

Merck & Co., Inc. Study Synopsis

1. Proprietary Drug Name: CANCIDAS™	2. Generic Drug Name: caspofungin acetate	3. Therapeutic area and FDA-approved indications: Invasive Aspergillosis, Invasive Candidiasis, and Esophageal Candidiasis
4. Name of Sponsor/Company: Merck & Co., Inc.		
5. Title of Study: A Multicenter, Open-Label, Noncomparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Acetate in Children With Documented <i>Candida</i> or <i>Aspergillus</i> Infections NCT00082524 (PN 043)		
6. Study Investigators/Study Center(s): Multicenter (21 centers, 11 in the United States and 10 outside the United States). Twelve of the 21 centers (6 U.S. and 6 outside the United States) enrolled patients.		
7. Studied Period (years): <i>(Date of first enrollment) (date of last completed)</i> 21-May-2004 to 05-July-2007	8. Phase of development: IIa	
9. Primary Hypotheses and Secondary Hypothesis: This was an estimation study. No formal hypotheses were predefined.		

10. <u>Study Design/ Methodology:</u>	Open-label, non-comparative study to evaluate the safety, tolerability and efficacy of caspofungin in children or adolescents (ages 3 months to 17 years) with documented <i>Candida</i> or <i>Aspergillus</i> infection at the time of enrollment. Patients with proven esophageal candidiasis or proven invasive candidiasis were enrolled into the study as primary or salvage therapy. Patients with proven or probable invasive aspergillosis were only enrolled if they had failed or were intolerant of standard antifungal therapy. All patients were to have a 14-day post-treatment follow-up visit to monitor safety. Patients who responded favorably at the end of study therapy were also monitored for relapse of the fungal infection at 14- and 28-days posttherapy.
11. <u>Number of Patients (planned and analyzed):</u>	

SUBJECT/PATIENT DISPOSITION:

	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. discontin.	0	(0.0)	9	(23.7)	0	(0.0)	9	(18.4)
for other §								
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. discontin.	0	(0.0)	1	(2.6)	0	(0.0)	1	(2.0)
for other								
pat. moved	0	(0.0)	1	(2.6)	0	(0.0)	1	(2.0)

[†]"Completed Therapy" is defined as having a status of "pat. continuing 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.

<p>12. <u>Diagnosis and main criteria for inclusion:</u></p>	<p>Children and adolescents aged 3 months to 18 years with documented invasive aspergillosis, invasive candidiasis, or esophageal candidiasis were enrolled. Patients with proven esophageal candidiasis or proven invasive candidiasis were enrolled into the study as primary or salvage therapy. Patients with proven or probable invasive aspergillosis were only enrolled if they had failed to respond to or were intolerant of standard antifungal therapy.</p>
<p>13. <u>Test product and reference therapy (if applicable); dose and mode of administration; batch number:</u></p>	<p>IV caspofungin acetate given as a loading dose of 70mg/m² on Day 1 and 50 mg/m² on Day 2 onward (formulation numbers: 0991HLS016B003, 0991HLS016B004, 0991HLS017B004, 0991HLS017B005, 0991HLS016B005, 0991HLS017B002, 0991HLS017B006, 0091HLS017B001, WL00008764, WL00020744, WL00017427, WL00024008). The maximum daily dose was 70 mg/day.</p>

14. <u>Duration of treatment:</u>	Variable by patient, ranged 2 to 87 days
15. <u>Criteria for Evaluation:</u>	<p>EFFICACY MEASUREMENTS: The investigator monitored the resolution or progression of each patient’s fungal infection by assessment of signs and symptoms, cultures, and/or radiographic studies, as appropriate at timepoints specified in the protocol. The primary efficacy assessment was made at the end of caspofungin therapy. Relapse assessments were made at the 14- and 28-day posttherapy follow-up visits for patients who had a favorable response at the end of caspofungin study therapy. For invasive aspergillosis, efficacy was based on the clinical response that incorporated signs/symptoms of the <i>Aspergillus</i> infection, radiographic data, and other relevant information. For invasive candidiasis, efficacy was based on the overall response which incorporated the clinical and microbiological assessments. For esophageal candidiasis, efficacy was based on both symptoms and endoscopic findings.</p> <p><u>Safety:</u> Evaluation of the presence or absence of adverse clinical or laboratory experiences (AEs). Patients were monitored for adverse experiences during study therapy and for 14 days following the completion of caspofungin study therapy. Laboratory safety studies were carried out at specified time points.</p>
16. <u>Statistical methods:</u>	<p>This study was analyzed as an estimation study with no formal hypothesis testing.</p> <p>Efficacy: The primary efficacy endpoints were:</p> <ul style="list-style-type: none"> • Invasive Aspergillosis: the proportion of patients with a favorable clinical response (complete or partial response) at the end of caspofungin therapy. • Invasive Candidiasis: the proportion of patients who had a favorable overall response (which must include both a favorable clinical response and a favorable microbiological response) at the end of caspofungin therapy. • Esophageal Candidiasis: the proportion of patients with a favorable response at the end of caspofungin therapy based on the assessments of signs/symptoms of infection and the endoscopic findings. <p><u>Safety:</u> The main safety evaluation was the proportion of pediatric patients, by treatment group, who reported one or more clinical and/or laboratory drug-related adverse experience(s) during the study drug therapy period plus 14 days posttherapy.</p>

17. Summary:**RESULTS:****Efficacy:**

Of the 49 patients enrolled in this study, 48 had confirmed disease including 10 patients with invasive aspergillosis who were refractory to prior antifungal treatments, 37 patients with invasive candidiasis, and 1 patient with esophageal candidiasis.

In the MITT population, 5 (50%) of the patients enrolled with invasive aspergillosis had a favorable clinical response at the end of caspofungin study therapy. The 5 patients with a favorable clinical response at the end of caspofungin therapy continued to have a favorable response at both the 14- and 28-day posttherapy follow-up visits.

Thirty (81.1%) of the 37 patients with invasive candidiasis had a favorable overall response at the end of caspofungin therapy. Twenty-eight of the 30 patients with a favorable overall response at the end of caspofungin therapy continued into the follow-up period. Only 1 patient had a relapse at the 28-day posttherapy follow-up visit.

The one patient with esophageal candidiasis had a complete response at the end of caspofungin study therapy. The patient continued to have a favorable response (no relapse) at the 14- and 28-day posttherapy follow-up visit.

Safety:**Clinical adverse experiences:**

Clinical Adverse Experience Summary	Invasive Aspergillosis (N = 10)		Invasive Candidiasis (N = 38)		Esophageal Candidiasis (N = 1)		Total (N = 49)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:								
With one or more adverse experiences	9	(90.0)	34	(89.5)	0	(0.0)	43	(87.8)
With no adverse experience	1	(10.0)	4	(10.5)	1	(100)	6	(12.2)
With drug-related adverse experiences [†]	4	(40.0)	9	(23.7)	0	(0.0)	13	(26.5)
With serious adverse experiences	5	(50.0)	3	(7.9)	0	(0.0)	8	(16.3)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Who died	5	(50.0)	0	(0.0)	0	(0.0)	5	(10.2)
Discontinued due to adverse experiences	2	(20.0)	0	(0.0)	0	(0.0)	2	(4.1)
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	2	(20.0)	0	(0.0)	0	(0.0)	2	(4.1)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be possibly, probably or definitely drug related.

Laboratory adverse experiences:

Laboratory Adverse Experience Summary	Invasive Aspergillosis (N = 10)		Invasive Candidiasis (N = 38)		Esophageal Candidiasis (N = 1)		Total (N = 49)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:								
With at least one lab test postbaseline	10		38		1		49	
With one or more adverse experiences	7	(70.0)	24	(63.2)	1	(100.0)	32	(65.3)
With no adverse experiences	3	(30.0)	14	(36.8)	0	(0.0)	17	(34.7)
With drug-related adverse experiences [†]	2	(20.0)	15	(39.5)	0	(0.0)	17	(34.7)
With serious adverse experiences	0	(0.0)	0	(0.0)	1	(100.0)	1	(2.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be possibly, probably or definitely drug related.

[‡] The percent = number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline.

18 Date of the report:	25-Apr-08
19. Contact:	Merck National Service Center 1.800.672.6372