EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Cancidas

(CASPOFUNGIN)

Procedure No. EMEA/H/C/000379/P46/060.1

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

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

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PRODUCT INFORMATION

Name of the medicinal product:	Cancidas
MAH:	Merck Sharp & Dohme Ltd.
INN (or common name) of the active substance(s):	Caspofungin
Pharmaco-therapeutic group (ATC Code):	J02AX04
Currently approved therapeutic indication(s):	Caspofungin is indicated for: - Treatment of invasive candidiasis in adult or paediatric patients, - Treatment of invasive aspergillosis in adult or paediatric 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, neutropaenic adult or paediatric patients
Pharmaceutical form(s) and strength(s):	Powder for concentrate for solution for infusion 50 and 70 mg
Method of administration	Intravenous infusion

1. Introduction

The MAH submitted the clinical study report of the P074 clinical study in accordance with Article 46 of Regulation (EC) No 1901/2006.

The MAH has conducted the Phase II P074 clinical study, a multicenter, open-label, non-comparative study to estimate the safety, efficacy, and pharmacokinetics of MK-0991 (caspofungin) in Japanese children and adolescents with *Candida* or *Aspergillus* infections, to obtain the additional indication in Japanese pediatric patients.

The study synopsis and clinical overview were written in English, but the detailed study report was available in Japanese only. Therefore, only the data presented in the synopsis of the study and the clinical overview were discussed in the original assessment report.

Upon request of the Agency, the MAH provided more details in English on the four paediatric patients who discontinued treatment due to hepatic insufficiency.

2. Study P074

2.1. Study procedures and subject disposition

OBJECTIVES:

1) To evaluate the safety and tolerability of caspofungin in Japanese pediatric patients.

2) To evaluate the proportion of Japanese pediatric patients with a favorable efficacy response (based on overall response) to caspofungin therapy in each of the different infection types (invasive candidiasis, esophageal candidiasis, and aspergillosis).

3) To evaluate caspofungin plasma concentration profiles and pharmacokinetic parameters obtained in Japanese pediatric patients.

DESIGN:

This clinical study was a multicenter, non-comparative, open-label study to estimate the safety, efficacy, and pharmacokinetics of caspofungin in Japanese paediatric patients aged 3 months to 17 years with candidiasis or aspergillosis.

POSOLOGY and TREATMENT DURATION:

The posology was in accordance with the one in the SmPC for paediatric patients (12 months to 17 years). The treatment regimen for caspofungin differed slightly based on the underlying fungal infections. Patients with esophageal candidiasis were to be treated for at least 7 days and a maximum of 28 days. Patients with invasive candidiasis were to be treated for at least 14 days and a maximum of 56 days. Patients with aspergillosis were to be treated for at least 14 days and a maximum of 84 days. Patients were to be followed for 14 days after the last dose of caspofungin.

SUBJECT INCLUSION:

Protocol 074 enrolled patients in whom causative fungi of candidiasis or aspergillosis were detected or fungal infection with Candida spp. or Aspergillus spp. was strongly suspected based on clinical symptoms, diagnostic imaging, fungal serology, or microbiological examination (culture, direct microscopy/ histopathology) before dosing of the study drug. The target number of patients was 20.

Among the 20 patients who received caspofungin at least once, 12 patients had invasive candidiasis (8 with candidemia, 2 with pulmonary candidiasis, 1 with Candida liver abscess, and 1 with Candida splenic abscess). None of the enrolled patients had esophageal candidiasis. 8 patients had invasive aspergillosis. None of the enrolled patients had chronic necrotizing pulmonary aspergillosis or pulmonary aspergilloma.

The mean age of patients with invasive candidiasis was 9.8 years (3 to 17 years). The mean duration of treatment (range) was 14.4 days (2 to 31 days). The mean age of patients with invasive aspergillosis was 9.8 years (1 to 15 years). The mean duration of treatment (range) was 15.6 days (3 to 57 days).

The caspofungin dose was increased to 70 mg/m^2 (daily dose: not more than 70 mg) according to the protocol in 3 out of 20 patients (15.0%). Of these, 2 patients had invasive candidiasis and 1 patient had invasive aspergillosis.

SUBJECT DISPOSITION:

	Invasive candidiasis		Aspergillosis		Total	
	n	(%)	n	(%)	n	(%)
Not Included	2		1		3	
Patients in population	12		8		20	
Study Medication Disposition						
COMPLETED	9	(75.0)	4	(50.0)	13	(65.0)
DISCONTINUED	3	(25.0)	4	(50.0)	7	(35.0)
Adverse clinical experience was reported for the patient.	2	(16.7)	1	(12.5)	3	(15.0)
Laboratory adverse experience was reported for the patient.	1	(8.3)	0	(0.0)	1	(5.0)
Patient discontinued because of lack of efficacy of test drug.	0	(0.0)	2	(25.0)	2	(10.0)
Patient discontinued for other reason.	0	(0.0)	1	(12.5)	1	(5.0)
Each patient is counted once for Study Medication Disposition based on the latest corresponding disposition record. There were no patients with esophageal candidiasis enrolled in this study.						

Twenty patients were included in the study, of which 13 patients completed the study. Seven patients discontinued the study, 3 because of adverse clinical experience, 1 for a laboratory adverse experience and 2 because of lack of efficacy of the test drug.

2.2. Clinical pharmacology

Pharmacokinetics

The provided study (protocol 74) administered intravenous caspofungin therapy as a single loading dose of 70 mg/m2 on Day 1, followed by 50 mg/m2 as a single once-daily maintenance dose on all subsequent days to 20 Japanese pediatric patients with *Candida* or *Aspergillus* infections. The pharmacokinetics of caspofungin in these Japanese pediatric patients were submitted and succinctly analyzed.

Sampling for plasma caspofungin concentration measurements was collected throughout the caspofungin treatment period, including Days 1, 4, 7, and 14 of therapy (provided the patient was still receiving caspofungin at that time). An assessment of various pharmacokinetic parameters (C1 hr, C24 hr, AUC0-24 hr) was conducted.

Summary statistics for pharmacokinetic parameters (C1 hr, C24 hr, and AUC0-24 hr,) in each age group (infant/toddlers [3 months to 1 years], children [2 to 11 years] and adolescents [12 to 17 years]) was provided. These parameters were compared in a descriptive fashion to historical data from adult Japanese patients with *Candida* or *Aspergillus* infections (Protocol 062). Pharmacokinetic parameters were also descriptively compared to historical data from non-Japanese pediatric patients with *Candida* or *Aspergillus* infections (Protocol 043).

The geometric means of AUC0-24 hr, C1 hr and C24 hr in patients of all age categories were 175.05 µg•hr/mL, 20.60 µg/mL and 3.34 µg/mL, respectively. By age category, the geometric means of AUC0-24 hr, C1 hr and C24 hr were 202.43 µg•hr/mL, 25.96 µg/mL and 3.62 µg/mL in patients of the age group of 2 to 11 years, respectively, and 148.26 µg•hr/mL, 15.88 µg/mL and 3.01 µg/mL in patients of the age group of 12 to 17 years, respectively. One patient in the age group of 3 months to 1 year was enrolled in this study, but the phamacokinetics parameters of this patient could not be calculated because this patient discontinued from the study on Day 3 due to lack of efficacy. The pharmacokinetics parameters in Japanese pediatric patients were compared to those in Japanese adult patients (Protocol 062). The C1 hr of Japanese pediatric patients was a little higher than that of Japanese adult patients, but AUC0-24 hr and C24 hr were similar to those of Japanese adult patients, thus the overall exposure of caspofungin was generally comparable. In addition, the pharmacokinetics parameters in Japanese pediatric patients were generally similar to those in non-Japanese pediatric patients (Protocol 043).

Based on the pharmacokinetic data, the efficacy of caspofungin in Japanese pediatric patients was evaluated and compared relative to those of clinical studies in adults (both Japanese and non-Japanese) and in non-Japanese pediatric patients. However, the results of the study are limited due to the small number of pediatric patients included and do not contribute new information to the known efficacy and safety profiles of caspofungin in paediatric patients.

Therefore, the EU SmPC does not need to be updated.

<u>Cancidas EU SmPC</u>

● Section 4.2

Paediatric patients (12 months to 17 years)
In paediatric patients (12 months to 17 years of age), dosing should be based on the patient's body surface area (see Instructions for Use in Paediatric Patients, Mosteller1 Formula). For all indications, a single 70-mg/m2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50 mg/m2 daily thereafter (not to exceed an actual dose of 70 mg daily). If the 50-mg/m2 daily dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg/m2 daily (not to exceed an actual daily dose of 70 mg).

The safety and efficacy of caspofungin have not been sufficiently studied in clinical trials involving neonates and infants below 12 months of age. Caution is advised when treating this age group. Limited data suggest that caspofungin at 25 mg/m2 daily in neonates and infants (less than 3 months of age) and 50 mg/m2 daily in young children (3 to 11 months of age) can be considered (see section 5.2).

● Section 5.2

Paediatric Patients:

In adolescents (ages 12 to 17 years) receiving caspofungin at 50 mg/m2 daily (maximum 70 mg daily), the caspofungin plasma AUC0-24 hr was generally comparable to that seen in adults receiving caspofungin at 50 mg daily. All adolescents received doses >50 mg daily, and, in fact, 6 of 8 received the maximum dose of 70 mg/day. The caspofungin plasma concentrations in these adolescents were reduced relative to adults receiving 70 mg daily, the dose most often administered to adolescents.

In children (ages 2 to 11 years) receiving caspofungin at 50 mg/m2 daily (maximum 70 mg daily), the caspofungin plasma AUC0-24 hr after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg/day.

In young children and toddlers (ages 12 to 23 months) receiving caspofungin at 50 mg/m2 daily (maximum 70 mg daily), the caspofungin plasma AUC0-24 hr after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg daily and to that in older children (2 to 11 years of age) receiving the 50 mg/m2 daily dose.

Overall, the available pharmacokinetic, efficacy, and safety data are limited in patients 3 to 10 months of age. Pharmacokinetic data from one 10-month old child receiving the 50 mg/m2 daily dose indicated an AUC0-24 hr within the same range as that observed in older children and adults at the 50 mg/m2 and the 50 mg dose, respectively, while in one 6-month old child receiving the 50 mg/m2 dose, the AUC0-24 hr was somewhat higher.

In neonates and infants (<3 months) receiving caspofungin at 25 mg/m2 daily (corresponding mean daily dose of 2.1 mg/kg), caspofungin peak concentration (C1 hr) and caspofungin trough concentration (C24 hr) after multiple doses were comparable to that seen in adults receiving caspofungin at 50 mg daily. On Day 1, C1 hr was comparable and C24 hr modestly elevated (36 %) in these neonates and infants relative to adults. However, variability was seen in both C1 hr (Day 4 geometric mean 11.73 µg/ml, range 2.63 to 22.05 µg/ml) and C24 hr (Day 4 geometric mean 3.55 µg/ml, range 0.13 to 7.17 µg/ml). AUC0-24 hr measurements were not performed in this study due to the sparse plasma sampling. Of note, the efficacy and safety of caspofungin have not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

Assessor's comments: *The investigation of a medicinal product in (very) young patients is difficult and PK data may be used to extrapolate efficacy and/or safety from data obtained in adults, by comparison of the exposures. In accordance with the guideline on the role of PK in the development of medicinal products in the pediatric population, EMEA/CHMP/EWP/147013/2004, June 2006, the PK results of this study (protocol 74) are presented as descriptive statistics of PK parameters in different age groups. A comparative statistical analysis (i.e. geometric mean ratios and 90 CIs) relative to adults is not available in module 2 and the module 5 is only provided in Japanese.*

Ideally, the data should enable assessment of variability at different maturational stages and facilitate the identification of cut-off points for posology adjustments. However, the number of pediatric patients is limited (n=20) to give an appropriate estimate of the inter-variability in each subgroup and detailed conclusions on PK cannot be drawn. Only a general observation can be made, namely that the PK data in Japanese pediatric patients were generally similar to those in Japanese adult patients or in non-Japanese pediatric patients with Candida or Aspergillus infections.

In the age group of 3 months to 1 year, the only patient discontinued from the study on Day 3 due to lack of efficacy and therefore, no new data is available for this age group.

This study does not represent the first evaluation of caspofungin in pediatric patients: between 2003 and 2009, within the pediatric program of Cancidas, protocols 33 and 42 (under the original FUM 25, called later FU2 029) gave important PK information leading to adequate dosing recommendations in neonates and infants and in children aged 2 to 17 years (see above section 4.2 and 5.2 of the Cancidas EU SmPC).

In this context, the assessor takes note of this additional phase II study in Japanese pediatric population and agrees that the SmPC should not be updated from a PK perspective.

2.3. Efficacy

The proportion of patients in the full analysis set with a favorable overall response rate for each infection category was 66.7% (8/12 patients) in patients with invasive candidiasis and 62.5% (5/8 patients) in patients with aspergillosis. There were no patients with esophageal candidiasis enrolled in this study.

The overall response rates were generally consistent with those reported in Japanese adult patients and non-Japanese pediatric patients with *Candida* or *Aspergillus* infections.

Assessor's comments:

Because of the open-label and non-comparative character of this study in a very small paediatric population, this study does not lead to different insight regarding efficacy or any change of the indication/dosing recommendations in the SmPC.

2.4. Safety

Brief summary of prior paediatric safety data for caspofungin [ref. Safety experience with caspofungin in pediatric patients, Zaoutis T. et al. *The pediatric Infecious Disease Journal,* 2009, 28, *12*, 1132-1135]

Safety data in non-Japanese pediatric patients treated with at least 1 dose of caspofungin (171 patients) were available from 5 prospective clinical studies, including 3 pharmacokinetic studies and 2 safety/efficacy studies.

The incidence of drug-related clinical and laboratory adverse events in children receiving caspofungin was 26% and 16%, respectively. The most common drug-related clinical adverse events following caspofungin use were fever (12%), rash (5%), and headache (3%). Most of these adverse events were mild in intensity and transient in nature. Increased aspartate transaminase (AST; 7.6%), increased alanine transaminase (ALT; 6.5%) and decreased potassium (3.5%) were the most common drug-related laboratory adverse events in pediatric patients treated with caspofungin. The maximum value during treatment ranged from 17 to 570 (median 89) IU/L for AST and from 16 to 434 (median 128) IU/L for ALT. The minimum value during treatment ranged from 2.1 to 2.8 (median 2.6) mmol/L for serum potassium. These events resolved (ie, values returned to within the normal range) during subsequent caspofungin therapy or by the time of the 14 day follow-up visit in 10 (77%) of the patients with increased AST, 6 (55%) of those with increased ALT, and 4 (67%) of those with

decreased potassium. None of these laboratory adverse events were serious or led to caspofungin discontinuation.

Although 37 (22%) of the 171 patients receiving caspofungin had a serious clinical adverse event, only 1 event (hypotension) was considered related to caspofungin therapy. Eleven patients (6%) died during or within 14 days of completing caspofungin therapy, but none of the adverse events resulting in death were considered by the reporting investigator to be related to caspofungin. Two patients (1%) discontinued caspofungin because of a drug-related adverse event: moderate hypotension in 1 patient and moderate rash in the other; the hypotension resolved after a normal saline bolus was given, and the rash resolved without treatment 10 days later.

% of Patients With	Caspofungin (All Doses) All Pediatric Studies Combined					Comparator-Controlled Study of Empirical Therapy†	
	Age <3 mo (N = 18)	Age 3–23 mo (N = 12)	Age 2–11 yr (N = 103)	Age 12–17 yr (N = 38)	Total (N = 171)	Caspofungin 50 mg/m^2 (N = 56)	L-AmB 3 mg/kg (N = 26)
Clinical drug-related events	0	8‡	33	26	26	48	46
Chills	0	0	2	3	2	2	8
Fever	0	0	16	11	12	29	23
Headache	0	0	2	8	3	9	0
Pruritus	0	0	3	0	2	4	0
Rash	0	0	6	5	5	9	0
Flushing	0	0	3	0	2	4	0
Hypotension	0	0	3	0	2	4	4
Laboratory drug-related events	0	42	16	18	16	11	19
Alanine aminotransferase (ALT) increased	0	17	6	8	6	4	0
Aspartate aminotransferase (AST) increased	0	25	6	11	8	2	0
Blood phosphorus decreased	0	8	2	0	2	2	0
Blood potassium decreased	0	8	3	5	4	4	12
Serious drug-related events	0	0	1	0	1	2	12
Discontinuation due to drug-related events	0	0	2	0	1	4	12

*Events occurring in >2 caspofungin patients overall.
†Patients in this study were 2 to 16 years of age; L-AmB = liposomal amphotericin B.
‡One patient in this age group (3–23 mo) had a drug-related clinical adverse event (edema).

Overall, the proportion of pediatric patients who experienced a drug-related clinical adverse event following caspofungin use (26%) is not substantially different from the corresponding incidence reported in adult patients (29%–55%). The laboratory safety profile among caspofungin-treated pediatric patients was also favorable, and the 16% rate of drug-related laboratory adverse events reported in pediatric patients compares favorably with incidence rates reported in adult patients (23%–49%).

The most common drug-related laboratory adverse events, which included increases in hepatic transaminases (AST and ALT) and decreases in serum potassium, were also the most common laboratory findings in the adult population. Liver transaminase elevations in pediatric patients were transient and occurred primarily in patients receiving concomitant hepatotoxic drugs. Most elevations routinely resolved either with continued caspofungin therapy or immediately following its cessation, and these findings were not associated with other liver test abnormalities or clinical sequelae. None of the drug-related laboratory adverse events resulted in discontinuation of caspofungin therapy.

Safety in study P074

Among the 20 patients in the all-patient-as-treated population, **clinical adverse experiences** occurred in 16 patients (80.0%). Among these, drug-related clinical adverse experiences occurred in 8 patients (40.0%). Major clinical adverse experiences (in ≥ 3 patients) in Japanese pediatric patients were rash (5/20 patients, or 25.0%), vomiting, pyrexia and abnormal hepatic function (3/20 patients each, or 15.0%). Major drug-related clinical adverse experiences (in ≥ 2 patients) were abnormal hepatic function (3/20 patients, or 15.0%).

Serious clinical adverse experiences occurred in 3 patients (15.0%). Of these, sepsis was reported in 1 patient, hyperventilation was reported in 1 patient and sepsis and pneumonia were reported in 1 patient. None of these serious clinical adverse events was considered to be related to the study drug. There were no deaths reported in this study.
Clinical adverse experiences leading to study therapy discontinuation occurred in **3 patients** (15.0%). All of the clinical adverse experiences leading to study therapy **discontinuation** were **abnormal hepatic function**, and were considered to be related to the study drug. The intensity of abnormal hepatic function in the "hepatobiliary disorders (SOC)" in the 3 patients was mild in 1 patient and moderate in 2 patients. Two patients of 3 patients with abnormal hepatic function recovered following the study therapy discontinuation and 1 patient did not recover following the study therapy discontinuation.

Among the 20 patients in the all-patient-as-treated population, **laboratory adverse experiences** occurred in 7 patients (35.0%). Among these, drug-related laboratory adverse experiences occurred in 6 patients (30.0%). Major laboratory adverse experiences (in ≥ 3 patients) reported in Japanese pediatric patients were ALT increased (5/20 patients, or 25.0%), AST increased (4/20 patients, or 20.0%) and gamma-glutamyltransferase increased (3/20 patients, or 15.0%). Major drug-related laboratory adverse experiences (in ≥ 3 patients) were ALT increased (5/20 patients, or 25.0%) and AST increased (4/20 patients, or 20.0%). Overall, events related to hepatic insufficiency were commonly reported.
There were no deaths and other serious laboratory adverse experiences reported in this study.
Laboratory adverse experiences leading to study therapy **discontinuation** occurred in 1 patient (5.0%). The laboratory adverse experiences leading to study therapy discontinuation were **increased blood lactate dehydrogenase (LDH) and increased C-reactive protein (CRP)**, and both were considered to be related to the study drug. The 1 patient with LDH increased had not recovered during at the study therapy discontinuation, CRP increased recovered following study therapy discontinuation. Both events were non-serious.

Conclusion

Caspofungin is safe and well tolerable without drug-related adverse experiences specific to Japanese pediatric patients.
Although statistical comparison is difficult due to the limited number of patients in each study, in the Japanese Phase II study in Japanese pediatric patients (Protocol 074), the frequencies of drug-related adverse experiences in Japanese pediatric patients were numerically higher than in Japanese adult patients (Protocol 062) and in non-Japanese pediatric patients (Protocols 033, 042, 058, 043 and 044).

Clinical significant laboratory abnormalities

In the Phase II study in Japanese pediatric patients (PN074), frequent CSLAs (reported by ≥40% of patients) were increase in ALT (> 2.5 times the baseline) in 9/20 (45.0%) patients, increase in ALT (> 2.5 times ULN) in 8/20 (40.0%) patients, platelet count decreased (<25,000/μL), and increases in AST and ALT (both > 2.5 times ULN) 8/20 (40.0%) patients.

Hepatic events

In the study in Japanese pediatric patients (PN074), hepatic insufficiency reported was reported in 9/20 (45.0%) patients. The breakdown for these is liver function test abnormal in 3/20 (15.0%) patients, and ALT increased in 5/20 (25.0%) patients, AST increased in 4/20 (20.0%) patients, gamma-glutamyltransferase increased and LDH increased in 2/20 (10.0%) patients and blood bilirubin increased in 1/20 (5.0%) patients as laboratory adverse experiences. The timing of initial onset of

hepatic insufficiency was 2 to 22 days following the treatment and the duration was 4 to 27 days. Overall, 2 (22.2%) of the 9 patients who reported hepatic insufficiency had not fully recovered at completion of therapy, while the remaining 7 patients recovered following study therapy discontinuation or while on therapy.
Hepatic insufficiency led to study therapy discontinuation in 4/9 (44.4%) patients. The breakdown for these is abnormal hepatic function in 3 patients and LDH increased in 1 patient. Two (2) patients of 3 patients with abnormal hepatic function recovered following the study therapy discontinuation and 1 patient did not recover following the study therapy discontinuation. In addition, 1 patient with LDH increased had not recovered during at the study therapy discontinuation. Although there were events which were not recovered following the study therapy discontinuation, all of these events were determined to be non-serious. Moreover, the intensity of abnormal hepatic function in the "hepatobiliary disorders (SOC)" in the 3 patients was mild in 1 patient and moderate in 2 patients.

Conclusion

Also the incidence of hepatic insufficiency in Japanese pediatric patients was numerically higher compared to those of non-Japanese pediatric patients and Japanese adult patients. The relatively commonly reported events in Japanese pediatric patients were AST increased and ALT increased.

Effect of dose escalation

All 3 Japanese pediatric patients who had the caspofungin daily dose increased (from 50 mg/m^2 daily to 70 mg/m^2 daily, maximum daily dose: 70 mg) started dose escalation on Day 5 or Day 6 and received caspofungin for a total of 14 to 20 days. Of the 3 patients who increased their caspofungin dose, 1 patient reported diarrhoea, blood bilirubin increased, AST increased, ALT increased and LDH increased. All of these events were determined to be drug-related but the patient continued on study drug without discontinuation, and the events recovered during the study period.
The caspofungin dose increase within the stipulated range has no significant effect on the safety of caspofungin.

Assessor's remark 1st round:

The reported adverse events in Japanese paediatric patients were similar to the ones reported in non-Japanese paediatric patients. However, the incidence of hepatic insufficiency in Japanese pediatric patients was numerically higher than in non-Japanese pediatric patients. All events of abnormal hepatic function were mild to moderate in intensity and determined to be non-serious. However, hepatic insufficiency led to study therapy discontinuation in 4 patients (out of 20).
Details of these cases were in Japanese. Therefore, the MAH is asked to provide details on these cases in English and discuss causality, reporting observed values, time-to-onset, concomitant medications, comorbidities, dechallenge/rechallenge and outcome.

Summary of the Company's response:

The Applicant did provide data on the 4 patients who discontinued therapy due to hepatic insufficiency related adverse reactions.

These four patients had serious underlying medical conditions (concomitant leukaemia or leukaemia in medical history) and were receiving multiple concomitant medications.

Two patients with increased AST, ALT (and LDH in one case) values recovered after therapy discontinuation. The other patient with increased AST, ALT and bilirubine did not recover, but the patient's concomitant GVHD (graft versus host disease) and venoocclusive disease could be affecting

the patient's hepatic function.
In the fourth patient, with increased lactate dehydrogenase and increased C-reactive protein, CRP value resolved after study drug discontinuation, the blood lactate dehydrogenase level did not resolve, but it was decreasing.

The adverse reactions were assessed as possibly or probably related to the study drug.

Assessor's comment 2nd round:

For these four cases, the time to onset and dechallenge data suggest a possible causal relationship, but there is no definite proof of causality given the serious underlying medical conditions and multiple concomitant medications.

Of the two patients that did not recover, one patient had decreasing blood lactate dehydrogenase and the other patient developed venoocclusive disease that could be affecting the patient's hepatic function.

Point solved

Rapporteur's remark 1st round:

The MAH should give the used definition for "laboratory adverse experience" and "clinical significant laboratory abnormalities", as figures for ALT and AST increase are higher when reporting clinical significant laboratory abnormalities.

Company's response:

During conduct of the Phase II study in Japanese pediatric patients (PN074) trial, the determination that ALT or AST increase was a laboratory adverse experience was judged by the investigator. Clinical significant laboratory abnormalities for AST and ALT were determined during data analysis using the predefined criteria of > 2.5, 5, 7.5 times ULN and > 2.5 times the baseline value. The MAH classified and summarized the patients with ALT and AST increase in accordance with the predefined "clinical significant laboratory abnormalities" criteria. However, these criteria were not used as the criteria for judgement of "laboratory adverse experience" by the investigator.

Point solved

2.5. Influence on the benefit-risk balance

The reported adverse events in Japanese paediatric patients were similar to the ones reported in non-Japanese paediatric patients. However, the incidence of hepatic insufficiency in Japanese pediatric patients was numerically higher than in non-Japanese pediatric patients. All events of abnormal hepatic function were mild to moderate in intensity and determined to be non-serious. Hepatic insufficiency led to study therapy discontinuation in 4 patients (out of 20). The time to onset and dechallenge data suggest a possible causal relationship, but there is no definite proof of causality given the serious underlying medical conditions (concomitant leukaemia or leukaemia in medical history) and multiple concomitant medications. Two patients did not recover, one patient with increased blood lactate dehydrogenase had decreasing values, but these were not at the same level observed at screening and the other patient with increased AST, ALT and bilirubine values developed venoocclusive disease, which could be affecting the patient's hepatic function.

In 2010, the MAH was requested to perform an in-depth analysis including time-to-onset and dechallenge with all cases of serious hepatic ADR, especially the cases of acute hepatic failure, hepatic

failure, and hepatitis.
The rapporteur's conclusion on this post-authorisation commitment (FU2 055.1) was that the reporting rates for the hepatic ADR's of interest were indeed low (<1/100.000 patients treated cumulatively). Assessment of causality was difficult due to the presence of several concomitant medications, pre-existing hepatic disease and/or serious underlying medical conditions associated with hepatotoxicity. The reported TTO and dechallenge data only suggest a possible causal relationship, but are no definite proof of causality.

Therefore, patients who develop abnormal liver function tests during caspofungin therapy should be monitored for evidence of worsening hepatic function and the risk/benefit of continuing caspofungin therapy should be re-evaluated.

The MAH commits to submit a Type IB variation at the next possible EMA submission timeline, i.e. by 14th August 2014 to add a warning to section 4.4 of the SmPC on abnormalities in liver function test, as included e.g. in the FDA product labelling:

"Hepatic Effects
Laboratory abnormalities in liver function tests have been seen in healthy volunteers and adult and pediatric patients treated with CANCIDAS®. In some adult and pediatric patients with serious underlying conditions who were receiving multiple concomitant medications with CANCIDAS®, cases of clinically significant hepatic dysfunction, hepatitis and hepatic failure have been reported; a causal relationship to CANCIDAS® has not been established. Patients who develop abnormal liver function tests during CANCIDAS® therapy should be monitored for evidence of worsening hepatic function and the risk/benefit of continuing CANCIDAS® therapy should be re-evaluated."

The benefit-risk of Cancidas® remains positive.

3. Conclusion

In the study (protocol 74), the PK data in Japanese pediatric patients were generally similar to those in Japanese adult patients or in non-Japanese pediatric patients with Candida or Aspergillus infections. Between 2005 and 2009, within the pediatric program of Cancidas, protocols 33 and 42 (FUM 25, called later FU2 029) gave important PK information leading to adequate dosing recommendations in neonates and infants and in children aged 2 to 17 years (see sections 4.2 and 5.2 of the Cancidas EU SmPC). Due to the limited number of pediatric patients enrolled, this study does not provide new relevant PK information and the SmPC should not be updated from a PK perspective.

Because of the open-label and non-comparative character of this study in a very small paediatric population, this study does not lead to different insight regarding efficacy or posology.

The reported adverse events in Japanese paediatric patients were similar to the ones reported in non-Japanese paediatric patients. However, the incidence of hepatic insufficiency in Japanese pediatric patients was numerically higher than in non-Japanese pediatric patients and led to study therapy discontinuation in 4 patients (out of 20). *The time to onset and dechallenge data suggest a possible causal relationship, but there is no definite proof of causality given the serious underlying medical conditions (concomitant leukaemia or leukaemia in medical history) and multiple concomitant medications. Two patients did not recover, one patient with increased blood lactate dehydrogenase had decreasing values, but these were not at the same level observed at screening and the other patient with increased AST, ALT and bilirubine values developed venoocclusive disease, which could be*

affecting the patient's hepatic function.

In 2010, the MAH was requested to perform an in-depth analysis including time-to-onset and dechallenge with all cases of serious hepatic ADR, especially the cases of acute hepatic failure, hepatic failure, and hepatitis.
The rapporteur's conclusion on this post-authorisation commitment (FU2 055.1) was that the reporting rates for the hepatic ADR's of interest were indeed low (<1/100.000 patients treated cumulatively). Assessment of causality was difficult due to the presence of several concomitant medications, pre-existing hepatic disease and/or serious underlying medical conditions associated with hepatotoxicity. The reported TTO and dechallenge data only suggest a possible causal relationship, but are no definite proof of causality.

Therefore, patients who develop abnormal liver function tests during caspofungin therapy should be monitored for evidence of worsening hepatic function and the risk/benefit of continuing caspofungin therapy should be re-evaluated.

The MAH commits to submit a Type IB variation at the next possible EMA submission timeline, i.e. by 14th August 2014 to add a warning to section 4.4 of the SmPC on abnormalities in liver function test:

"Hepatic Effects
Laboratory abnormalities in liver function tests have been seen in healthy volunteers and adult and pediatric patients treated with CANCIDAS®. In some adult and pediatric patients with serious underlying conditions who were receiving multiple concomitant medications with CANCIDAS®, cases of clinically significant hepatic dysfunction, hepatitis and hepatic failure have been reported; a causal relationship to CANCIDAS® has not been established. Patients who develop abnormal liver function tests during CANCIDAS® therapy should be monitored for evidence of worsening hepatic function and the risk/benefit of continuing CANCIDAS® therapy should be re-evaluated."