2. Synopsis

MERCK RESEARCH LABORATORIES MK-0991 caspofungin acetate, IV Non-Blood Invasive Candidiasis	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Multicenter, Open, Noncomparative Study to Estimate the Safety, Tolerability, and Efficacy of Caspofungin Acetate in the Treatment of Adults With Invasive Candida Infections (Excluding Patients With Candidemia as the Sole Site of Infection) #045

INVESTIGATORS/STUDY CENTERS: Multicenter (17 sites, 4 in the United States and 13 in Europe).

PUBLICATION(S): NA

PRIMARY THERAPY PERIOD: 03-Aug-2004 to 16-Sep-2005 **CLINICAL PHASE:** IIb

DURATION OF TREATMENT: Variable by patient; ranged from 1 to 108 days.

OBJECTIVES: Primary: To estimate in caspofungin-treated patients with non-blood sites of invasive candidiasis, the favorable overall response rate (favorable clinical response and a favorable microbiologic assessment) at the end of caspofungin therapy. Secondary: To estimate in caspofungin-treated patients with non-blood sites of invasive candidiasis, (1) the favorable overall response rate (favorable clinical response and a favorable microbiologic assessment) on Day 10 of caspofungin therapy; (2) the favorable overall response rate (favorable clinical response and a favorable microbiologic assessment) at the end of all antifungal therapy (caspofungin and/or subsequent oral fluconazole); (3) the occurrence of relapse during the 12-week follow-up period following the completion of all antifungal therapy in patients successfully treated with caspofungin; (4) the development of serious, drug-related adverse experience(s) during caspofungin therapy and the 14-day posttherapy period; (5) the development of drug-related adverse experience(s) during caspofungin therapy and the 14-day posttherapy period; and (6) the development of drug-related adverse experiences that necessitate discontinuation of study therapy.

STUDY DESIGN: This was a multicenter, open-label, non-comparative study to estimate the safety, tolerability, and efficacy of caspofungin for the treatment of non-blood sites of invasive candidiasis. Patients were eligible for inclusion if they manifested clinical evidence of *Candida* infection, had at least 1 positive culture for invasive *Candida* from an otherwise sterile, non-blood related body site, and fulfilled all other entry criteria. The duration of antifungal therapy was variable and dependent on a variety of factors, including (1) the rapidity of the patient's clinical and microbiological response, (2) the patient's immunosuppressive status, and (3) the underlying site of *Candida* infection. In general, most patients received a 70-mg loading dose of caspofungin on Day 1, followed thereafter by 50 mg daily. Patients with either *Candida* endocarditis, *Candida* meningitis, or *Candida* osteomyelitis/septic arthritis received caspofungin at 100 mg daily (without a loading dose). After completing at least 10 days of caspofungin therapy, patients who had evidence of clinical and microbiological improvement and met other protocol-specified criteria were permitted to complete their antifungal treatment course with a therapeutic dose of oral fluconazole (≥400 mg daily). Upon successful completion of all antifungal therapy, either exclusively with caspofungin or after completion of oral fluconazole therapy, patients continued into a 12 week posththerapy follow-up period. Patients who responded favorably at the end of caspofungin study therapy were monitored for relapse of invasive candidiasis at 3 subsequent time points: 2-, 6-, and 12-weeks posttherapy.

SUBJECT/PATIENT DISPOSITION:

	Caspofungin 70/50 mg (N† = 41)		Caspofungin 100 mg (N† = 7)		Total (N† = 48)	
	n‡	(%)	n‡	(%)	n‡	(%)
PATIENTS ENTERED:						
Male (age range)	19	(21 to 73)	4	(40 to 76)	23	(21 to 76)
Female (age range)	22	(18 to 79)	3	(38 to 75)	25	(18 to 79)
COMPLETED THERAPY§:	**35**	**(85.4)**	**5**	**(71.4)**	**40**	**(83.3)**
DISCONTINUED THERAPY:	**6**	**(14.6)**	**2**	**(28.6)**	**8**	**(16.7)**
Clinical AE	4	(9.8)	0	(0.0)	4	(8.3)
Lack of efficacy	1	(2.4)	2	(28.6)	3	(6.3)
Patient withdrew consent	1	(2.4)	0	(0.0)	1	(2.1)
COMPLETED STUDY‖:	**28**	**(68.3)**	**4**	**(57.1)**	**32**	**(66.7)**
DISCONTINUED STUDY:	**13**	**(31.7)**	**3**	**(42.9)**	**16**	**(33.3)**
Clinical AE	6	(14.6)	2	(28.6)	8	(16.7)
Lack of efficacy	1	(2.4)	0	(0.0)	1	(2.1)
Patient lost to follow-up	3	(7.3)	1	(14.3)	4	(8.3)
Patient discontinued for other reason	2	(4.9)	0	(0.0)	2	(4.2)
Patient withdrew consent	1	(2.4)	0	(0.0)	1	(2.1)

† N = Number of patients in treatment regimen that received a dose of caspofungin study therapy.
‡ n = Number of patients either completing or discontinuing caspofungin study therapy or study.
§ "Completed Therapy" is defined as having a status of "patient continuing trial" on the last day of caspofungin study therapy.
‖ "Completed Study" is defined as completion of the 12-week posttherapy follow-up visit period.

DOSAGE/FORMULATION NOS.: Caspofungin 50 mg vials were reconstituted, prepared to the appropriate concentration, and infused as a single dose over approximately 1 hour. In general, patients received a 70-mg loading dose of caspofungin on Day 1, followed thereafter by 50 mg/day. However, patients with either *Candida* endocarditis, *Candida* meningitis, or *Candida* osteomyelitis/septic arthritis received caspofungin at 100 mg/day (without a loading dose).

DIAGNOSIS/INCLUSION CRITERIA: Men and women, 18 years or older, with both clinical and microbiological evidence of invasive candidiasis at a sterile, non-blood body site were eligible for enrollment, provided all other inclusion and exclusion criteria were fulfilled. In addition to those patients with newly diagnosed infections, patients who were refractory or intolerant of prior antifungal therapy were also eligible for enrollment. Electrocardiogram (ECG), chest X-ray, blood cultures, and laboratory safety studies were required prior to study entry.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: A detailed description and evaluation of the *Candida* infection, including body temperature and blood pressure evaluation and an overall clinical assessment, was performed at screening, daily while on antifungal therapy, the last day of antifungal therapy, and at the 3 predefined follow-up visits after completion of antifungal therapy. The investigator monitored the resolution or progression of each patient's *Candida* infection by assessment of signs and symptoms, radiographic studies, and, whenever possible, by follow-up cultures. Based on all available data, the efficacy assessment of the status of invasive candidiasis was made by the investigator at Day 10 of caspofungin therapy, the last day of caspofungin therapy, and the last day of all antifungal therapy (whether caspofungin or subsequent oral fluconazole). In addition, relapse assessments were also performed at the 3 follow-up visits following the completion of all antifungal therapy. Blood samples for

drug level assays collected from all patients performed pretreatment (trough) and within 5 minutes prior to the completion of the caspofungin dose (peak) on Days 1, 2, 4, 7, 14, and every 2 weeks thereafter (provided the patient was still receiving caspofungin therapy on those days).

SAFETY MEASUREMENTS: All patients were required to have a complete physical examination performed at pre-study, twice weekly throughout the caspofungin therapy period, Day 10 of caspofungin therapy, the last day of caspofungin therapy, the last day of all antifungal therapy (whether caspofungin or subsequent oral fluconazole), and at each of the 3 follow-up visits. Laboratory safety tests (hematology, coagulation, and blood chemistry) were performed at screening, twice weekly during caspofungin therapy, and for the 14-day post-caspofungin therapy period. The patients were monitored for clinical and laboratory adverse experiences throughout the caspofungin treatment period and up to 14-days post-caspofungin therapy period.

STATISTICAL PLANNING AND ANALYSIS: This study was analyzed as an estimation study with no formal statistical hypothesis testing. Each investigator independently evaluated the diagnosis of invasive candidiasis and assessed the efficacy based on definitions of response outlined in the protocol. The primary efficacy endpoint displayed is the proportion of caspofungin-treated patients with a favorable overall response (a favorable clinical response and a favorable microbiological response) at the end of caspofungin therapy. Other efficacy endpoints displayed are the proportion of caspofungin-treated patients: (1) with a favorable overall response rate on Day 10 of caspofungin therapy, (2) with a favorable overall response rate at the end of all antifungal therapy (caspofungin and/or subsequent oral fluconazole therapy), and (3) with relapse of the invasive *Candida* infection during the 12-week posttherapy follow-up period. Primary safety endpoints displayed are the proportion of caspofungin-treated patients: (1) who develop at least one serious, drug-related adverse experience during caspofungin therapy and the 14-day posttherapy period, (2) who develop at least one drug-related adverse experience during caspofungin therapy and the 14-day posttherapy period, (3) who develop at least one drug-related adverse experience that necessitates discontinuation of study therapy. Other safety variables of interest included the proportion of patients: (1) who died during the study, (2) with at least one moderate or severe local adverse event at the site of infusion, and (3) with at least one moderate or severe systemic infusion-related adverse event. Two patient populations were identified for the purpose of efficacy analyses: (1) the modified-intention-to-treat (MITT) population, and (2) the evaluable-patient population. The MITT population was defined as the primary patient population.

RESULTS: All 48 patients who entered into the study were included in the MITT patient population. Forty-one (85.4%) patients received caspofungin initially at 50 mg daily (following a 70-mg loading dose on Day 1). The remaining 7 (14.6%) patients initially received caspofungin at 100 mg daily (3 patients with *Candida* endocarditis and 4 patients with *Candida* osteomyelitis/septic arthritis). The mean age of the patients was 51.6 years, and approximately one-third of the patients were at least 65 years of age. The mean APACHE II score for the study was 14.3 (range 3 to 34), with the majority of the patients (83.3%) having an APACHE II score of ≤20 at study entry. Only 4 patients (8.3%) were neutropenic (ANC <500 cells/μL) at study entry. *Candida* peritonitis was the most common *Candida* infection (27.1%), followed by *Candida* intra-abdominal abscess (18.8%), and chronic disseminated (hepatosplenic) candidiasis (16.7%). Eight patients (16.7%) also had acutely disseminated or multiple infections at study entry. The majority of patients (60%) had an infection with *C. albicans*. Other common pathogens included *C. glabrata* (14%), *C. tropicalis* (8%), and *C. krusei* (5%). All 16 (33%) patients who received caspofungin as salvage therapy were refractory to prior antifungal therapy.

EFFICACY: The primary efficacy evaluation was the proportion of patients with a favorable overall response (favorable clinical and favorable microbiological response) at the end of caspofungin therapy. The proportion of patients with a favorable overall response at the end of caspofungin therapy was 39/48 (81.3%) in the MITT population and 37/42 (88.1%) in the evaluable-patient population.

Favorable responses were consistently high in the MITT patient population, even for high risk patients (i.e., 3/4 patients with neutropenia [success 75%] or 6/7 patients with a high APACHE II score [>20] at study entry [success 86%]). Favorable overall and microbiological responses were noted across all the different *Candida* species. Caspofungin was also effective in patients who were refractory to prior antifungal therapy; the majority (14/16 patients, 88%) of these patients had a favorable overall response at the end of caspofungin therapy.

The proportion of patients with a favorable overall response at Day 10 of caspofungin therapy was 68.8%. Additionally, 38 (79.2%) of the 48 patients had a favorable overall response at the end of all antifungal therapy. Of the 38 patients with a favorable overall response at the end of all antifungal therapy, 35 were evaluated for relapse during the follow-up period. The 3 excluded patients died shortly after their end-of-all-antifungal-therapy assessment, and none of the deaths in these 3 patients were attributed to *Candida* infection. None of the 35 patients included in the relapse assessment experienced a clinical relapse during the 12-week posthterapy follow-up period. However, 2 (5.7%) patients, one from each treatment regimen, developed a microbiological relapse.

SAFETY: There were 3 secondary safety objectives for this study, designed to estimate the following: (1) the development of serious, drug-related adverse experiences during caspofungin study therapy and in the 14 day posttherapy period, (2) the development of drug-related adverse experiences during caspofungin study therapy and in the 14 day posttherapy period, and (3) the development of drug-related adverse experiences that necessitated discontinuation of caspofungin study therapy. Notably, none of the patients in this study developed a serious drug-related adverse experience or were discontinued from caspofungin study therapy as a result of a drug-related adverse experience.

Clinical adverse experiences: Overall, 43 (89.6%) reported at least 1 clinical adverse experience during caspofungin therapy or during the 14-day posttherapy period. The most frequently reported clinical adverse experiences across the 2 caspofungin treatment regimens included pyrexia (fever, 27.1%), nausea (16.7%), pneumonia (12.5%), hypotension (12.5%), diarrhea (12.5%), and vomiting (12.5%). Nineteen (39.6%) patients reported one or more serious clinical adverse experiences while on caspofungin therapy or in the 14 days post-therapy. Nine (18.8%) patients died as a result of serious adverse experiences during this timeframe either due to the progression of their fungal infection or by other causes. Nine (18.8%) patients had at least 1 clinical adverse experience determined by the investigator to be at least possibly related to study therapy. The only drug-related adverse experience reported in ≥2 patients was vomiting (4.2%). None of the drug-related clinical adverse experiences were considered serious or led to discontinuation of study therapy.

	Caspofungin 70/50 mg (N = 41)		Caspofungin 100 mg (N = 7)		Total (N = 48)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With one or more adverse experiences	36	(87.8)	7	(100)	43	(89.6)
With no adverse experience	5	(12.2)	0	(0.0)	5	(10.4)
With drug-related adverse experiences[†]	8	(19.5)	1	(14.3)	9	(18.8)
With serious adverse experiences	16	(39.0)	3	(42.9)	19	(39.6)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Who died	7	(17.1)	2	(28.6)	9	(18.8)
Discontinued[‡] due to adverse experiences	4	(9.8)	0	(0.0)	4	(8.3)
Discontinued[‡] due to drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued[‡] due to serious adverse experiences	3	(7.3)	0	(0.0)	3	(6.3)
Discontinued[‡] due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)

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

[‡] Refers to discontinuation of caspofungin study therapy.

Laboratory Adverse Experiences: All 48 patients enrolled in this study had post-baseline laboratory tests. Of these patients, 29 (60.4%) experienced one or more laboratory adverse experiences and only 1 patient (2.1%) had a serious, non-fatal laboratory adverse experience. The most common laboratory adverse experience was a decrease in serum potassium, reported in 14 (29.2%) patients. The second most common laboratory adverse experience reported in 13 (27.1%) patients was elevations in alkaline phosphatase. Fourteen patients (29.2%) experienced at least 1 laboratory adverse experience which was determined by the investigator to be at least possibly related to caspofungin study therapy. None of the drug-related laboratory adverse experiences were considered serious or led to discontinuation of study therapy. The most common drug-related laboratory adverse events were decreased serum (blood) potassium (5 patients, 10.4%) and increased alkaline phosphatase (5 patients, 10.4%).

	Caspofungin 70/50 mg (N = 41)		Caspofungin 100 mg (N = 7)		Total (N = 48)	
	n	(%)‡	n	(%)‡	n	(%)‡
Number (%) of patients:						
With at least one lab test postbaseline	41		7		48	
With one or more adverse experiences	25	(61.0)	4	(57.1)	29	(60.4)
With no adverse experience	16	(39.0)	3	(42.9)	19	(39.6)
With drug-related adverse experiences†	13	(31.7)	1	(14.3)	14	(29.2)
With serious adverse experiences	1	(2.4)	0	(0.0)	1	(2.1)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued§ due to adverse experiences	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)
Discontinued§ due to serious adverse experiences	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)

† 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.

Other Safety Variables: Other specific safety variables, including adverse events at the local site of infusion, systemic infusion-related events, and adverse experiences in relation to gender, age, race, and duration of caspofungin therapy were also reviewed and their pattern was relatively similar across both dosage groups. Local and systemic adverse events were relatively uncommon in this study. Only 2 (4%) and 4 patients (8%) developed local and systemic adverse events, respectively. The occurrence of drug-related clinical or laboratory adverse experiences were generally similar among the different genders, races, and age groups. Additionally, the general pattern of adverse experiences was similar among patients receiving <28 and ≥28 days of caspofungin therapy. All drug-related clinical adverse experiences and all but 1 laboratory adverse experience reported in group receiving ≥28 days of caspofungin therapy occurred prior to Day 28. Adverse experiences and laboratory values were also carefully reviewed in the 2 patients who received concomitant caspofungin and cyclosporin A therapy. Overall, caspofungin was generally well tolerated in these 2 patients receiving concomitant therapy with cyclosporin A for a range of 15 to 26 days.

CONCLUSIONS: In patients with non-blood forms of invasive candidiasis receiving caspofungin either as primary or salvage therapy (at maintenance daily doses ranging between 50 and 100 mg daily): (1) Caspofungin therapy is effective in the treatment of non-blood forms of invasive candidiasis. Favorable overall responses are seen in all the different patient subgroups, including patients with high APACHE II scores, underlying neutropenia, or difficult-to-treat sites of infection (i.e., osteomyelitis and endocarditis); (2) Caspofungin monotherapy, when administered for up to 108 days, is generally well tolerated. Drug-related adverse experiences that are reported as serious or necessitate therapy discontinuation are not routinely encountered.

AUTHORS: ***PPD***
Medical Program Clinical Specialist
Clinical Research - Infectious Disease

PPD
Biometrician
Clinical Biostatistics & Research Decision Sciences

PPD
Senior Director
Clinical Research - Infectious Diseases