter	Young Children (Age 3-24 Months)		Older Children (Ages 2-11 Years)		GMR (90% CI)† Young Children/Older Children
	N	LSM (95% CI)†	N	LSM (95% CI)†	
Day 1					
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	7	120.20 (88.39, 163.45)	9	96.40 (73.51, 126.42)	1.25 (0.89, 1.75)
$C_{1\ hr}$ (µg/mL)	9	17.46 (13.90, 21.93)	10	13.99 (11.27, 17.37)	1.25 (0.96, 1.62)
$C_{24\ hr}$ (µg/mL)	7	1.34 (0.87, 2.08)	9	1.09 (0.74, 1.60)	1.24 (0.76, 2.00)
β-phase $t_{1/2}$ (hr)	7	7.79 (2.31)‡	9	7.63 (1.61)‡	--
Day 4 or 3 to 14 Time Averaged§					
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	8	130.29 (105.26, 161.26)	9	115.23 (94.24, 140.89)	1.13 (0.89, 1.44)
$C_{1\ hr}$ (µg/mL)	8	17.21 (13.76, 21.54)	9	15.61 (12.64, 19.28)	1.10 (0.85, 1.42)
$C_{24\ hr}$ (µg/mL)	8	1.64 (1.10, 2.43)	9	1.46 (1.00, 2.12)	1.12 (0.72, 1.76)
β-phase $t_{1/2}$ (hr)	8	8.80 (2.10)‡	9	8.21 (2.35)‡	--

N = Number of patients included in the analysis.

† Least Square Means (LSM) and Geometric Mean Ratios (GMR) are reported for $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, and $C_{24\ hr}$.

‡ Harmonic means (jackknife SD) are reported for β-phase $t_{1/2}$.

§ Time-averaged parameters determined as the geometric mean of all values obtained between Day 3 and 14. The Day 4 $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$ and β-phase $t_{1/2}$ for young children were compared to Day 3 to 14 time-averaged $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$ and β-phase $t_{1/2}$ for older children ages 2 to 11 years. The Day 3 to 14 time-averaged $C_{24\ hr}$ for young children were compared to the Day 3 to 14 time-averaged $C_{24\ hr}$ for older children ages 2 to 11 years.

Scatterplots of the individual pharmacokinetic parameters (C_{24h}, C_{1h} and $AUC_{0\text{-}24h}$)versus age in the group 3-24 months were presented by the MAH.

For the age group 3-12 months, the youngest child included in this pharmacokinetic study was 10 months, and all other children were 12 months or older. The pharmacokinetics in the age group can therefore not be considered evaluated. As there might be many developmental changes in this age group, it might not be appropriate to extrapolate data from the older children.

However, although data are limited, there are no apparent trends of pharmacokinetics changing with age over the age 12-24 months. Thus, from a pharmacokinetic point of view, 50 mg/m^2 per day appears to be a sufficiently appropriate dose for children from 12 months and older and might be suggested for the SPC. A better estimation could possibly have been obtained by modelling the available data, as discussed under population pharmacokinetic analysis below.

Pharmacokinetic Study in 0 to 3 Month Old Patients (Protocol 058)

This study enrolled a total of 18 patients less than 3 months of age, with 6 in the single-dose panel (Panel A) and 12 in the multiple-dose panel (Panel B). All patients enrolled in this study received caspofungin at 25 mg/m^2 as a single dose or multiple once-daily dose. The study population included 5 term (gestational age at birth >36 weeks) and 13 preterm neonates.

Pharmacokinetic sampling in this study was limited to peak ($C_{1\ hr}$) and trough ($C_{24\ hr}$) samples. In neonates and infants less than 3 months of age receiving caspofungin at 25 mg/m^2, the Day 1 $C_{1\ hr}$ and Day 1 $C_{24\ hr}$ were generally similar to that in adults receiving caspofungin at 50 mg/day. The Day 4 $C_{1\ hr}$ in neonates and infants was also generally comparable to that in adults. The Day 4 $C_{24\ hr}$ in neonates and infants was somewhat elevated in comparison to the adults, but was within the range of clinical experience previously seen in adult patients who have received multiple doses of caspofungin up to 100 mg/day (see Table 8 below)

Table 8. Statistical Comparison of Caspofungin Plasma Concentration Between Neonates and Infants (Age <3 Months) receiving Caspofungin 25 mg/m^2 and Adult Patients receiving 50 mg daily

Day Parameter (µg/mL)	Neonates and Infants			Historical Data from Adult Patients (Protocols 003, 004, 007)			Ratio (Neonates and Infants / Adult Patients)	
	N	Geometric † Mean	95% CI for Geometric Mean	N	Geometric † Mean	95% CI for Geometric Mean	Geometric † Mean Ratio	90% CI for GMR
Day 1								
$C_{1\ hr}$	18	8.2	(6.8, 10.0)	38	7.7	(6.7, 8.7)	1.07	(0.89, 1.30)
$C_{24\ hr}$	18	1.8	(1.4, 2.4)	33	1.3	(1.1, 1.6)	1.36	(1.04, 1.78)
Day 4*								
$C_{1\ hr}$	12	11.1	(8.8, 13.9)	38	9.4	(8.2, 10.7)	1.18	(0.95, 1.46)
$C_{24\ hr}$	11	2.4	(1.8, 3.4)	60	2.0	(1.7, 2.3)	1.21	(0.90, 1.63)

† Based on least squares means from a mixed effects model performed on the natural-log transformed values.
* For the adult patients, Day 4 values were calculated by time-averaging Days 3-14 data.

Comparisons with the pharmacokinetic results in older children suggest that the caspofungin peak ($C_{1\ hr}$) concentrations in neonates and infants at doses of 25 mg/m^2/day were somewhat reduced on Day 1 and Day 4 relative to those in these older paediatric patients at doses of 50 mg/m^2/day. Conversely, trough ($C_{24\ hr}$) concentrations in the neonates and infants at doses of 25 mg/m^2/day were somewhat increased on both Day 1 and Day 4 relative to the trough concentrations achieved in older paediatric patients at doses of 50 mg/m^2/day (see Table 9 Children 3-24 months, Table 10 Children 2-11 years and Table 11 Adolescents below). Thus, at doses of 25 mg/m^2/day, the peak-to-trough ratios for caspofungin on Days 1 and 4 were somewhat decreased in neonates and infants relative to those of the older paediatric patients at doses of 50 mg/m^2/day.

Table 9. Statistical Comparison of Caspofungin Plasma Concentration Between Neonates and Infants (Age <3 Months) receiving Caspofungin 25 mg/m^2 and **Children (Age 3-24 Months)** receiving 50 mg/m^2 daily

Day Parameter (µg/mL)	Neonates and Infants			Historical 3-24 Month Old Children (Protocols 042)			Ratio (Neonates and Infants / 3-24 Month. Old Children)	
	N	Geometric † Mean	95% CI for Geometric Mean	N	Geometric † Mean	95% CI for Geometric Mean	Geometric † Mean Ratio	90% CI for GMR
Day 1								
$C_{1\ hr}$	18	8.2	(6.3, 10.8)	8	17.0	(11.3, 25.6)	0.48	(0.32, 0.72)
$C_{24\ hr}$	18	1.8	(1.2, 2.7)	6	1.3	(0.7, 2.6)	1.37	(0.72, 2.62)
Day 4								
$C_{1\ hr}$	12	11.0	(8.0, 15.3)	7	16.5	(10.7, 25.4)	0.67	(0.43, 1.04)
$C_{24\ hr}$	11	2.4	(1.5, 3.9)	7	1.4	(0.8, 2.7)	1.67	(0.86, 3.24)

† Based on least squares means from an ANOVA performed on the natural-log transformed values.

Table 10. Statistical Comparison of Caspofungin Plasma Concentration Between Neonates and Infants (Age <3 Months) receiving Caspofungin 25 mg/m^2 and **Children (Age 2-11 Years)** receiving 50 mg/m^2 daily

Day Parameter (µg/mL)	Neonates and Infants			Historical Data from 2-11 Year Old Children (Protocol 033)			Ratio (Neonates and Infants / 2-11 Year Old Children)	
	N	Geometric † Mean	95% CI for Geometric Mean	N	Geometric † Mean	95% CI for Geometric Mean	Geometric † Mean Ratio	90% CI for GMR
Day 1								
$C_{1\ hr}$	18	8.2	(6.3, 10.7)	10	14.0	(9.8, 19.9)	0.59	(0.41, 0.85)
$C_{24\ hr}$	18	1.8	(1.2, 2.7)	9	1.0	(0.6, 1.8)	1.77	(1.00, 3.13)
Day 4								
$C_{1\ hr}$	12	11.1	(8.1, 15.1)	9	15.6	(10.8, 22.5)	0.71	(0.48, 1.06)
$C_{24\ hr}$	11	2.4	(1.4, 3.9)	9	1.3	(0.7, 2.3)	1.85	(1.00, 3.43)

† Based on least squares means from an ANOVA performed on the natural-log transformed values.

Table 11. Statistical Comparison of Caspofungin Plasma Concentration Between Neonates and Infants (Age <3 Months) receiving Caspofungin 25 mg/m^2 and **Adolescents (Age 12-17 Years)** receiving 50 mg/m^2 daily

Day Parameter (μg/mL)	Neonates and Infants			Historical Data from 12-17 Year Old Adolescents (Protocol 033)			Ratio (Neonates and Infants / 12-17 Year Old Adolescents)	
	N	Geometric † Mean	95% CI for Geometric Mean	N	Geometric † Mean	95% CI for Geometric Mean	Geometric † Mean Ratio	90% CI for GMR
Day 1								
$C_{1\ hr}$	18	8.2	(6.1, 11.1)	8	9.0	(5.8, 13.9)	0.92	(0.59, 1.43)
$C_{24\ hr}$	18	1.8	(1.2, 2.7)	7	1.2	(0.6, 2.3)	1.49	(0.79, 2.81)
Day 4								
$C_{1\ hr}$	12	11.2	(7.9, 15.9)	8	13.5	(8.7, 21.1)	0.83	(0.52, 1.32)
$C_{24\ hr}$	11	2.4	(1.4, 4.0)	8	2.2	(1.2, 4.0)	1.11	(0.58, 2.14)

† Based on least squares means from an ANOVA performed on the natural-log transformed values.

The MAH presented data on the relationship between trough or peak concentration and total age on Day 1 and Day 4 in children age <3 months and the relationship between trough or peak concentration and weight on Day 1 and Day 4 in children age <3 months, which showed that the variability in caspofungin concentrations in neonates was large with a possible but not statistically significant trend towards decreasing concentrations with increasing age and weight.

The MAH also submitted scatterplots comparing individual data for Day 4 C_{max} and C_{min} in all age groups tested that showed that the variability in clearance was largest in the youngest group as especially the variability in C_{min} on Day 4 was larger than in the other groups.

The scatterplots as well as the 90% confidence intervals for the ratio when comparing $C_{24\ hours}$ in the infants with that of other age groups indicated a large variability in clearance over the first three months after birth, possibly due to maturation.
The MAH suggested that a dose of 25 mg/m^2 can be used, based on the average pharmacokinetic data. However, there is a large variability in pharmacokinetics within the studied group of 0-3 months and there is no pharmacokinetic data for children between 3 and 12 months, as discussed above, but the variability may be large also within this group, which makes difficult to give a dosing recommendation for children <12 months of age.

During the assessment, the MAH was requested to clarify the choice of dosing per m^2 and not per kg for the youngest population while dosing regimen expressed in (m)g per kg body weight are preferred by neonatologists and paediatricians for prescription purpose in the clinical units. The reasons are clearly practical, namely related to less calculation and medication errors, the body surface of a neonate being an estimate deduced from published scales/formulas.

In the answer to the RSI adopted in May 2008, the MAH performed a simulation for the 12 subjects who received multiple doses of caspofungin at 25 mg/m2 daily in the pharmacokinetic study in neonates and infants <3 months of age (Protocol 058) in an effort to assess whether a weight-based dosing regimen would overcome the variability in plasma concentration seen in this youngest age group. As shown in Table 12 below, the actual dose in milligrams (mg) received by each patient in Protocol 058 is presented based on that patient's body-surface area (BSA). When these doses were then adjusted based on patient's weight, the mean mg/kg once-daily dose equivalent to 25 mg/m2 once daily was 2.1 mg/kg. Therefore, the weight-based simulations were performed based on a hypothetical 2 mg/kg once-daily dose. Actual Day 4 C1 hr and C24 hr data were adjusted based on the dose the patient would have received had a 2 mg/kg dose been administered. These simulated Day 4 C1 hr and C24 hr data appear in the last two columns of Table 12. Depending on the relative weight-to-BSA ratio of a given patient, caspofungin concentrations may have increased or decreased using a weight-based dosing scheme as compared to a BSA-based dosing scheme. However, the mean C1 hr and C24 hr values were similar for the BSA-based and weight-based regimens: mean C1 hr 11.7 μg/ml vs. 11.4 μg/ml, respectively, and C24 hr 3.2 μg/ml vs. 3.0 μg/ml, respectively. The overall impact of a weight-based regimen as compared to a BSA-regimen on the pharmacokinetic variability (as assessed by the standard deviation around the mean C1 hr and C24 hr estimates) was small.

Table 12. Protocol 058: Comparison of Actual Pharmacokinetic Data Using a BSA-based Dosing Regimen with Simulations of a Hypothetical Weight-Based Dosing Regimen in Infants and Neonates <3 Months of Age

	Actual Pharmacokinetic Data Based on the 25 mg/m^2 Daily Dose			Simulated Pharmacokinetic Data Based on a Hypothetical 2 mg/kg Daily Dose		
Allocation Number	Actual Dose (mg)	Day 4 C_{1hr} (µg/ml)	Day 4 C_{24hr} (µg/ml)	Simulated Dose (mg)	Day 4 C_{1hr} (µg/ml)	Day 4 C_{24hr} (µg/ml)
7635	3.1	8.3	-	2.8	7.4	--
7643	4.3	8.8	0.8	4.3	8.8	0.8
7644	2.2	22.1	7.2	1.6	15.8	5.1
7645	2.0	18.0	6.5	1.4	12.4	4.5
7647	3.7	10.2	2.8	3.8	10.5	2.8
7648	6.3	9.6	1.9	6.4	11.6	2.3
7649	5.0	14.6	3.9	5.8	16.9	4.5
7650	5.9	14.2	2.7	7.6	18.3	3.5
7651	2.7	13.0	5.3	2.1	10.2	4.2
7659	5.1	2.6	0.1	5.6	2.9	0.1
7660	5.3	7.0	1.7	6.2	8.3	2.0
7667	4.3	12.5	2.7	4.6	13.5	2.9
Mean	4.1	11.7	3.2	4.4	11.4	3.0
St. Dev.	1.3	5.2	2.3	2.0	4.3	1.6

This analysis was repeated for the 3 patients between 3 and 12 months of age for whom all of the relevant data were available in Protocol 042. The data for these 3 patients, whose actual ages were 10, 12, and 12 months of age, are included in Table 13 below. As was seen in the neonatal/infant population less than 3 months of age, the corresponding weight-based dose in these toddlers receiving the 50 mg/m2 daily maintenance dose was approximately 2 mg/kg (mean 2.3 mg/kg). In these patients, the mean C1 hr and C24 hr values were similar for the BSA-based and weight-based regimens: mean C_{1hr} 16.4 µg/ml vs. 14.5 µg/ml, respectively, and C24 hr 1.5 µg/ml vs. 1.3 µg/ml, respectively. However, for this older group of patients, the standard deviation of both Day 4 C_{1hr} and C_{24hr} actually increased slightly when a weight-based dosing regimen was used as compared to a BSA-based regimen.

Table 13. Protocol 042: Comparison of Actual Pharmacokinetic Data Using a BSA-based Dosing Regimen with Simulations of a Hypothetical Weight-Based Dosing Regimen in Children 3 to 12 Months of Age

	Actual Pharmacokinetic Data Based on the 50 mg/m^2 Daily Dose			Simulated Pharmacokinetic Data Based on a Hypothetical 2 mg/kg Daily Dose		
Allocation Number	Actual Dose (mg)	Day 4 C_{1hr} (µg/ml)	Day 4 C_{24hr} (µg/ml)	Simulated Dose (mg)	Day 4 C_{1hr} (µg/ml)	Day 4 C_{24hr} (µg/ml)
3701	25.0	18.0	1.7	22.8	16.4	1.6
3546	22.5	15.9	1.3	18.8	13.3	1.1
3545	24.0	15.2	1.6	21.8	13.8	1.4
Mean	23.8	16.4	1.5	21.1	14.5	1.3
St. Dev.	1.3	1.4	0.2	2.1	1.7	0.3

Overall, these analyses demonstrate minimal impact in the pharmacokinetic variability of caspofungin in paediatric patients <12 months of age when a weight-based dosing scheme is used, in comparison to the proposed BSA-based regimen. Based on these findings, the MAH proposed to maintain the use of a BSAbased dosing regimen in patients under 12 months of age. In doing so, a consistent approach to paediatric dosing with caspofungin would be employed across all paediatric age groups, thereby reducing prescriber confusion and the potential for dosing errors.

Consequently the MAH proposed to include in addition to the BSA-based dosing, the corresponding daily dose in mg/kg in section 5.2 of the SPC, which has been agreed by the CHMP.

Population pharmacokinetic analysis

Although increases in C_{1hr}, C_{24hr}, and $AUC_{0\text{-}24\ hr}$ for caspofungin are noted in paediatric patients relative to adults, the occurrence of clinical adverse experiences and/or clinically significant laboratory abnormalities does not appear to be increased by higher caspofungin plasma concentrations over the range of pharmacokinetic parameters examined. Furthermore, neither $C_{1\ hr}$ nor $C_{24\ hr}$ concentrations predict overall efficacy outcome with caspofungin.

A drug interaction screening analysis did not suggest any concomitant medications that are likely to alter caspofungin pharmacokinetics. However, the MAH acknowledged that regarding drug interactions, a number of factors confounded clear interpretation of the results, including overlapping administration of more than one concomitant medication. Trends seen with concomitant use of dexamethasone may be consistent with a similar moderate reduction in caspofungin concentration associated with concomitant inducer use in adults. Therefore, a dose elevation from 50 mg/m^2 daily to 70 mg/m^2 daily (not to exceed 70 mg daily) should be considered in paediatric patients if they are receiving caspofungin concomitantly with certain inducers of drug clearance.

In the multiple-regression covariate analysis, weight and disease state were the only covariates found to be statistically significant determinants of caspofungin pharmacokinetics in paediatric patients. Body weight was a significant determinant of caspofungin $C_{1\ hr}$, but not $AUC_{0\text{-}24\ hr}$ or $C_{24\ hr}$. On average, a 10 kg reduction in weight is associated with a 7% increase in $C_{1\ hr}$ in paediatric patients. The modest alteration in $C_{1\ hr}$ is not anticipated to be clinically meaningful. These results are in line with the previous analysis indicating that BSA and not BW might be a better determinant of caspofungin pharmacokinetics.

Disease state was a significant covariate for $AUC_{0\text{-}24\ hr}$ and $C_{24\ hr}$, but not $C_{1\ hr}$. The significant change was only seen for the diagnosis new onset fever and neutropenia (Protocols 033 and 042;) where there was a 25% decrease in $AUC_{0\text{-}24\ hr}$ ($p=0.004$) and a 35.9% decrease in $C_{24\ hr}$ ($p<0.001$). This modest decrease was observed consistently across paediatric patients in all age groups (young children [3-24 months], older children [2-11 years], and adolescents [12-17 years]), but is unlikely to be clinically significant, since all groups of paediatric patients had $AUC_{0\text{-}24\ hr}$ and C_{24hr} values equivalent or greater than the corresponding group of adult patients.

The described analysis was merely a statistical analysis using a two stage approach where individual observations (C1h or C24 hour) or AUC0-24 (which is assumed to have been estimated with non-compartmental analysis) was related to patient factors with univariate and multiple regression techniques. The MAH states that time average data (3-14 days) was used in the analysis. Thus, as steady state was likely not achieved in all patients, the values may be depending on when the samples were obtained and the results should be viewed with some caution.

Nonlinear mixed effects modelling was not applied. Using such techniques, all data from all doses (including neonates) could have been included rather than discarding data.

By applying modelling more information could have been extracted from the obtained data and possibly provide further support to the proposed dosing in age groups where pharmacokinetic data are sparse. In such an analysis, with a priori inclusion of body size effect in the base model, a maturation effect could possibly have been estimated as data from a large age span was available. If the model adequately described the paediatric data and was of sufficient quality the model could then have been used for simulations e.g. to show that adequate exposure is obtained at steady state with the suggested dose over the entire age span, or at least over the age ranges evaluated but where data are sparse.

Using the simple two-stage regression model, similar trends as previously observed in adults were seen in the PK/PD analysis of paediatric data, i.e. that there appears to be no strong correlation between plasma concentrations and efficacy, possibly since only the clinically effective doses were studied and the plasma concentrations achieved may therefore be at the maximum of the concentration-effect curve.

Although the results of the population pharmacokinetic analysis, including the effects of concomitant medications, should be interpreted with caution the CHMP has agreed to add information in section 4.2 of the SPC that the dose might need to be increased to 70 mg/m^2 if inducers of metabolic enzymes are co-administered with caspofungin to paediatric patients (12 months to 17 years of age).

During the assessment the MAH was requested to discuss the co-administration with inducers of metabolic enzymes including dexamethasone for neonates and infants below 3-12 months of age (e.g. for the proposed 25mg/m^2 dosage below 3 months).
To answer to this request, the MAH conducted additional caspofungin pharmacokinetic analyses focused on the paediatric patients <2 years of age. Dexamethasone was used for this analysis, as this drug was the most common inducer prescribed in this particular patient age group. The MAH included for these analyses, all subjects 23 months or younger from their 3 caspofungin paediatric studies. The data were combined and stratified based on the co-administration of dexamethasone during the caspofungin treatment course.
The analysis indicated that a caspofungin dose adjustment may be necessary in young children (3 to 23 months of age), given that the GMR for C_{24hr} is less than 1, the lower bound of the 90% confidence interval for C_{24hr} GMR is well below 0.7, and the lower bound of the 90% confidence interval for $AUC_{0\text{-}24hr}$ is close to 0.7. This analysis is supported by the finding of the paediatric population pharmacokinetic analysis (performed in paediatric patients ranging in age from 3 months to 17 years), which found a clinically significant reduction in C_{24hr} levels when caspofungin was administered with dexamethasone across the entire paediatric age range.
In order to ensure efficacious drug levels, the MAH proposed to reflect in the section 4.5 of the SPC a dose adjustment for caspofungin from 50 mg/m^2 daily to 70 mg/m^2 daily in paediatric patients from 12 months to 17 years of age during concomitant use of metabolic inducers, like dexamethasone.
For neonates and children less than 3 months of age, since the lower bound of the 90% confidence interval for C_{24hr} GMR in neonates/infants is below 0.7, no dose adjustment for caspofungin in this age group can be given from the limited data available.

Concentrations in CSF (cerebrospinal fluid)

In summary, at least 1 CSF sample was collected from 7 patients. Very low caspofungin concentrations in the CSF (~0.1% of peak plasma concentration) were observed for 2 of the 7 paediatric patients, with concentrations from the remaining patients falling below the limit of quantification (10 or 25 ng/ml). However CSF concentrations were predominantly collected from patients who did not have fungal involvement of the meninges. Studies with other antimicrobial agents (e.g., penicillin) have demonstrated that CSF concentrations may correlate with the extent of inflammation in the meninges. Such a finding was also confirmed with caspofungin in preclinical rodent studies.

- ***Conclusion***

The first study (in children 2-11 years) indicated that weight-based dosing might not be the most appropriate in children, since it resulted in suboptimal concentrations and high variability with weight. Therefore, a body surface area-based dosing regimen was tested, and was confirmed to be at better regimen.

The data from the three pharmacokinetic studies suggest that a dosing regimen of 50 mg/m^2/day (with a maximum of 70 mg/day) in paediatric patients between 12 months to 17 years of age results in plasma exposures relatively similar to those obtained in adults receiving caspofungin at 50 mg/day. Neonates and infants (<3 months of age) receiving single or multiple, once-daily doses of caspofungin at 25 mg/m^2 achieved on average fairly similar plasma exposures to that of adults receiving caspofungin at 50 mg/day. However, the variability was very large in this group and a clear dosage recommendation cannot be made based on the available pharmacokinetic data. Moreover, there is no pharmacokinetic data for children between 3 and 12 months of age, and it is unknown whether this age group should have a dose more close to the 50 mg/m^2 dose for older children or to the 25 mg/m^2 dose

for smaller babies. Furthermore, efficacy and safety data are limited in the smallest children. Thus, data are not considered sufficient to fully support the indication in children <12 months of age without caution. Therefore it has been agreed that the lack of data for this specific population should be highlighted in section 4.2 of the SPC together with consideration of dose when treating children <12 months of age. It has also been agreed to mention the available pharmacokinetic data, including the large variability observed in neonates, and the lack of data for 3-11 months old children in section 5.2 of the SPC.

The data on exposure might suggest that caspofungin clearance is lowest at birth, increases from infancy to childhood and then decreases from childhood to adolescence and subsequently to adulthood. The MAH presented data on dose escalation to be considered when the clearance is higher. Although dose regimen adaptation can be needed in a real minority of patients across all age groups, this change only concerns a restricted minority in percentage (about 5-10% whatever the age is). In practice, there is therefore no need for a potential recommendation for any particular age subset in the SPC.

The mechanism(s) for possible changes in plasma clearance with age are unknown. In *vitro* data suggest that caspofungin tissue distribution may be mediated by uptake transporters, and the data are suggestive that the OATP1B1 transporter may be involved in hepatic uptake of caspofungin. Thus, one potential explanation is that the expression levels of uptake transporter or transporters for which caspofungin is a substrate could be altered throughout the course of developmental maturity. Another possibility is that the difference in caspofungin clearance with age could be due to differences in physiological factors, such as relative blood flow rates and organ sizes.

The covariate and PK/PD analysis is not considered optimal as it is a simple statistical regression analysis. By instead using non-linear mixed effects modelling, more information could possibly have been extracted from available data, which might have provided further support of the proposed dosing in age groups where pharmacokinetic data are sparse. The regression analysis of paediatric data led to the same results as previously seen for adults, i.e. that there was no apparent relationship between plasma exposure and efficacy, possibly because the plasma concentrations obtained at normal clinical doses are at the top of the concentration-effect curve. Finally, the population pharmacokinetic analysis indicated that when caspofungin is administered to paediatric patients concomitantly with inducers of drug clearance a dose escalation should be considered and stated in section 4.5 of the SPC, as is previously recommended also for adults.

3.3 Clinical efficacy

- ***Introduction***

Because the pathophysiology and the fungal pathogens causing the infectious diseases for which caspofungin is currently licensed are generally similar for paediatric and adult patients, these infections in pediatric patients, as in adult patients, would be expected to respond to caspofungin. For this reason, efficacy in adults in these indications was expected to be reliably extrapolated to children. Thus, the principal objective of the caspofungin paediatric development program was to assess the overall safety of caspofungin in children and adolescents across all indications in order to establish a generally safe and efficacious paediatric dose for all currently licensed indications.

- ***Main studies***

- Safety/Efficacy Study (**Protocol 043**): A Multicenter, Open-Label, Noncomparative Study to Evaluate the Safety and Efficacy of Caspofungin in Pediatric Patients (3 Months to 17 Years of Age) With Documented *Candida* and *Aspergillus* Infections

    - ***Methods***

<u>*Study Design*</u>
Protocol 043 was a prospective, open-label, non-comparative study. Efforts were made to design the study as closely as possible to the corresponding studies in adults (phase III study Protocol 014 (caspofungin versus AmB in treatment of invasive candidiasis), phase IIb study Protocol 019 (the Aspergillus salvage study), and phase III study Protocol 020 (caspofungin versus fluconazole in the treatment of Candida oesophagitis)). The study was conducted between May 2004 and July 2007. Diagnosis of infection was based on clinical history, signs and symptoms of illness, radiographic evidence, and positive histopathology and/or culture for fungal organisms. Patients with proven oesophageal candidiasis or proven invasive candidiasis were enrolled into the study as primary or salvage therapy. Patients with proven or probable invasive aspergillosis according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/ MSG) criteria were only enrolled if they had failed or were intolerant of standard antifungal therapy. All patients received caspofungin monotherapy 50 mg/m2 daily after a 70-mg/m2 loading dose on Day 1. The maximum daily dose was 70 mg/day. Intravenous caspofungin was infused over a 1-hour period. The duration of antifungal therapy varied based on the infection and was in accordance with the Infectious Disease Society of America (IDSA) Treatment Guidelines.

Table 14

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Diagnosis Incl. criteria	Primary Endpoint
043	12	Open-label, Non-comparative	50 mg/m2 daily after a 70-mg/m2 loading dose on Day 1. The maximum daily dose was 70 mg/day. In patients who failed to improve clinically after 4 days if study drug had been well tolerated, the caspofungin dosage could be increased to 70-mg/m2 day (not to exceed the maximum daily dose of 70 mg) on Day 5 onward.	To estimate the safety, tolerability, and efficacy of caspofungin therapy in paediatric patients (3 months through 17 years of age) with invasive aspergillosis (salvage therapy), Invasive candidiasis, or esophageal candidiasis.	50 children or adolescents (ages 3 months to 17 years) with documented aspergillosis, esophageal candidiasis, or invasive candidiasis at the time of enrolment.	Individualized for each infection. Efficacy was assessed at the end of caspofungin therapy Relapse was also assessed through 28 days post-therapy for patients with a favourable treatment outcome at the end of caspofungin therapy.

Outcomes/endpoints

Each investigator independently evaluated the diagnosis of invasive aspergillosis, invasive candidiasis, and esophageal candidiasis based on the criteria provided in the protocol and assessed the efficacy based on definitions of response outlined in the protocol. Efficacy assessments based on clinical, microbiological, and/or radiographic (endoscopic) criteria, were made at the end of caspofungin study therapy and, if applicable, at the 14- and 28-day post-therapy follow-up visits. The primary endpoint for efficacy was the proportion of patients with a favourable treatment outcome at the end of caspofungin therapy. A favourable clinical response could either be a "complete response" or a "partial response", as defined for each of the fungal infections. The efficacy time points and endpoints used in Protocol 043 reflected those used in the corresponding adult studies for the same indications.

During the assessment of this type II variation II/33, the MAH provided an analysis of their investigational data allowing addressing the question raised in terms of "complete response" and "partial response". The analysis was presented according to type of fungal disease. The data displaying the treatment outcome as either a "complete response" or a "partial response"for the paediatric patients with invasive aspergillosis or invasive candidiasis were merged from different paediatric protocols. The results indicate, similar outcomes when compared with the corresponding outcome data from the adult studies. Indeed, based on the investigator's assessment, "the proportion of subjects with invasive aspergillosis who had a "complete response" and a "partial response", respectively, were generally similar between pediatric patients (30.0% and 20.0%) and the adult patients (17.7% and 30.2%). Although a "partial response" designation was considered favorable for the paediatric patients enrolled with invasive candidiasis in Protocol 043, all patients with a favorable overall response actually had a "complete response". Therefore, the proportion of patients with invasive candidiasis with a a"complete response" is generally similar between pediatric patients (81.1%) and adult patients (73.4%)."

Because of the difficulties inherent in microbiological diagnosis of *Aspergillus* infection, primary outcome of treatment focused on clinical response. A "complete response" required resolution of symptoms attributed to invasive aspergillosis and resolution of all radiographic and other relevant investigative (e.g., bronchoscopy) abnormalities due to *Aspergillus* infection.

Efficacy in invasive candidiasis was based on both the clinical and microbiological assessments. A favourable "overall response" mandated both a favourable clinical response and a favourable microbiological response.

Sample size and Statistical methods

This study was initially focused on children and adolescents 2 to 17 years of age. However, the protocol was subsequently amended to include infants as young as 3 months of age once the preliminary data from the corresponding pharmacokinetic study in this age group (Protocol 042) became available. Enrolment accrual was set for approximately 50 patients.

The MITT patient population was defined as the primary patient population and included those patients who received at least 1 full dose of caspofungin study therapy and had a documented diagnosis of invasive aspergillosis, invasive candidiasis, or oesophageal candidiasis.

Protocol 043 was designed as an estimation study. The main efficacy evaluation was the proportion of caspofungin-treated patients with a favourable treatment outcome at the end of caspofungin therapy. The proportion and its respective 95% Clopper-Pearson exact Confidence Interval (CI) were calculated for each specific infection. Confidence intervals were displayed only if the denominator of the proportion was ≥5 patients.

- ***Results***

Patients and treatment

Table 15

	Invasive Aspergillosis (N=10)		Invasive Candidiasis (N=38)		Esophageal Candidiasis (N=1)		Total (N=49)	
	n	(%)	n	(%)	n	(%)	n	(%)
PATIENTS ENTERED:								
Male (age range)	8	(4 yr. to 16 yr.)	22	(6 mo. to 16 yr.)	1	(17 yr. to 17 yr.)	31	(6 mo. to 17 yr.)
Female (age range)	2	(3 yr. to 11 yr.)	16	(13 mo. to 17 yr.)	0		18	(13 mo. to 17 yr.)
COMPLETED THERAPY†:	**5**	**(50.0)**	**23**	**(60.5)**	**1**	**(100)**	**29**	**(59.2)**
DISCONTINUED THERAPY:	**5**	**(50.0)**	**15**	**(39.5)**	**0**	**(0.0)**	**20**	**(40.8)**
clinical AE	2	(20.0)	0	(0.0)	0	(0.0)	2	(4.1)
lack efficacy	3	(30.0)	6	(15.8)	0	(0.0)	9	(18.4)
pat. discont. for other §	0	(0.0)	9	(23.7)	0	(0.0)	9	(18.4)
COMPLETED STUDY‡:	**6**	**(60.0)**	**36**	**(94.7)**	**1**	**(100)**	**43**	**(87.8)**
DISCONTINUED STUDY:	**4**	**(40.0)**	**2**	**(5.3)**	**0**	**(0.0)**	**6**	**(12.2)**
clinical AE	4	(40.0)	0	(0.0)	0	(0.0)	4	(8.2)
pat. discont. for other	0	(0.0)	1	(2.6)	0	(0.0)	1	(2.0)
pat. moved	0	(0.0)	1	(2.6)	0	(0.0)	1	(2.0)

†"Completed Therapy" is defined as having a status of "pat. contin. trial" on the last day of caspofungin study therapy.
‡"Completed Study" is defined as completion of the 14 Day posttherapy Follow-up visit period.
§ 6 patients discontinued caspofungin study therapy due to being discharged from the hospital, 1 due to loss of IV access, 1 was changed to oral antifungal therapy as a result of hospital discharge, and 1 was a protocol deviation due to a blood culture with *Trichosporon beigellii* instead of *Candida* spp.

Forty-nine (49) patients entered and received study therapy, 10 with invasive aspergillosis, 1 with esophageal candidiasis and 38 with invasive candidiasis. Of these 49 patients, 48 were included in the primary efficacy (Modified Intention-To-Treat) MITT analysis. Thirty-one (31) of the enrolled patients were males and 18 were female. Age ranged from 6 months to 17 years. Duration of treatment ranged from 2 to 87 days, mean duration 11.8 days. Five (5) of the 49 patients had their caspofungin dose escalated to 70 mg/m^2 daily (maximum not to exceed 70 mg/day) during the treatment period as allowed by protocol; one patient with invasive aspergillosis and 4 patients with invasive candidiasis.

Of the patients with invasive aspergillosis (n=10), the mean age was 8.3 years (range 3 to 16), with 80% of the patients <12 years of age. Most had pulmonary aspergillosis (60%). Extrapulmonary disease was reported in 40% of the patients and included multiple sites (1 patient with probable pulmonary and definite skin; 1 patient with probable pulmonary, CNS (Central Nervous System), and skin), middle ear, and CNS aspergillosis. All patients were refractory to prior antifungal therapy as defined in the protocol. Hematologic malignancy (60%) was the most common risk factor. Three (3) (30%) of the patients with invasive aspergillosis were neutropenic at study entry.

In patients enrolled with invasive candidiasis the mean age was 7.9 years (range 6 months to 17 years, with 65.7% of the patients in the <12 years of age group, and 60.% were Caucasian. Candidemia accounted for the majority of the invasive candidiasis cases (92.1%). Most patients received caspofungin study therapy as primary treatment (81.6%). The majority of the patients (84.2%) were not neutropenic at study entry. The presence of an intravascular catheter (78.9%) was the most

common risk factor in patients with invasive candidiasis, followed by use of broad spectrum antibiotics (73.7%), total parenteral nutrition (63.2%), and immunosuppression (55.3%). Common primary background condition of the patients with invasive candidiasis were underlying malignancies (34.2%) and congenital disorders (21.1%). Five (13.2%) of the 38 patients with invasive candidiasis were solid organ transplant recipients. An additional 5 patients (13.2%) has gastrointestinal disorders.

The one patient with esophageal candidiasis caused by *C. albicans* was a 17 year-old Caucasian male with recurrent AML (Acute Myeloid Leukemia) and a history of allogeneic BMT (bone marrow transplant).

All 49 patients had 1 or more secondary diagnoses within 1 year prior to study entry. Across the 3 types of fungal infections, the most frequently reported secondary diagnoses included anemia (49%), central venous catherisation (36.7%), and pyrexia (32.7%). Of note, 90% of the invasive aspergillosis patients had blood and lymphatic system disorders, infection and infestations, and surgical and medical procedures. Of the invasive candidiasis patients, 97.4% had surgical and medical procedures and 94.7% had gastrointestinal disorders.

There were very few patients below the age of 19 months.

Table 16 Number of Patients Entered by Age Category and Gender

	Invasive Aspergillosis			Invasive Candidiasis			Total		
Age	male (N = 8)	female (N = 2)	total (N = 10)	male (N = 22)	female (N = 16)	total (N = 38)	male (N = 31)	female (N = 18)	total (N = 49)
3 to 6 months	0	0	0	1	0	1	1	0	1
7 to 12 months	0	0	0	0	0	0	0	0	0
13 to 18 months	0	0	0	0	1	1	0	1	1
19 to 23 months	0	0	0	1	0	1	1	0	1
2 to 6 years	2	1	3	9	7	16	11	8	19
7 to 11 years	4	1	5	4	2	6	8	3	11
12 to 14 years	1	0	1	5	2	7	6	2	8
15 to 17 years	1	0	1	2	4	6	4	4	8
Mean (years)	8.6	7.0	8.3	7.4	8.6	7.9	8.0	8.4	8.2
SD (years)	3.8	5.7	3.9	5.1	5.7	5.3	5.0	5.5	5.1
Median (years)	7.5	7.0	7.5	6.0	6.5	6.5	7.0	6.5	7.0
Range (years)	4.0 to 16.0	3.0 to 11.0	3.0 to 16.0	0.5 to 16.0	1.1 to 17.0	0.5 to 17.0	0.5 to 17.0	1.1 to 17.0	0.5 to 17.0

Clinical efficacy

Five (5) of the patients enrolled with invasive aspergillosis had a favourable clinical response at the end of caspofungin study therapy as well as at both the 14- and 28-day posttherapy follow-up visits. A favourable microbiological response was seen in 2 of the 4 patients with baseline isolates [*A. fumigatus* (CNS), and *A. terreus* (middle ear) infection].

Thirty (30) (81.1%) of the 37 patients with invasive candidiasis had a favourable overall response at the end of caspofungin therapy. Thirty-four (91.9%) of the 37 patients with confirmed invasive candidiasis had candidaemia and 28 (82.4%) had a favourable overall response. Of the other 3 patients, (1 with psoas muscle abscess and 2 with multiple sites of *Candida* infection [*Candida* peritonitis and candidaemia; nasal cavity with histopathologic confirmation and hepatosplenic candidiasis]), 2 responded favourably to caspofungin therapy.

The efficacy results in paediatric patients were comparable to those in adults.

Three (3) of the 5 patients who had dose escalation (all with invasive candidiasis) had a favourable response at the end of caspofungin therapy.

- ***Conclusion on study protocol 043***

The main aim of this open non-comparative study was to assess the overall safety of caspofungin in paediatric patients (3 months to 17 years of age), although clinical efficacy was naturally also of high interest. The diagnostic criteria for documented infections were strictly adhered to the established EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study Group) criteria or proven or probable infection. Since the studied population was small, no statistically verified results were anticipated, or were obtained. However, since the design of the study was very close to those of the corresponding studies in adult patients, which were the basis for approval of the adult indications, some conclusions could nevertheless be drawn from study Protocol 043. The results indicate that caspofungin, in the currently used dosage regimens, has a clinical efficacy in paediatric patients with invasive aspergillosis and invasive candidiasis, similar to that in adult patients, as would be predicted by PK/PD analysis. Favourable responses were seen in patients with haematologic malignancies, including those who underwent allogeneic BMT (Bone Marrow Transplantation) or PSCT (Peripheral blood Stem Cell Transplantation), as well as patients with solid tumours and chronic granulomatous disease. Outcome seemed not to be influenced by the patient age. All 3 patients less than 2 years of age responded favorably to caspofungin. The exact age of these 3 children was not specified. It seems like there were only 2 patients below 19 months, of which 1 was 6 months. Microbiological response was generally similar across all Candida pathogens. Only one patient (4%) had a relapse in the Candida infection by the 28-day post-therapy follow-up visit. Thus, in addition to PK/PD data and data from adult patients, the outcome of the present study supports these indications in the paediatric population. However, oesophageal candidiasis is not an approved indication for adult patients in EU, neither is this indication supported by the single paediatric subject.

- Safety/Efficacy Study (**Protocol 044**): A Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Liposomal Amphotericin B for Injection as Empirical Therapy in Pediatric Patients (2 to 17 Years of Age) With Persistent Fever and Neutropenia

  - ***Methods***

<u>*Study design*</u>
Protocol 044 was a prospective, randomized, double-blind study. The comparator was liposomal amphotericin B (AmBisome) which is approved for the empirical treatment of presumed fungal infections in patients with persistent fever and neutropenia, and commonly used for this indication.

The study design for this study closely mirrored the design utilized in the adult empirical therapy study Protocol 026 (A Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of MK-0991 Versus Amphotericin B Liposome for Injection as Empirical Therapy in Patients With Persistent Fever and Neutropenia.) in an effort to maximize the ability to extrapolate the data from adults to paediatric patients. Relative to Protocol 026, similar entry criteria, endpoints, time points, and the same comparator (liposomal amphotericin B) were used in Protocol 044. Safety was the primary objective, but efficacy data were also collected.

Table 17

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Diagnosis Incl. criteria	Primary Endpoint
044	17	Double-blind, Double dummy, in-house blind, randomi ed, comparative study. 2:1 rando mization	50 mg/m2 daily after a 70-mg/m2 loading dose on Day 1. The maximum daily dose was 70 mg/day. Patients on AmBisome™ received 3 mg/kg/day	To estimate the safety, tolerability, and efficacy of caspofungin versus AmBisome™ in paediatric patients, aged 2 to 17 years, with persistent fever and neutropenia.	2 to 17 years of age. Persistent fever and neutropenia. All patients must also have received chemotherapy for leukemia, lymphoma, or other cancers, or had undergone bone marrow or peripheral stem-cell transplanttation.	Overall response was based upon a 5-part composite endpoint.

Treatment

If, in the opinion of the investigator, a patient required an escalation in study therapy, the dose could be increased to either caspofungin 70 mg/m2day or AmBisome 5 mg/kg/day, for patients who tolerated study drug, if (1) fevers persisted for at least 5 days of study therapy and (2) there was clinical deterioration if appropriate radiographic studies, cultures, biopsies, and/or histopathology studies did not provide an alternative explanation for the clinical deterioration.

Study drug therapy was continued until the patient's ANC (Absolute Neutrophil Count) was at least 500 cells/µl and for up to 72 hours later. For patients without evidence of documented invasive fungal infection, the maximum recommended duration was 28 days. For patients with documented invasive fungal infections, the duration of study therapy was determined by the investigator but was recommended to continue for at least 14 days, and at least 7 days after resolution of neutropenia and of symptoms.

Outcomes/endpoints

The primary endpoint was favourable overall response. Overall response was based upon a 5-part composite endpoint. A successful outcome, or favourable overall response, was defined as meeting all of the following endpoints: (1) successful treatment of a baseline invasive fungal infection, if any; (2) absence of a breakthrough invasive fungal infection up to 7 days post-therapy; (3) survival to 7 days post-therapy; (4) absence of therapy discontinuation due to lack of efficacy or study drug toxicity; and (5) resolution of fever for 48 hours during the period of neutropenia. A failure in any one component resulted in an unfavourable response. All breakthrough infections were considered as failures.

Sample size and Statistical methods

The sample size was chosen based on logistical considerations, as enrolment in paediatric studies (particularly, those involving paediatric patients with cancer) is extremely challenging. A 2:1 randomization of caspofungin to AmBisome™ was employed to maximize the safety and efficacy experience with caspofungin in this study. Enrolment accrual was set for at least 75 patients (with at least 50 on caspofungin assuming a 2:1 randomization). As in the adult study (Protocol 026) patients were stratified as either high-risk or low-risk, with high-risk designated for patients who had undergone allogeneic bone marrow or peripheral stem-cell transplantation and/or had received chemotherapy for a relapse of acute leukemia.

The MITT patient population was defined as the primary patient population and included those patients who: (1) either received chemotherapy for leukemia, lymphoma, or other cancers or had undergone a hematopoietic stem-cell transplantation during the prestudy period, (2) received at least 1 dose of active study therapy and, (3) met the protocol-defined criteria for persistent fever and neutropenia.

For both treatments groups, the estimated proportion of patients with a favourable overall response was calculated using Cochran-Mantel-Haenszel weights to adjust for strata (low-risk, high-risk). Confidence intervals were displayed only if the denominator of the proportion was ≥5 patients.

- ***Results***

Patients and treatment

Table 18

	Caspofungin 70/50 mg/m^2 (N = 56)		AmBisome™ 3.0 mg/kg (N = 26)		Total (N = 82)	
	n	(%)	n	(%)	n	(%)
SCREENING FAILURES:	----	----	----	----	**1**	----
PATIENTS ENTERED:						
Male (age range)	35 (2 to 16)	(62.5)	20 (2 to 16)	(76.9)	55 (2 to 16)	(67.1)
Female (age range)	21 (2 to 16)	(37.5)	6 (2 to 13)	(23.1)	27 (2 to 16)	(32.9)
COMPLETED THERAPY†:	**46**	**(82.1)**	**19**	**(73.1)**	**65**	**(79.3)**
DISCONTINUED THERAPY:	**10**	**(17.9)**	**7**	**(26.9)**	**17**	**(20.7)**
Clinical AE	3	(5.4)	5	(19.2)	8	(9.8)
Lack of efficacy	3	(5.4)	1	(3.8)	4	(4.9)
Patient discontinued. for other‡	3	(5.4)	1	(3.8)	4	(4.9)
Patient withdrew consent	1	(1.8)	0	(0.0)	1	(1.2)
COMPLETED STUDY§:	**56**	**(100)**	**25**	**(96.2)**	**81**	**(98.8)**
DISCONTINUED STUDY:	**0**	**(0.0)**	**1**	**(3.8)**	**1**	**(1.2)**
Clinical AE	0	(0.0)	1	(3.8)	1	(1.2)

† "Completed Therapy" is defined as having a status of "patient continuing trial" on the last day of study therapy.
‡ "Other" reasons for discontinuation of study therapy were as follows: caspofungin group – patient discharged **from hospital (AN 4170 and AN 4225) and** 'to exclude drug-**induced fever**' (AN 4007); AmBisome™ group- 'primary MD stopped antifungal therapy'
§ "Completed Study" is defined as completion of the 14 Day follow-up visit period.

Eighty-two (82) patients were enrolled and received study therapy, 56 on caspofungin and 26 on AmBisome. The 2 treatment groups were generally comparable with respect to age, race, and ethnicity. The mean age for both of the treatment groups was 7.4 years.
In both treatment groups, the most common primary diagnoses (greater than 60% of patients in both treatment groups) were AML (acute myelogenous leukemia) and ALL (acute lymphocytic leukemia). The caspofungin and AmBisome treatment groups had similar proportions of patients with allogeneic hematopoietic stem cell transplantation (10.7% and 11.5%, respectively). The treatment groups were generally comparable with respect to risk category, receipt of prior antifungal prophylaxis, extent of neutropenia at study entry, and duration of neutropenia prior to study entry.
Similar proportions of patients received prior antifungal therapy with amphotericin B, fluconazole, or itraconazole. The distribution of patients who received prior growth-factor therapies was also similar across the treatment groups.

Treatment duration ranged from 2 to 87 days, mean duration was 11.8 days.

Three (3) patients were dose escalated in the caspofungin (1) and AmBisome (2) treatment groups.

Clinical efficacy
The efficacy results in paediatric patients were comparable between the treatment groups and to results obtained in the adult studies. Eighty-one (81) of the 82 patients who received study therapy were included in the primary efficacy population (MITT). The proportion of patients with a favourable overall response rate was numerically higher in the caspofungin treated group than in the AmBisome treated group. However, these results must be viewed cautiously as the number of patients is small.

One (1) patient was dose escalated to caspofungin 70 mg/m2 daily on Day 15 and had a favorable overall response to caspofungin. Two (2) patients were dose escalated to AmBisome 5 mg/kg daily (on Day 6 and 55), both had an unfavourable overall response.

None of the patients included in this study had a microbiologically-confirmed infection, and, therefore, there is no available microbiology data from this study.

- ***Conclusion on study Protocol 044***

The design of this paediatric study was very similar to a previous multicenter, double-blind, randomized study (Protocol 026) submitted to support the extension of indication to empirical treatment (type II variation II/20). In that study, caspofungin was compared to AmBisome for the empirical treatment of suspected invasive fungal infections in adult patients with persistent fever and neutropenia. Besides the suitability to use the same comparator as in the corresponding adult studies, AmBisome was considered as a clinically relevant comparator since it is commonly used in this indication in clinical practice. Children between 2-17 years of age were included. Younger children were not included because empirical therapy for persistent fever and neutropenia is not routinely administered to children below the age of 2. Similarities in design included the key inclusion and exclusion criteria, the clinical and laboratory measurement for safety, the efficacy assessment based upon a 5-part composite endpoint, and the use of an independent committee to review all cases of suspected fungal infection. Despite the relatively low number of included patients, generating wide confidence intervals, the stringency and similarity in designs helped to provide strong indications that efficacy of caspofungin as empirical therapy in paediatric patients with persistent fever and neutropenia, was similar to that seen with AmBisome, as well as generally similar to that observed in the previous adult study. No significant effect of age or gender was noticed. As in adult studies, unsuccessful treatment was generally attributed to persistent fever during neutropenia. None of the caspofungin treated subjects and one in the AmBisome group experienced breakthrough infection. Thus, the results of the present study, supported by PK/PD data, indicate that caspofungin is as effective for paediatric patients (2-17 years) in this indication as for adult patients.

It should be noted that a correlation between plasma concentrations and treatment outcome could not be demonstrated, suggesting that the range of concentrations obtained from paediatric patients were sufficient for efficacy, which is consistent with the results obtained in previous population pharmacokinetics and pharmacodynamics studies in adult patients with different disease indications.

- ***Discussion on clinical efficacy***

The 2 paediatric safety/efficacy studies, Protocols 043 and 044, enrolled a total of 131 patients, including 105 patients on caspofungin, from over 25 study sites worldwide. Effort was put to harmonise the designs of the studies with the corresponding adult studies. The results from the open uncontrolled paediatric efficacy study (study Protocol 043), indicated that caspofungin, administered intravenously at 50 mg/m^2 daily (following a 70-mg/m^2 loading dose on Day 1), was effective in the treatment of documented Candida or Aspergillus infections in children and adolescents ages 6 months through 17 years. Additionally, the results from the comparative study Protocol 044 also supported an efficacy of caspofungin comparable to AmBisome in the empirical treatment of suspected fungal infections in paediatric patients with persistent fever and neutropenia, using the same dose regimen.

There was no indication that the efficacy was related to dose, gender or underlying disease. However the information regarding age and efficacy were scarce.
During the assessment, the MAH submitted safety and efficacy data from paediatric clinical studies by the requested narrower age-groups [3-6 months, 7-12 months, 13-24 months, 2-5 years, 6-11 years, and 12-17 years]. Overall, even though the total number of patients in many of the age groups was small, there did not appear to be significant differences in specific drug-related clinical or laboratory adverse experiences in any particular age group as compared to the other age groups.

No signals of dose-related serious adverse events have been detected. Similarly, with regard to efficacy, there were no indications of age-related differences in any of the studied indications. However, numbers in each age category are small, which precludes any firm conclusions. See tables 19 and 20 below.

Table 19 . Proportion of Caspofungin-treated Patients with a Favorable Overall Response in the Paediatric Documented Infection Study (Protocol 043) - By Infection Type and Age Category. MITT-Population

	Invasive Aspergillosis		Invasive Candidiasis		Esophageal Candidiasis	
Age Category	**n/m**	**(%)**	**n/m**	**(%)**	**n/m**	**(%)**
3 to 6 months	--	--	1/1	(100)	--	--
7 to 12 months	--	--	--	--	--	--
13 to 24 months	--	--	2/2	(100)	--	--
2 to 6 years	2/3	(66.7)	12/15	(80.0)	--	--
7 to 11 years	2/5	(40.0)	6/6	(100)	--	--
12 to 17 years	1/2	(50.0)	9/13	(69.2)	1/1	(100)
Total	**5/10**	**(50.0)**	**30/37**	**(81.1)**	**1/1**	**(100)**
n/m = Number of patients with a favorable response/number of patients in the subgroup.						

Table 20 . Proportion of Patients with a Favorable Overall Response in the Paediatric Empirical Therapy Study (Protocol 044) - By Treatment Group and Age Category. MITT-Population

	Caspofungin 70/50[7] mg/m^2		AmBisome™ 3.0 mg/kg	
Age Category	**n/m**	**(%)**	**n/m**	**(%)**
2 to 6 years	10/29	(34.5)	7/14	(50.0)
7 to 11 years	6/15	(40.0)	0/4	(0.0)
12 to 17 years	10/12	(83.3)	1/7	(14.3)
Total	**26/56**	**(46.6)**	**8/25**	**(32.0)**
[7] 70/50 mg/m^2 = patients received a 70 mg/m^2 loading dose on day 1 followed by 50 mg/m^2 on subsequent treatment days n/m = Number of patients with a favorable response/number of patients in the subgroup.				

In addition, the MAH provided supportive data from 3 publications (Natarajan et al 2005 [*Natarajan G, Lulic-Botica M, Rongkavilit C, Pappas A, Bedard M. Experience with caspofungin in the treatment of persistent fungemia in neonates. J Perinatol 2005;25(12):770-7.*]; Odio et al, 2004 [*Odio CM, Araya R, Pinto LE, Castro CE, Vasquez S, Alfaro B, et al. Caspofungin therapy of neonates with invasive candidiasis. Pediatr Infect Dis J 2004;23(12):1093-7.*]; and Odio et al 2005 [*Odio CM, Pinto LE, Alfaro B, Vasquez S, Castro CE, Hernandez M, et al. Pharmacokinetics (PK) of caspofungin (CAS) in six premature neonates (PNN) with invasive candidiasis (IC) at a neonatel intensive care unit (NNICU). Presented at the 45th annual ICAAC Meeting, December 16-19, 2005. Washington, (DC), 2005:LB-16.)*]. In these publications, retrospective data on a total of 59 neonates or infants with invasive candidiasis, treated with caspofungin as second line or as add-on treatment to conventional antifungal agents were provided. The doses were mostly 25 mg/m2 or slightly lower. Success rates were 85%, 100% and 97%, respectively. Caspofungin was generally well tolerated and no serious adverse events were directly correlated to caspofungin treatment. Thus, these published data support the efficacy and safety of the dose 25 mg/m^2 in children less that 3 months.

The critical age group here is considered to be children 3-11 months, where there are only safety data for two subjects; PK data from one child (10 months; study 042), and efficacy data on one child (6 months old patients from study Protocol 043). Thus, the MAH suggestion that children between 3-12 months should be dosed 50 mg/m2 in contrast to children less than 3 months (25 mg/m2) is not based on firm data. The choice of dosage in this age group, that was not well studied, must currently be based on a theoretical benefit-risk assessment, i.e. the risk for under dosing in severe infections in seriously ill patients, contra the risk for dose-related adverse events. In the age group 3-9 months, there is only very limited PK data from one 6 months old subject, which indicated somewhat higher exposure than in older children.

Thus, efficacy results from the 2 paediatric multicenter, clinical trials supported by PK/PD data and in conjunction with efficacy results from corresponding adult clinical trials support a positive opinion for

those infectious disease indications currently licensed for caspofungin use in adults in EU. However until further data are available in neonates and infants below 12 months of age , no definite dosage recommendations can be given, which is highlighted in section 4.2 of the SPC.

3.3.4 Clinical safety

- ***Patient exposure***

Safety data were available from 171 paediatric patients who received at least 1 dose of caspofungin in these 5 trials. Of these, 66 patients received caspofungin in the 3 pharmacokinetic studies (Protocols 033, 042, and 058) and 105 patients received caspofungin in the safety/efficacy studies (Protocol 043 and 044). An additional 26 patients enrolled in the paediatric empirical therapy study (Protocol 044) were treated with AmBisome™ at 3.0 mg/kg daily.

The majority (132/171, 77.2%) received caspofungin at a once-daily maintenance dose of 50 mg/m^2 (including all 105 patients in the 2 safety/efficacy studies, 18 patients in Protocol 033, and 9 patients in Protocol 042). The remaining 39 patients received caspofungin at a daily dose of either 1 mg/kg (9 patients in Protocol 033), 25 mg/m^2 (18 patients in Protocol 058), or 70 mg/m^2 (12 patients in Protocol 033).

The duration of study therapy ranged from 1 to 87 days for the patients in the caspofungin group and 1 to 55 days for the patients in the AmBisome group. The mean duration of study therapy was 12.1 and 11.4 days for the caspofungin and the AmBisome treatment groups, respectively. In the safety/efficacy studies (Protocol 043 and 044), the investigators had the option to increase the dose of study therapy for lack of efficacy. A total of 6 (5.7%) caspofungin-treated patients in Protocols 043 or 044 had the caspofungin dose increased from 50 mg/m^2 daily to 70 mg/m^2 daily due to lack of efficacy. Two (2) (7.7%) patients in Protocol 044 had the AmBisome dose increased from 3 mg/kg to 5 mg/kg due to lack of efficacy.

The distribution of age and gender for the 5 clinical studies is summarised in the Table 21 below.

Table 21 Distribution of age and gender in the paediatric studies.

Study Population	**Treatment Groups/Doses**	**Number of Patients Gender (B/G) Age Range**
Study 033 PK (Plasma concentration profile in children and adolescents 2 to 17 Years of Age)	Dose I: Caspofungin: 1.0 mg/kg/day Dose II: Caspofungin: 50 mg/m2/day Dose III: Caspofungin: 70 mg/m2/day	N = 39 (20 /19) Aged 2-6 years: 18 Aged 7-11 years: 11 Aged 12-14 years: 7 Aged 15-17 years: 3
Study 042 PK (Plasma concentration profile in young children 3 to 24 Months)	Dose I: Caspofungin: 50 mg/m2/day	N = 9 (6/3) Aged 7-12 months: 4 Aged 13-24 months: 5
Study 058 PK (Plasma concentration profile in neonates and infants 0 to 3 months of age)	Panel A†: Caspofungin 25 mg/m2 Panel B†: Caspofungin 25 mg/m2/day	N = 18 (12/6) Aged ≤2 weeks: 5 Aged 3-4 weeks: 7 Aged 5-8 weeks: 4 Aged 9-12 weeks: 2
Study 043 (Safety/efficacy study in pediatric patients 3 months to 17 years of age with documented Candida or Aspergillus	Caspofungin: 50 mg/m2/day following 70 mg/m2 loading dose on Day 1 (maximum daily dose of 70 mg)	N = 49 (31/18) Aged ≤2 years: 3 Aged 2-6 years: 19 Aged 7-11 years: 11 Aged 12-14 years: 8 Aged 15-17 years: 8
Study 044 (Safety/efficacy study in pediatric patients with persistent fever and neutropenia (PFN)	Treatment Group 1: Caspofungin: 50 mg/m2/day following 70 mg/m2 loading dose on Day 1 (maximum daily dose of 70 mg) + placebo Treatment Group 2: AmBisome™ 3 mg/kg/day + placebo	N = 82 (56 caspofungin; 26 AmBisome™) (55/27) Aged 2-6 years: 43 Aged 7-11 years: 19 Aged 12-14 years: 10 Aged 15-17 years: 10

B = Boys; G = Girls

In all 5 paediatric studies, patients were monitored for adverse experiences throughout study therapy and up to the 14-day post-treatment follow-up visit.

- ***Adverse events***

Of the 171 patients who received caspofungin across the 5 paediatric trials, 157 (92%) patients had at least one clinical adverse experience, which is not unexpected in this patient population. Clinical adverse experience is summarised in the Table 22 below.

Table 22 Clinical Adverse Experience Summary Treatment and Follow-Up Phases

	Total Caspofungin Treated Patients (N = 171)	
	n	(%)
Number (%) of patients:		
With one or more adverse experiences	157	(91.8)
With no adverse experience	14	(8.2)
With drug-related adverse experiences	45	(26.3)
With serious adverse experiences	37	(21.6)
With serious drug-related adverse experiences	1	(0.6)
Who died	11	(6.4)
Discontinued due to adverse experiences	13	(7.6)
Discontinued due to drug-related adverse experiences	2	(1.2)
Discontinued due to serious adverse experiences	5	(2.9)
Discontinued due to serious drug-related adverse experiences	1	(0.6)

Overall, the most common clinical adverse experiences were fever (pyrexia, 29%), diarrhea (14%), rash (11.7%), chills (11%), and hypotension (11%). Consequently these 4 adverse reactions are reported in section 4.8 of the SPC. The incidence of clinical adverse experiences was generally similar for each of the caspofungin dose levels. The incidence of clinical adverse experience in the patients receiving caspofungin in the pharmacokinetic studies (92%) was similar to the incidence reported in the patients receiving caspofungin in the safety/efficacy studies (91%). The overall incidence of clinical adverse experiences was higher in the total caspofungin group (92%) than in the AmBisome group (73%).

Of the 171 caspofungin-treated patients, 45 (26%) patients had a drug-related clinical adverse experience. All of these drug-related clinical adverse experiences occurred in the 50 mg/m^2 and 70 mg/m^2 caspofungin dose groups. The most common drug-related adverse experience was fever, occurring in 20 (12%) patients. Other common drug-related clinical adverse experience included rash (8/171, 5%) and headache (5/171, 3%). The incidence of drug-related clinical adverse experiences in AmBisome-treated patients was numerically higher than the incidence of drug-related clinical adverse experience in the caspofungin-treated patients (46% versus 26%, respectively).

The proportion of paediatric patients who experienced a drug-related clinical adverse experience following caspofungin use was lower than that in adult patients receiving caspofungin.

The spectrum of adverse events and in particular the drug-related clinical adverse events in paediatric patients seem to generally be similar to those recorded for adult patients. The incidence of events by system organ class was numerically inferior to that known from the adult safety study population, which is reassuring provided the relatively low number of subjects in the paediatric study data base.

- ***Serious adverse event/deaths/other significant events***

A total of 37 (22%) of the 171 caspofungin-treated patients had at least one serious clinical adverse experience. Most of these serious adverse experiences are consistent with those expected in hospitalized patients with haematological malignancies, neutropenia, or other predisposing factors for infection. The most common serious clinical adverse experiences were fever (2%), pneumonia (2%), and hypotension (2%). The incidence of serious clinical adverse experiences was generally similar among the caspofungin and AmBisome groups (22% and 23%, respectively).

There were no apparent differences in rates of serious clinical adverse experiences by initial caspofungin maintenance dose level, study type (pharmacokinetic vs. safety/efficacy) or treatment group (caspofungin vs. AmBisome).

Overall, 11 (6.4%) of the 171 paediatric patients treated with caspofungin died during the treatment and follow-up phase. Of these 11 patient deaths, 5 occurred in patients enrolled in the pharmacokinetic studies and the rest in the safety/efficacy studies. One (1) additional caspofungin-treated patient enrolled in Protocol 044 (Paediatric Empirical Therapy Study) died during the post study period. None of the adverse experiences resulting in death were considered by the reporting investigator to be related to caspofungin study therapy. One (1) (3.8%) of the 26 paediatric patients treated with AmBisome had a serious clinical adverse experience resulting in death. This death was also not considered by the reporting investigator as related to AmBisome study therapy.

Of the 171 caspofungin-treated patients, one (1) patient (0.6%) had a serious, clinical adverse experience that was considered by the reporting investigator to be related to caspofungin study therapy. This patient, enrolled in Protocol 044, discontinued prematurely from caspofungin study therapy as a result of the drug-related serious clinical adverse experience of hypotension. In comparison, 3 patients (11%) in the AmBisome group had one or more serious, drug-related clinical adverse experiences.

- ***Laboratory findings***

Of the 171 patients who received caspofungin across the 5 paediatric trials, 78 (46%) patients had one or more laboratory adverse experience in the caspofungin treatment group and (50% in the AmBisome treatment group). Overall, the most common laboratory adverse experiences in the caspofungin treatment group were decreased blood potassium (15%), increased aspartate aminotransferase (AST, 12%), and increased alanine aminotransferase (ALT, 11%). The incidences of laboratory adverse experiences were relatively similar across all caspofungin dose levels and also relatively similar for patients who received caspofungin in the pharmacokinetic studies (42%) and patients who received caspofungin in the safety/efficacy studies (48%).

Of the 171 caspofungin-treated patients, 28 (16%) had one or more drug-related laboratory adverse experiences, all receiving caspofungin at a 50 mg/m^2 dose. Overall, the most common drug-related laboratory adverse experiences in the caspofungin treatment group were increased AST (8%), increased ALT (6%), and decreased blood potassium (3%). The incidence of drug-related laboratory adverse experiences was higher for patients receiving caspofungin in the safety/efficacy studies (22%) than among patients receiving caspofungin in the pharmacokinetic studies (8%). The incidences of drug-related laboratory adverse experiences were similar among the two treatment groups: 16% in caspofungin group and 19% in the AmBisome group. The occurrence of drug-related laboratory adverse experiences in paediatric patients was similar to that observed in adults.

One (0.6%) patient in the caspofungin group was reported to have had a serious laboratory adverse experience. This patient, who was enrolled in Protocol 043, had an increase in C-reactive protein during the post-therapy period. The event was not considered by the investigator as related to caspofungin. None of the patients in the AmBisome group developed a serious laboratory adverse experience.

The incidences of drug-related laboratory adverse experiences in the different caspofungin age groups were as follows: age <3 months 0%, age 3 to 24 months 42%, age 2 to 11 years 15%, and age 12 to 17 years 18%. A similar proportion of older children 2 to 11 years of age had one or more drug-related laboratory adverse experiences in the caspofungin group (15%) and the AmBisome group (22%). A similar proportion of adolescents 12 to 17 years of age had one or more drug-related laboratory adverse experiences in the caspofungin group (18%) and the AmBisome group (12%). The occurrence of drug-related laboratory adverse experiences in paediatric patients was similar to that observed in adults.

In addition to investigator reports of adverse experiences, the assessment of relative laboratory safety was accomplished by predefining CSLAs (Clinically Significant Laboratory Abnormalities) for specified tests, primarily blood chemistries and coagulation tests. CSLAs include all abnormalities outside of the predefined limit, regardless of whether the change was considered an adverse experience by the investigator or if the abnormal value occurred on a single measurement. Overall, the proportion of patients with CSLAs was similar in caspofungin and AmBisome-treated patients. However, the proportion of patients with AST and ALT >2.5 times baseline was higher in the AmBisome group (33% for AST and ALT) than the caspofungin group (16.5% for AST and 17.7% for ALT). Based on review of these data, the occurrence of CSLAs in pediatric patients were generally infrequent. There were no apparent differences in rates of CSLAs by initial caspofungin maintenance dose level, study type (pharmacokinetic vs. safety/efficacy) or treatment group (caspofungin vs. AmBisome).

The incidence of laboratory adverse experiences in paediatric patients receiving caspofungin were relatively low and mostly caused by increases in hepatic enzymes, similar to what is previously reported for adults. In fact, the number of drug-related adverse events according to System Organ Class was numerically lower for the studied paediatric population, compared to previous data for adult patients. This is positive, but no firm conclusion can be drawn due to the limited number of subjects in the studies. Furthermore, caspofungin did not seem to cause more laboratory adverse events or CSLA compared to AmBisome, the current commonly used drug for these indications. The incidences of drug-related laboratory adverse experiences were similar among the two treatment groups: 16% in caspofungin group and 19% in the AmBisome group, with an occurrence in paediatric patients similar to that observed in adults. The laboratory adverse experiences in paediatric patients receiving caspofungin were mostly caused by increases in hepatic enzymes, similar to what is previously reported for adults (see Table 25 below in Caspofungin-Treated Paediatric Patients).

Table 25 Reversibility of the Most Common Drug-Related Laboratory Adverse Experiences in Caspofungin-Treated Paediatric Patients

Drug-Related Laboratory AE Term	Number of Patients with Drug-Related AE	Number of Patients with Resolution While on Therapy	Number of Patients with Resolution During Follow-up	Number Patients without Resolution	Patients without Resolution but with 25% Improvement in Lab Results:	
					During Therapy	During Follow-up
↑ ALT	11	1	5	5[*,$]	1	2
↑ AST	13	2[≠]	8	3[*]	0	2
↓ Potassium	6	1	3	2	0	1

[*] Includes 1 patient with AE onset after end of caspofungin study therapy
[$] Includes 1 patient without data during post-therapy period (patient lost to follow-up)
[≠] Includes 1 patient with AST value within normal range considered to be drug-related adverse experience by investigator; AST levels in this patient decreased during subsequent caspofungin therapy

Overall, data suggest that most laboratory abnormalities that were considered by the investigator to be related to caspofungin therapy were transient and generally returned to within normal limits by the time of the 14-day post therapy follow-up visit. None of the drug-related laboratory adverse events were considered as serious or resulted in discontinuation of caspofungin therapy. Thus, there were no signals on an increased risk for laboratory adverse events in children compared to adults treated with caspofungin, or compared to children treated with AmBisome.

- ***Systemic Infusion-Related Events***

Systemic infusion-related events were recorded daily during intravenous study therapy. Overall, 37 (21.6%) of the 171 caspofungin-treated patients enrolled in the paediatric studies had at least one systemic infusion-related event. The most common systemic infusion-related events among caspofungin-treated patients were fever (10.5%), headache (2.9%), chills (1.8%) and hyperventilation (1.8%). The majority of these infusion-related events were of mild or moderate intensity. Six (6) (9.1%) of the 65 patients who received caspofungin in the pharmacokinetic studies experienced a systemic infusion related event. All of these events were considered mild in intensity by the reporting investigator. The most commonly reported systemic infusion related event in this population was

hyperventilation (4.5%). Thirty-one (31) (29.5%) of the patients receiving caspofungin in the safety/efficacy studies experienced a systemic infusion related event, with most considered mild/moderate intensity. The most frequently reported systemic infusion-related event in the safety/efficacy studies was fever (16.2%). The overall incidence of systemic infusion related events was numerically higher in the AmBisome group (34.6%) than in the caspofungin group (21.6%).

The higher incidence of systemic infusion-related events in the safety/efficacy studies as compared to the PK studies is not entirely unexpected given the overall duration of caspofungin study therapy was longer among patients enrolled in the safety/efficacy studies than among patients enrolled in the pharmacokinetic studies (mean duration 15 days and 8 days, respectively).

- ***Effect of duration of therapy and dose escalation***

The incidence of drug-related clinical adverse experiences was similar for those patients who received <28 days of caspofungin study therapy (26.0%) as compared to the patients who received ≥28 days of caspofungin study therapy (29.4%). Similarly, the incidence of drug-related clinical adverse experiences was similar for those patients who received <28 days of AmBisome study therapy (45.8%) as compared to the patients who received ≥28 days of AmBisome study therapy (50%). The incidence of drug-related laboratory adverse experience was similar for those patients who received <28 days of caspofungin study therapy as compared to the patients who received ≥28 days of caspofungin study therapy (16.2% and 17.6%, respectively). In comparison, 20.8% of the patients who received <28 days of AmBisome study therapy had one or more drug-related laboratory adverse experiences. Neither of the two patients who received ≥28 days AmBisome study therapy had any drug-related laboratory adverse experiences.

Overall, six patients enrolled in these studies were dose-escalated. Four (4) of the 6 patients who had their caspofungin dose increased to 70 mg/m^2/day subsequently experienced at least one drug-related clinical and/or laboratory adverse experience. All of these drug-related adverse experiences subsequently resolved during the caspofungin therapy period and none of the drug-related adverse experiences were considered serious or led to discontinuation of caspofungin therapy.

There are too limited data on subjects who were dose-escalated to 70 mg/m^2/day, to be able to draw any conclusions, regarding the extent of dose-related adverse events.

- ***Safety in special populations***

Among patients treated with caspofungin, there was no apparent difference in rates of clinical adverse experience among the different patient subgroups based on patient gender or race.

The majority of the patients enrolled in both treatment groups were 2 to 11 years of age (60% in the caspofungin group and 70% in the AmBisome group). The incidences of drug-related clinical adverse experiences in the different caspofungin groups were as follows: age <3 months 0%, age 3 to 23 months 8%, age 2 to 11 years 33%, and age 12 to 17 years 26%. For all applicable age categories, the incidences of drug-related clinical adverse experiences were numerically higher in the AmBisome group than in the caspofungin group.

The incidences of drug-related laboratory adverse events were generally similar regardless of gender, age, race, weight and ethnicity, or by initial caspofungin maintenance dose or by study type (pharmacokinetic vs. safety/efficacy). Variations in numbers for specific subgroups did occur, but due to low numbers, no conclusions could be drawn.

- ***Discontinuations Due to Clinical Adverse Experience***

The incidence of caspofungin discontinuation due to a clinical adverse experience was 13/171 in the caspofungin group (8%) and 5/26 in the AmBisome group (19%). There were no apparent differences in rate of therapy discontinuations due to drug-related clinical adverse experiences by initial caspofungin maintenance dose level or study type (pharmacokinetic vs. safety/efficacy). Of the 13

patients discontinued from caspofungin study therapy as a result of a clinical adverse experience, two (1%) were discontinued as a result of a drug-related clinical adverse experience, both enrolled in the empirical therapy study (Protocol 044). As noted above, 1 of these 2 patients had a serious, drug-related clinical adverse experience that resulted in the discontinuation of caspofungin study therapy (hypotension). The other patient was discontinued from caspofungin study therapy due to a non-serious drug-related adverse experience (rash). In comparison, 3 (11%) of the AmBisome-treated patients were prematurely discontinued from study therapy due to a drug-related clinical adverse experience, all considered as serious (1 patient with hyperbilirubinemia, one patient with perioral oedema, and one patient with laryngospasm, Quicke's oedema, tachycardia and dyspnoea).

The most common serious clinical adverse experiences were fever, pneumonia, and hypotension, which is in line with what is expected in this group of seriously ill patients. The incidence of serious clinical adverse experiences was generally similar among the caspofungin and AmBisome groups, 22% and 23%, respectively. There were no apparent differences in rates of serious clinical adverse experiences by initial caspofungin maintenance dose level or study type. Only 1/171 subject had a drug-related serious clinical adverse event (hypotension) in the caspofungin group, compared to 3/26 in the Ambisome group. All these led to discontinuation of the therapy. These results do not indicate any unexpected safety signals for paediatric use of caspofungin.

- ***Post marketing experience and literature***

A review of the Merck Worldwide Adverse Experience System (WAES) was conducted to summarize the post-marketing experience involving caspofungin use in the paediatric population. Between 14-Dec-2000 (date of initial approval of caspofungin) and 31-Aug-2007, a total of 153 adverse experience reports in paediatric patients treated with caspofungin were identified in the WAES database. In 104 (68%) of the 153 reports, adverse experiences were categorized as serious. The most frequently reported serious adverse experiences were: (1) those related to the serious, underlying medical conditions and/or concomitant medications of patients receiving caspofungin; (2) events related to the method utilized to code adverse experience reports in the paediatric population (i.e., reports of "prescribed overdose" and "overdose" reflect the local coding convention utilized for off label use of caspofungin in paediatric patients); and (3) pancreatitis. As of 30 April 2008, a total of 14 cases of pancreatitis following caspofungin use, including 3 in adult patients and 11 in paediatric patients, have been identified in the Merck Worldwide Adverse Experience System (WAES) database. This includes 6 cases of pancreatitis (all in paediatric patients) since the July 2006. The MAH mentioned that all 6 of these reports were received from the same reporter (in November 2006), and all contained insufficient information for proper assessment. The CHMP can not consider this answer as pertinent. Therefore the CHMP recommends that surveillance data on potential liver and pancreas toxicity are monitored and presented within the next PSUR.

Overall, the post-marketing adverse experience profile of the paediatric population is consistent with current labelling for caspofungin use in adults and proposed labelling for use in paediatric patients.

According to a comprehensive literature review of English-language abstracts/manuscripts through 31-Aug-2007 on the experience of caspofungin use in the paediatric patient population, all reports concluded that caspofungin was generally safe and well-tolerated in this patient population.

- ***Discussion on clinical safety***

As expected in seriously ill patients, clinical adverse experiences were common in these paediatric studies. The most common drug-related adverse experiences in the caspofungin group included **fever**, **rash**, and **headache**. The incidence of serious drug-related adverse experiences or discontinuations due to drug-related clinical toxicity was numerically lower in the caspofungin group than reported in the AmBisome group. Only 1 (0.6%) patient had a serious clinical adverse experience (**hypotension**) that was considered by the investigator as related to caspofungin therapy and further to assessment has been added in section 4.8 of the SPC under vascular disorders. Furthermore, the incidence of caspofungin therapy discontinuations due to a clinical drug-related adverse experience was low (1%). An assessment of different subset of patients who developed drug-related clinical adverse experiences

did not demonstrate any potential concern for the use of caspofungin in particular subsets of paediatric patients. The incidence of drug-related clinical adverse experiences in patients treated with caspofungin was generally similar across different paediatric age ranges, gender, race, ethnicity, weight, and duration of therapy, although data on the youngest children were scarce. The 26.3% (45/171) of paediatric patients who experienced a drug-related clinical adverse event is not substantially different from the 43.2% (427/989) of adult patients previously studied who experienced at least one drug-related clinical adverse experience.

The pattern of these adverse experiences in paediatric patients treated with caspofungin, including the most commonly reported clinical adverse experiences in paediatric patients, was similar to that reported previously for adults in the original and supplemental Marketing Applications and described in the current product labelling.

The overall incidence of clinical adverse experiences was higher in the caspofungin group (92%) than in the AmBisome group (73%). This finding is not unexpected since there were differences in patient characteristics; all AmBisome treated subjects were included in study 044, the empirical treatment study, while the caspofungin treated patients originated from different studies. However, drug-related clinical AE were lower in the caspofungin group vs. AmBisome group (26% vs. 46%).

The most common drug-related laboratory adverse experiences in the caspofungin group were **increased AST**, **increased ALT**, and **decreased blood potassium**. None of the laboratory events in the caspofungin group was serious or led to discontinuation of caspofungin study therapy. Transaminase elevations in paediatric patients was summarized as being transient, routinely resolved with the discontinuation of caspofungin therapy, and seemed not to be associated with other liver test abnormalities or clinical findings. Decreased potassium was not associated with any untoward clinical phenomena. Importantly, the incidence of these drug-related laboratory events in paediatric patients treated with caspofungin (16.4% 28/171) was similar to that reported previously for adults (26.4%, 260/985).

As of 30 April 2008, a total of 14 cases of pancreatitis following caspofungin use, including 3 in adult patients and 11 in paediatric patients, have been identified in the Merck Worldwide Adverse Experience System (WAES) database. This includes 6 cases of pancreatitis (all in paediatric patients) since the July 2006. The MAH mentioned that all 6 of these reports were received from the same reporter (in November 2006), and all contained insufficient information for proper assessment. The CHMP can not consider this answer as pertinent. Therefore the CHMP recommends that surveillance data on potential liver and pancreas toxicity are monitored and presented within the next PSUR.

4. Overall conclusions, risk/benefit assessment and recommendation

4.1. Non-clinical pharmacology and toxicology

As part of this application, the MAH submitted:
- an *In vivo* study "*Efficacy, pharmacokinetics and pharmacodynamics of caspofungin in a juvenile mouse model of central nervous system candidiasis*".
The animals used in this efficacy study were 7-11 weeks old at study initiation. As animals of that age are considered to be at the end of puberty / start of adulthood, this is study is not considered to be a juvenile animal study. Moreover, clinical data efficacy data are available for the older paediatric age groups. Consequently, the data presented here were not considered relevant in the frame of this extension to the paediatric population.

- a "*5-week intravenous toxicity study in infant rhesus monkey* (*Macaca mulatta*)", which was already part of the initial application for caspofungin.
This toxicity study together with the previously submitted repeat-dose intravenous toxicity studies as part of the initial application for Cancidas have shown that the toxicity profile of caspofungin consists of signs of histamine release in rats and rhesus monkeys, irritation at the injection sites in rats and monkeys, and slight elevations in serum transaminase values with or without very slight to slight subcapsular liver necrosis in monkeys.

4.2. Efficacy

The data from the three pharmacokinetic studies (Protocols 033, 042 and 058) suggest that a dosing regimen of 50 mg/m^2/day (with a maximum of 70 mg/day) in paediatric patients between 12 months to 17 years of age results in plasma exposures relatively similar to those obtained in adults receiving caspofungin at 50 mg/day. Neonates and infants (<3 months of age) receiving single or multiple, once-daily doses of caspofungin at 25 mg/m^2 achieved on average fairly similar plasma exposures to that of adults receiving caspofungin at 50 mg/day. However, the variability is very large in this group and a clear dosage recommendation cannot be made based on the available pharmacokinetic data. Moreover, there is no pharmacokinetic data for children between 3 and 12 months of age, and it is unknown whether this age group should have a dose more close to the 50 mg/m^2 dose for older children or to the 25 mg/m^2 dose for smaller babies. Furthermore, efficacy and safety data are limited in the smallest children. Thus, data are not considered sufficient to fully support the indication in children <12 months of age without caution. Therefore it has been agreed that the lack of data for this specific population should be highlighted in section 4.2 of the SPC together with consideration of dose when treating children <12 months of age. It has also been agreed to mention the available pharmacokinetic data, including the large variability observed in neonates, and the lack of data for 3-11 months old children in section 5.2 of the SPC.

The data on exposure might suggest that caspofungin clearance is lowest at birth, increases from infancy to childhood and then decreases from childhood to adolescence and subsequently to adulthood. The MAH presented data on dose escalation to be considered when the clearance is higher. Although dose regimen adaptation can be needed in a real minority of patients across all age groups, this change only concerns a restricted minority in percentage (about 5-10% whatever the age is). In pratice, there is therefore no need for a potential recommendation for any particular age subset in the SPC.

The covariate and PK/PD analysis is not considered optimal as it is a simple statistical regression analysis. By instead using non-linear mixed effects modelling, more information could possibly have been extracted from available data, which might have provided further support of the proposed dosing in age groups where pharmacokinetic data are sparse. The regression analysis of paediatric data led to the same results as previously seen for adults, i.e. that there was no apparent relationship between plasma exposure and efficacy, possibly because the plasma concentrations obtained at normal clinical doses are at the top of the concentration-effect curve. Finally, the population pharmacokinetic analysis indicated that when caspofungin is administered to paediatric patients concomitantly with inducers of drug clearance a dose escalation should be considered and stated in section 4.5 of the SPC, as is previously recommended also for adults.

The two paediatric safety/efficacy studies (Protocols 043 and 044) enrolled a total of 131 patients, including 105 patients on caspofungin, from over 25 study sites worldwide. Effort was put to harmonise the designs of the studies with the corresponding adult studies. The results from the open uncontrolled paediatric efficacy study (Protocol 043), indicated that caspofungin, administered intravenously at 50 mg/m^2 daily (following a 70-mg/m^2 loading dose on Day 1), was effective in the treatment of documented Candida or Aspergillus infections in children and adolescents ages 6 months through 17 years. Additionally, the results from the comparative study Protocol 044 also supported an efficacy of caspofungin comparable to AmBisome in the empirical treatment of suspected fungal infections in paediatric patients with persistent fever and neutropenia, using the same dose regimen.

There was no indication that the efficacy was related to dose, gender or underlying disease. However, numbers in each age category are small, which precludes any firm conclusions.

In addition, the MAH provided supportive data from 3 publications (Natarajan et al 2005; Odio et al, 2004; and Odio et al 2005). In these publications, retrospective data on a total of 59 neonates or infants with invasive candidiasis, treated with caspofungin as second line or as add-on treatment to conventional antifungal agents were provided. The doses were mostly 25 mg/m2 or slightly lower. Success rates were 85%, 100% and 97%, respectively. Caspofungin was generally well tolerated and

no serious adverse events were directly correlated to caspofungin treatment. Thus, these published data support the efficacy and safety of the dose 25 mg/m^2 in children less than 3 months.
The critical age group here is considered to be children 3-11 months, where there are only safety data for 2 subjects; PK data from 1 child (10 months; study 042), and efficacy data on 1 child (6 months old patients from study Protocol 043). Thus, the MAH suggestion that children between 3-12 months should be dosed 50 mg/m2 in contrast to children less than 3 months (25 mg/m2) is not based on firm data. The choice of dosage in this age group, that was not well studied, must currently be based on a theoretical benefit-risk assessment, i.e. the risk for under dosing in severe infections in seriously ill patients, contra the risk for dose-related adverse events. In the age group 3-9 months, there is only very limited PK data from one 6 months old subject, which indicated somewhat higher exposure than in older children.

4.3. Safety

As expected in seriously ill patients, clinical adverse experiences were common in these paediatric studies. The most common drug-related adverse experiences in the caspofungin group included **fever**, **rash**, and **headache**. The incidence of serious drug-related adverse experiences or discontinuations due to drug-related clinical toxicity was numerically lower in the caspofungin group than reported in the AmBisome group. Only 1 (0.6%) patient had a serious clinical adverse experience (**hypotension**) that was considered by the investigator as related to caspofungin therapy and further to assessment has been added in section 4.8 of the SPC under vascular disorders. Furthermore, the incidence of caspofungin therapy discontinuations due to a clinical drug-related adverse experience was low (1%). An assessment of different subset of patients who developed drug-related clinical adverse experiences did not demonstrate any potential concern for the use of caspofungin in particular subsets of paediatric patients. The incidence of drug-related clinical adverse experiences in patients treated with caspofungin was generally similar across different paediatric age ranges, gender, race, ethnicity, weight, and duration of therapy, although data on the youngest children were scarce. The 26.3% (45/171) of paediatric patients who experienced a drug-related clinical adverse event is not substantially different from the 43.2% (427/989) of adult patients previously studied who experienced at least one drug-related clinical adverse experience.

The pattern of these adverse experiences in paediatric patients treated with caspofungin, including the most commonly reported clinical adverse experiences in paediatric patients, was similar to that reported previously for adults in the original and supplemental Marketing Applications and described in the current product labelling.

The overall incidence of clinical adverse experiences was higher in the caspofungin group (92%) than in the AmBisome group (73%). This finding is not unexpected since there were differences in patient characteristics; all AmBisome treated subjects were included in study 044, the empirical treatment study, while the caspofungin treated patients originated from different studies. However, drug-related clinical AE were lower in the caspofungin group vs. AmBisome group (26% vs. 46%).

The most common drug-related laboratory adverse experiences in the caspofungin group were **increased AST**, **increased ALT**, and **decreased blood potassium**. None of the laboratory events in the caspofungin group was serious or led to discontinuation of caspofungin study therapy. Transaminase elevations in paediatric patients was summarized as being transient, routinely resolved with the discontinuation of caspofungin therapy, and seemed not to be associated with other liver test abnormalities or clinical findings. Decreased potassium was not associated with any untoward clinical phenomena. Importantly, the incidence of these drug-related laboratory events in paediatric patients treated with caspofungin (16.4%, 28/171) was similar to that reported previously for adults (26.4%, 260/985).

Thus, efficacy results from the two paediatric multicenter clinical trials, supported by PK/PD data and in conjunction with efficacy results from corresponding adult clinical trials, support a positive opinion for those infectious disease indications currently licensed for caspofungin use in adults in European Union. However until further data are available in neonates and infants below 12 months of age, no definite dosage recommendations can be given, which has been highlighted in section 4.2 of the SPC.

4.4. Risk/benefit assessment

Based on the review of the data on safety and efficacy, the CHMP considers that the variation application EMEA/H/C/379/II/33 for Cancidas (caspofungin), in the treatment of invasive candidiasis, invasive aspergillosis and empirical therapy for presumed fungal infections in febrile neutropenic patients for the following proposed changes: Addition of paediatric indication and dosage can be approved for children between 12 months and 17 years of age.

For children <12 months of age, the data provided are not considered sufficient to fully support the extension of indication without caution. Consequently, it has been agreed to mention the available pharmacokinetic data and to enhance in the SPC the lack of data for this specific population together with consideration of dose when treating children <12 months of age.

4.5. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Cancidas in the paediatric population was favourable.

and

Furthermore, the CHMP took note that the PDCO adopted on 4 June 2008 an Opinion on Compliance (Opinion EMEA-C-000010-PIP01-07-MO1, see attachment 5) with the agreed PIP (Decision P/30/2008 adopted on 23 May 2008, see attachment 6) under Article 23 of Regulation EC (No) 1901/2006, as amended, for the above mentioned product and that the PDCO concluded in accordance with Article 28(3) and Article 45(3) of the said Regulation that:

- The development of this product has complied with all measures in the agreed PIP. For the purpose of the application of the Article 45(3) of Regulation EC (No) 1901/2006, significant studies in the agreed paediatric investigation plan have been completed after the entry into force of that Regulation,

In addition, the Summary of Product Characteristics reflects the results of studies conducted in compliance with this agreed paediatric investigation plan.

5. Conclusion

On 25 September 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.