Study Synopsis

1. Proprietary Drug Name: CANCIDAS™	**2. Generic Drug Name:** Caspofungin acetate	**3. Therapeutic area/ indications:** Antifungal/ Pharmacokinetic study
4. Name of Sponsor/Company:	Merck & Co., Inc., Whitehouse Station, New Jersey, USA	
5. Title of Study:	A Multicenter, Open, Sequential Dose-Escalation Study to Investigate the Safety, Tolerability, and Pharmacokinetics of 2 Separate Doses of MK-0991 in Children With New Onset Fever and Neutropenia (Protocol 033)	
6. Study Investigators/Study Center(s):	Multicenter (8) in the United States	
7. Studied Period (years): *(Date of first enrollment) (date of last completed)* Jan-2001 to Dec-2002		**8. Phase of development:** IIa
9. Primary Hypothesis: 1) The Day 1 plasma caspofungin $AUC_{0\text{-}24\ hr}$ in children (ages 2 to 11 years) treated with a 50-mg/m^2 (maximum 70 mg/day) IV dose is similar to the Day 1 plasma caspofungin $AUC_{0\text{-}24\ hr}$ in adult controls treated with a single 50-mg IV dose (i.e., the ratio of geometric means [2 to 11 years old/adults] of $AUC_{0\text{-}24\ hr}$ lies within the interval [0.70, 1.50]). 2) The Day 1 plasma caspofungin $AUC_{0\text{-}24\ hr}$ in children (ages 12 to 17 years) treated with a 50-mg/m^2 (maximum 70 mg/day) IV dose is similar to the Day 1 plasma caspofungin $AUC_{0\text{-}24\ hr}$ in adult controls treated with a single 50-mg IV dose (i.e., the ratio of geometric means [12 to 17 years old/adults] of $AUC_{0\text{-}24\ hr}$ lies within the interval [0.70, 1.50]).		
10. Study Design/ Methodology:	Open, serial-panel, 2-dose study involving patients between the ages of 2 and 17 years. Clinically stable, immunocompromised children or adolescents with a history of underlying hematological or solid organ malignancies and documented fever received caspofungin at the onset of fever and neutropenia. While on caspofungin therapy, plasma pharmacokinetic samples were obtained.	
11. Number of Patients (planned and analyzed):		
ERROR! REFERENCE SOURCE NOT FOUND.**PATIENT DISPOSITION:**		

	Caspofungin 1.0 mg/kg, Age 2 to 11 Years (N†=7)		Caspofungin 1.0 mg/kg, Age 12 to 17 Years (N†=2)		Caspofungin 50 mg/m^2, Age 2 to 11 Years (N†=10)		Caspofungin 50 mg/m^2, Age 12 to 17 Years (N†=8)		Caspofungin 70 mg/m^2, Age 2 to 11 Years (N†=12)		Total (N†=39)	
	n‡	(%)	n‡	(%)	n‡	(%)	n‡	(%)	n‡	(%)	n‡	(%)
PATIENTS ENTERED												
Male	4	(57.1)	0	(0.0)	5	(50.0)	6	(75.0)	5	(41.7)	20	(51.3)
Female	3	(42.9)	2	(100.0)	5	(50.0)	2	(25.0)	7	(58.3)	19	(48.7)
COMPLETED THERAPY§	4	(57.1)	1	(50.0)	5	(50.0)	4	(50.0)	7	(58.3)	21	(53.8)
DISCONTINUED THERAPY	3	(42.9)	1	(50.0)	5	(50.0)	4	(50.0)	5	(41.7)	18	(46.2)
Clinical adverse experience	2	(28.6)	0	(0.0)	3	(30.0)	0	(0.0)	1	(8.3)	6	(15.4)
Patient discontinued for other reason	1	(14.3)	1	(50.0)	2	(20.0)	4¶	(50.0)	4	(33.3)	12	(30.8)
COMPLETED STUDY‖	7	(100.0)	2	(100.0)	10	(100.0)	8	(100.0)	12	(100.0)	39	(100.0)
DISCONTINUED STUDY	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† N= Number of patients in the treatment group.
‡ n = Number of patients in subgroup.
§ "Completed Therapy" is defined as having a visit 3.0 status of "patient continuing in trial."
‖ "Completed Study" is defined as completion of the 14 Day Follow-up visit period.
¶ The 1 patient (AN 7531) was listed as discontinuing for lack of efficacy as a result of the development of fungal pneumonia. Of note, the pneumonia was also considered a clinical adverse experience.

12. Diagnosis and main criteria for inclusion:	Children (2 to 11 years of age) and adolescents (12 to 17 years of age) with a medical history of underlying hematological or solid organ malignancies, bone marrow or peripheral stem cell transplantation, or aplastic anemia were enrolled if they had an ANC <500/mm^3 and a temperature >38.0°C within 24 hours of screening. Study therapy needed to be administered within 48 hours of the onset of empirical antibacterial therapy for this episode of febrile neutropenia.
13. Test product and reference therapy (if applicable); dose and mode of administration; batch number:	IV caspofungin at a daily dose of 1 mg/kg, 50 mg/m^2, or 70 mg/m^2. Study drug was infused over ~1 hour (Formulation Number: MK-0991-HLS012B005).
14. Duration of treatment:	Patients were allowed to continue on study therapy with caspofungin until the recovery of neutropenia (absolute neutrophil count [ANC] post nadir value ≥250/mm^3). In general, patients were to be treated for a minimum of 4 days and a maximum of 28 days.
15. Criteria for Evaluation:	At each of the dosing regimens, full (7-point) plasma samples were collected on Day 1, Day 4, and, if applicable, Day 9 of study therapy. Pharmacokinetic parameters, including $AUC_{0\text{-}24\ hr}$, peak ($C_{1\ hr}$), and trough ($C_{24\ hr}$) concentrations and half-life determinations, were evaluated on all pediatric patients and compared relative to adult controls from the Phase II esophageal/oropharyngeal candidiasis studies (Protocols 003,

	004, and 007).
16. Statistical methods:	Methods: The Day 1 $AUC_{0\text{-}24\ hr}$ values for children (2 to 11 years), adolescents (12 to 17 years), and adults (pooled from Protocols 004 and 007) were natural log-transformed and evaluated in an analysis of variance (ANOVA) model having one 5-level factor identifying age and dose. A 95% CI for the difference in Day 1 $AUC_{0\text{-}24\ hr}$ means (adolescents at 50 mg/m^2 − adults at 50 mg) were calculated using the mean square error from the ANOVA and referencing a t-distribution with 87 degrees of freedom. These limits were exponentiated to obtain the 95% CI for the ratio of Day 1 $AUC_{0\text{-}24\ hr}$ geometric means (adolescents at 50 mg/m^2 to adults at 50 mg). The 95% CI for the ratio of Day 1 $AUC_{0\text{-}24\ hr}$ geometric means for the other comparisons were calculated in similar fashion.
17. Summary:	

RESULTS:

Pharmacokinetics (Weight-based Dosing): An exploratory comparison of the pharmacokinetics in children (ages 2 to 11 years) receiving caspofungin 1.0 mg/kg/day and adults receiving caspofungin 50 mg/day is in the following table:

Parameter	Pediatric Patients (Ages 2 to 11 Years) N	Pediatric Patients (Ages 2 to 11 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)	6	41.53 (34.12, 50.55)	32	70.60 (64.84, 76.87)	0.59	(0.47, 0.73)
$C_{1\ hr}$ (µg/mL)	6	6.59 (5.33, 8.15)	38	7.67 (7.05, 8.35)	0.86	(0.68, 1.08)
$C_{24\ hr}$ (µg/mL)	7	0.45 (0.34, 0.59)	33	1.35 (1.19, 1.53)	0.33	(0.24, 0.45)
β-phase $t_{½}$ (hr)	6	7.42 (1.23)‡	6	11.70 (2.92)‡	--	--
Day 3 to 14 Time-Averaged§						
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	7	56.33 (45.72, 69.39)	38	103.38 (94.52, 113.06)	0.54	(0.43, 0.68)
$C_{1\ hr}$ (µg/mL)	7	8.38 (6.83, 10.29)	38	9.39 (8.59, 10.25)	0.89	(0.71, 1.12)
$C_{24\ hr}$ (µg/mL)	7	0.63 (0.47, 0.85)	60	2.01 (1.82, 2.22)	0.31	(0.23, 0.43)
β-phase $t_{½}$ (hr)	7	8.18 (0.96)‡	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.

Pharmacokinetics (BSA Dosing in Children 2 to 11 Years): The pharmacokinetics in children (ages 2 to 11) receiving caspofungin 50 mg/m^2/day and adults receiving caspofungin 50 mg/day are compared in the following table:

Parameter	Pediatric Patients (Ages 2 to 11 Years) 50 mg/m^2/day N	Pediatric Patients (Ages 2 to 11 Years) 50 mg/m^2/day LSM (95% CI)†	Historical Adult Controls (Protocols 003, 004 and 007) 50 mg/day N	Historical Adult Controls (Protocols 003, 004 and 007) 50 mg/day LSM (95% CI)†	GMR (95% CI)† (Pediatric/Adult)	
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.

Pharmacokinetics (BSA Dosing in Adolescents 12 to 17 Years): The pharmacokinetics in adolescents (ages 12 to 17) receiving caspofungin 50 mg/m^2/day and adults receiving caspofungin 50 mg/day are compared in the following table:

Parameter	Pediatric Patients (Ages 12 to 17 Years) 50 mg/m^2/day N	Pediatric Patients (Ages 12 to 17 Years) 50 mg/m^2/day LSM (95% CI)†	Historical Adult Controls (Protocols 003, 004 and 007) 50 mg/day N	Historical Adult Controls (Protocols 003, 004 and 007) 50 mg/day 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.

Safety:

Clinical Adverse Experience Summary

Number (%) of Patients	Caspofungin 1.0 mg/kg, Age 2 to 11 Years (N†=7) n‡	(%)	Caspofungin 1.0 mg/kg, Age 12 to 17 Years (N†=2) n‡	(%)	Caspofungin 50 mg/m^2, Age 2 to 11 Years (N†=10) n‡	(%)	Caspofungin 50 mg/m^2, Age 12 to 17 Years (N†=8) n‡	(%)	Caspofungin 70 mg/m^2, Age 2 to 11 Years (N†=12) n‡	(%)	Total (N†=39) n‡	(%)
With one or more clinical adverse experiences (AEs)	7	(100.0)	1	(50.0)	9	(90.0)	8	(100.0)	12	(100.0)	37	(94.9)
With no AE	0	(0.0)	1	(50.0)	1	(10.0)	0	(0.0)	0	(0.0)	2	(5.1)
With drug-related AEs§	0	(0.0)	0	(0.0)	1	(10.0)	2	(25.0)	2	(16.7)	5	(12.8)
With serious AEs	1	(14.3)	0	(0.0)	2	(20.0)	5	(62.5)	3	(25.0)	11	(28.2)
With serious drug-related AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	1	(2.6)
Discontinued due to AEs	2	(28.6)	0	(0.0)	3	(30.0)	1	(12.5)	1	(8.3)	7	(17.9)
Discontinued due to drug-related AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious AEs	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	1	(2.6)
Discontinued due to serious drug-related AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† N = Number of patients in treatment group that received a dose of study therapy.
‡ n = Number of patients with a clinical adverse experience.
§ Determined by the investigator to be possibly, probably, or definitely drug related.

Laboratory Adverse Experience Summary

Number (%) of Patients	Caspofungin 1.0 mg/kg, Age 2 to 11 Years (N†=7) n‡	(%)	Caspofungin 1.0 mg/kg, Age 12 to 17 Years (N†=2) n‡	(%)	Caspofungin 50 mg/m^2, Age 2 to 11 Years (N†=10) n‡	(%)	Caspofungin 50 mg/m^2, Age 12 to 17 Years (N†=8) n‡	(%)	Caspofungin 70 mg/m^2, Age 2 to 11 Years (N†=12) n‡	(%)	Total (N†=39) n‡	(%)
With at least one laboratory test postbaseline	7		2		10		8		12		39	
With one or more adverse experiences (AEs)	2	(28.6)	1	(50.0)	3	(30.0)	4	(50.0)	5	(41.7)	15	(38.5)
With no AE	5	(71.4)	1	(50.0)	7	(70.0)	4	(50.0)	7	(58.3)	24	(61.5)
With drug-related AEs§	0	(0.0)	0	(0.0)	0	(0.0)	2	(25.0)	0	(0.0)	2	(5.1)
With serious AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
With serious drug-related AEs	0	(0.0)	0	(0.0)	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)	0	(0.0)	0	(0.0)
Discontinued due to AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to drug-related AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† N = Number of patients in each treatment group.
‡ n = Number of patients meeting this criteria.
§ Determined by the investigator to be possibly, probably, or definitely drug related.

18. Date of the report: 01-Feb-08

19. Contact: Sponsor National Service Center

1.800.672.6372