

TABLE OF CONTENTS

	<u>PAGE</u>
LIST OF TABLES	5
LIST OF FIGURES	10
1. Introduction and Organization of Document	11
2. Synopsis	12
2.1 Introduction	12
2.2 Preclinical Safety (Section 3)	13
2.3 Preclinical Microbiology (Section 4)	13
2.4 Pharmacokinetics (Section 5)	14
2.5 Clinical Efficacy (Section 6)	14
2.6 Clinical Safety (Section 7)	16
2.7 Summary of Benefits and Risks	17
2.8 Conclusions	18
3. Preclinical Pharmacotoxicology of Caspofungin	20
3.1 Introduction	20
3.2 Preclinical Safety Evaluation of Metabolites, Impurities, and Degradates	20
3.3 Acute Toxicity Studies	21
3.4 Subacute and Chronic Toxicity Studies	21
3.4.1 Treatment-Related Findings	22
3.4.1.1 Signs of Histamine Release	22
3.4.1.2 Injection Site Irritation	22
3.4.1.3 Elevations in Serum Transaminase Values	23
3.4.2 Pharmacokinetic/Toxicokinetic Data	24
3.4.3 Irreversible Plasma Protein Binding	25
3.5 Reproductive Toxicology and Embryo-Fetal/Perinatal Toxicology	26
3.5.1 Reproductive Toxicology	26
3.5.2 Embryo-Fetal and Perinatal Toxicology	26
3.6 Genetic Toxicology	27
3.7 Carcinogenic Potential	27
3.8 Local Tolerance	27
3.9 Other Information	28
3.10 Conclusions	28
4. Microbiology	30
4.1 Introduction	30
4.2 Mechanism of Action	30
4.3 In Vitro Activity of Caspofungin on <i>Aspergillus</i> spp.	31
4.4 In Vitro Susceptibility Testing of Caspofungin Against <i>Aspergillus</i> spp.	32
4.4.1 Laboratory Clinical Isolates	32
4.4.2 <i>Aspergillus</i> Isolates From Caspofungin Clinical Trials	33

TABLE OF CONTENTS (CONT.)

	<u>PAGE</u>
4.5 In Vivo Activity of Caspofungin Against <i>A. fumigatus</i>	34
4.5.1 Disseminated Aspergillosis in Complement-Deficient and Neutropenic Mice	35
4.5.2 Disseminated Aspergillosis in Pancytopenic Mice	36
4.5.3 Pulmonary Aspergillosis in Immune Compromised Rats	38
4.6 Conclusions—Activity of Caspofungin Against <i>Aspergillus</i> spp.	39
4.7 In Vitro Activity of Caspofungin Against <i>Candida</i> spp.	39
4.7.1 Evaluation of Caspofungin Against Laboratory Yeast Isolates	40
4.7.2 Evaluation Against <i>Candida</i> spp. Clinical Trial Isolates	40
4.7.3 Time-Kill Curve Studies Against <i>Candida</i> spp.	41
4.7.4 Susceptibility of Antifungal-Resistant Isolates to Caspofungin	42
4.8 Animal Models of Infections With <i>Candida</i> spp.	43
4.9 Conclusions—Activity of Caspofungin Against <i>Candida</i> spp.	45
4.10 Resistance to Caspofungin	46
4.11 Drug Combination Studies	46
4.12 In Vitro Activity of Caspofungin Against Other Filamentous and Dimorphic Fungi	47
4.13 Conclusions	48
5. Pharmacokinetics and Metabolism	50
5.1 Overview	50
5.2 Drug Formulation	51
5.3 Nonclinical Pharmacokinetics	51
5.3.1 Disposition Kinetics	51
5.3.2 Distribution	51
5.3.3 Metabolism and Excretion	52
5.4 Pharmacokinetics in Healthy Subjects	53
5.4.1 In Vivo Fate of [³ H]Caspofungin	53
5.4.1.1 Distribution	54
5.4.1.2 Metabolism	56
5.4.1.3 Excretion	56
5.4.2 Single-Dose Pharmacokinetics in Healthy Subjects	56
5.4.3 Multiple-Dose Pharmacokinetics in Healthy Subjects	57
5.4.3.1 Steady State	57
5.4.3.2 Loading Dose	60
5.5 Pharmacokinetics in Patients With Fungal Infections	60
5.5.1 Definition of a Clinically Significant Alteration in Caspofungin Pharmacokinetics	61
5.6 Special Populations	62
5.6.1 Effect of Age and Gender	62
5.6.2 Renal Insufficiency	63

TABLE OF CONTENTS (CONT.)

	<u>PAGE</u>
5.6.3 Hepatic Insufficiency	64
5.6.4 Other Covariates From Population Pharmacokinetic Studies	65
5.7 Drug-Drug Interactions	65
5.7.1 Itraconazole	66
5.7.2 Amphotericin B	67
5.7.3 Cyclosporin A	67
5.7.4 Tacrolimus	69
5.7.5 Mycophenolate	69
5.7.6 Other Concomitant Medications in Population Pharmacokinetic Studies	69
5.8 Conclusions: Pharmacokinetics and Metabolism	70
6. Clinical Efficacy	72
6.1 Overview of the Caspofungin Clinical Development Program	72
6.2. Rationale for Dose Selection for Phase IIb/III Studies	79
6.3. Invasive Aspergillosis Studies	81
6.3.1 Efficacy of Caspofungin in Patients With <i>Aspergillus</i> Infections Who Are Refractory to or Intolerant of Standard Therapies (Protocol 019)	81
6.3.2 Demographics and Baseline Characteristics of Patients Enrolled in the Noncomparative <i>Aspergillus</i> Study (Protocol 019)	83
6.3.3 Efficacy Results in the Noncomparative <i>Aspergillus</i> Study (Protocol 019)	86
6.3.4 Efficacy of Caspofungin in 11 Additional Patients in the Noncomparative <i>Aspergillus</i> Study (Protocol 019)	91
6.3.5 Summary of Caspofungin Efficacy in the Noncomparative <i>Aspergillus</i> Study (Protocol 019)	92
6.3.6 Efficacy of Caspofungin in Patients With <i>Aspergillus</i> Infections Treated Under Compassionate Use (Protocol 024/025)	98
6.3.7 Efficacy Summary of Caspofungin in the Treatment of IA in Noncomparative or Compassionate Use Studies	99
6.3.8 Historical Data on Invasive Aspergillosis	99
6.3.9 Comparison of Patients in Protocol 019 to Patients in Protocol 028/029	104
6.3.10 Summary of Efficacy of Caspofungin in the Treatment of IA	114
6.4 Efficacy of Caspofungin in Esophageal and Oropharyngeal Candidiasis	115
6.4.1 Clinical Efficacy Studies of Caspofungin in Oropharyngeal and Esophageal Candidiasis (Protocols 003, 004, and 007)	115

TABLE OF CONTENTS (CONT.)

	<u>PAGE</u>
6.4.2 Demographics and Other Characteristics of the Patients Enrolled in the Phase II <i>Candida</i> Studies (Protocols 003, 004, and 007)	116
6.4.3 Efficacy of Caspofungin in the Phase II <i>Candida</i> Esophagitis Studies (Protocols 003, 004, 007)	116
6.4.4 Efficacy of Caspofungin in Oropharyngeal Candidiasis	121
6.4.5 Microbiology	121
6.4.6 Subgroup and Treatment by Factor Analysis	123
6.4.7 Summary of Clinical Efficacy Results in Patients With Oropharyngeal and Esophageal Candidiasis	123
6.5 Concentration-Effect Relationship for Treatment Outcome	124
7. Clinical Safety	125
7.1 Introduction	125
7.2 Overall Extent of Exposure of the Study Population	127
7.3 Overview of Safety Results	129
7.4 Clinical Pharmacology (Phase I) Studies	130
7.5 Clinical Safety in Patients with <i>Candida</i> Infections	136
7.6 Clinical Safety in Patients with <i>Aspergillus</i> Infections	149
7.7 Serious Adverse Experiences From Sources Other Than Case Report Forms	160
7.8 Drug-Drug Interactions in Clinical Studies	161
7.9 Drug-Demographic Interactions in Clinical Studies	162
7.10 Drug-Disease Interactions in Clinical Studies	162
7.11 Potential Risks Based on Structure/Chemical Properties	162
7.12 Concentration-Effect Relationship for Adverse Experiences	163
7.13 Overdose and Abuse	164
7.14 Safety Conclusions	164
8. Recommended Caspofungin Dosing Information for Patients With Invasive Aspergillosis	165
8.1 Conclusions	167
9. Summary of Benefits and Risks	168
10. Conclusions	172
10.1 Pharmacotoxicology Conclusions	172
10.2 Microbiology Conclusions	172
10.3 Pharmacokinetics Conclusions	173
10.4 Clinical Efficacy Conclusions	174
10.5 Clinical Safety Conclusions	175
10.6 Recommended Dosing Conclusions	176
References	--

LIST OF TABLES

		<u>PAGE</u>
Table 1	Caspofungin: Subacute and Chronic Toxicity Studies	21
Table 2	Caspofungin: 5-Week Intravenous Toxicity Study in Monkeys (TT #94-638-0) Average Values and % Increase in Transaminase Relative to Controls	23
Table 3	Caspofungin AUC Data ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	25
Table 4	Susceptibility (MIC) of <i>Aspergillus</i> spp. Isolates to Caspofungin	33
Table 5	Caspofungin Susceptibility Data Against <i>Aspergillus</i> Clinical Isolates Determined in RPMI-1640 and AM-3 Media	34
Table 6	Efficacy of Caspofungin and Amphotericin B Against a Disseminated <i>A. fumigatus</i> MF5668 Infection in Monoclonal Antibody Induced-Granulocytopenic C3H/HeN mice	36
Table 7	Efficacy (Survival ED ₅₀) against Disseminated Aspergillosis in Cytoxan-Treated Mice	37
Table 8	Disseminated Aspergillosis in Chronically Pancytopenic ICR Mice Day 28 Survival following Caspofungin or AmB Therapy	38
Table 9	Survival Study—Pulmonary Aspergillosis in Dexamethasone Treated Sprague-Dawley Rats—Treatment and Prophylaxis	39
Table 10	Susceptibility (MIC ₉₀) of Clinical Isolates to Caspofungin	40
Table 11	Caspofungin Susceptibility (MIC ₅₀ and MIC ₉₀) of Candida Clinical Trial Isolates Determined in RPMI-1640 and AM-3 Medi Medium	41
Table 12	In Vitro Killing Rates Against <i>C. Albicans</i>	42
Table 13	Suceptibility (MIC) of Selected Antifungal-Resistant Yeast Isolates	43
Table 14	Disseminated Candidiasis in Chronically Pancytopenic ICR Mice Log ₁₀ Reduction of Kidney Fungal Burden	44
Table 15	Disseminated Candidiasis in Chronically Pancytopenic ICR Mice Percentage of Mice With Kidney Tissue Sterilization	45

LIST OF TABLES (CONT.)		<u>PAGE</u>
Table 16	Efficacy Against a Disseminated <i>A. fumigatus</i> Infection in DBA/2N Mice Comparison of Therapy With Caspofungin Alone and in Combination With AmB	47
Table 17	Susceptibility of Other Filamentous Fungi to Caspofungin	48
Table 18	Susceptibility of Other Dimorphic Fungi Sensitive to Caspofungin	48
Table 19	Geometric Mean (90% CI) Plasma Pharmacokinetics of Caspofungin Following Daily 1-Hour Infusions to Young Healthy Men	59
Table 20	Summary of Results From Special Population Studies of Caspofungin Pharmacokinetics	62
Table 21	Summary of Results From Drug Interaction Studies	66
Table 22	Clinical Studies Supporting Caspofungin Efficacy	73
Table 23	Baseline Patient Characteristics for Patients Enrolled in the Noncomparative <i>Aspergillus</i> Study (Protocol 019)	85
Table 24	Distribution of Final Diagnoses of <i>Aspergillus</i> Infections As Determined by the Expert Panel (Protocol 019)	87
Table 25	Distribution of Patients by Treatment Reason and Prior Antifungal Treatment Expert Panel Assessment (Protocol 019)	88
Table 26	Patients Outcomes by Demographics and Disease Characteristics Protocol 019 Expert Panel Assessment	90
Table 27	Distribution of Final Diagnoses of <i>Aspergillus</i> Infections As Determined by the Expert Panel (Protocol 019)	94
Table 28	Distribution of Patients by Treatment Reason and Prior Antifungal Treatment Expert Panel Assessment (Protocol 019)	95
Table 29	Patients Outcomes by Demographics and Disease Characteristics Protocol 019 Expert Panel Assessment	97
Table 30	Baseline Patient Characteristics for Clinical Studies of <i>Aspergillus</i> Infections (Protocols 019, 028/029)	106
Table 31	Distribution of Patients by Primary Background Condition	107

LIST OF TABLES (CONT.)		<u>PAGE</u>
Table 32	Distribution of Patients With a Diagnosis of <i>Aspergillus</i> Infection	108
Table 33	Proportion of Patients With a Favorable Overall Response at End of Antifungal Therapy	109
Table 34	Proportion of Patients With a Favorable Response by Specific Extrapulmonary Infection Site	110
Table 35	Proportion of Patients With a Favorable Response by Underlying Disease	110
Table 36	Proportion of Patients' With a Favorable Response by Specific Hematologic Malignancy and Underlying Condition	111
Table 37	Proportion of Patients With a Favorable Response by Neutropenic Status and by Corticosteroid Use at Baseline	112
Table 38	Summary of Logistic Regression Analyses for the Comparison of Efficacy Between Protocol 019 and Protocol 028/029	114
Table 39	Baseline Patient Characteristics of Phase II Oropharyngeal and Esophageal Candidiasis Studies by Protocol	117
Table 40	Proportion (%) of Esophageal Patients With a Favorable Overall Response in the Modified Intent-to-Treat Analysis by Protocol	120
Table 41	Proportion (%) of Esophageal Patients With a Favorable Overall Response in the Evaluable-Patients Analysis by Protocol	120
Table 42	Duration of Caspofungin Treatment by Daily Dose for Phase I Studies	127
Table 43	Duration of Caspofungin Therapy by Dose for All Caspofungin Clinical Studies	128
Table 44	Clinical Adverse Experience Summary by Treatment Group for Phase I Studies	130
Table 45	Laboratory Adverse Experience Summary by Treatment Group for Phase I Studies	132

LIST OF TABLES (CONT.)		<u>PAGE</u>
Table 46	Number (%) of Subjects With Alanine or Aspartate Aminotransferase Laboratory Adverse Experiences in Phase I Studies	134
Table 47	Baseline Patient Characteristics by Disease and Therapy Group for All Completed Clinical Studies of <i>Candida</i> Infections (Protocols 003, 004, 007, and 020)	137
Table 48	Clinical Adverse Experience Summary by Treatment Group for Controlled Clinical Studies in <i>Candida</i> Infections (Protocols 003, 004, and 020)	138
Table 49	Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence $\geq 5.0\%$ in One or More Treatment Groups) by Body System in Controlled Clinical Studies for <i>Candida</i> Infections (Protocols 003, 004, and 020) Total and Drug Related	140
Table 50	Laboratory Adverse Experience Summary by Caspofungin Dose for Controlled Clinical Studies in <i>Candida</i> Infections (Protocols 003, 004, and 020)	144
Table 51	Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence $\geq 5.0\%$ in One or More Treatment Groups) by Laboratory Test Category in Controlled Clinical Studies for <i>Candida</i> Infections (Protocols 003, 004, and 020) Total and Drug Related	146
Table 52	Clinical Adverse Experience Summary by Caspofungin Dose in a Noncomparative <i>Aspergillus</i> Study (Protocol 019)	150
Table 53	Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence $\geq 5.0\%$) in a Noncomparative <i>Aspergillus</i> Study (Protocol 019) Total and Drug Related	151
Table 54	Laboratory Adverse Experience Summary in a Noncomparative <i>Aspergillus</i> Study (Protocol 019)	154
Table 55	Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence $\geq 5.0\%$) by Laboratory Test Category in a Noncomparative <i>Aspergillus</i> Study (Protocol 019) Total and Drug Related	156

Caspofungin Acetate
FDA Advisory Committee Meeting Background

-9-

LIST OF TABLES (CONT.)

		<u>PAGE</u>
Table 56	Number (%) of Patients With Increased Alanine or Aspartate Aminotransferase Laboratory Adverse Experiences in Caspofungin Clinical Studies	159

LIST OF FIGURES

		<u>PAGE</u>
Figure 1	In Vitro Effects of Caspofungin on <i>A. fumigatus</i> Using a Viability Stain	Insert
Figure 2	In Vitro Effects of Caspofungin on <i>A. fumigatus</i> Using Mortality Stain	Insert
Figure 3	Mean Plasma Profiles of Caspofungin and Total Radioactivity Following Administration of a Single 70-mg (200- μ Ci) Dose of [3 H]Caspofungin to Healthy Male Subjects	54
Figure 4	Mean Distribution and Excretion Profiles of Radioactivity Following Administration of a Single 70-mg (200- μ Ci) Dose of [3 H]Caspofungin to Healthy Male Subjects (n=6)	55
Figure 5	Mean Trough Concentrations of Caspofungin Following Multiple Daily 1-Hour Intravenous Infusions of 15 to 70 mg to Healthy Men	58
Figure 6	Mean Trough Concentrations in Men Receiving 50 mg Caspofungin Daily With or Without a 70-mg Loading Dose on Day 1	60
Figure 7	Individual Pharmacokinetic Values Versus Estimated Creatinine Clearance in Aspergillosis Patients Receiving 70 mg on Day 1 Followed by 50 mg Daily	64
Figure 8	Mean (SD) Plasma Concentration Profiles From 10 th Day of 70-mg Caspofungin (MK-0991) Daily Alone or Coadministered With a Single Dose (4 mg/kg) of Cyclosporin A (CsA)	68
Figure 9	Accounting of Protocol 019 Patients	83
Figure 10	Partition of Historical Control Patient Populations	103

1. Introduction and Organization of Document

Caspofungin is a glucan synthesis inhibitor that has been developed for the treatment of invasive and localized fungal infections. The overall objective of the clinical development program for caspofungin is to evaluate the efficacy and safety of caspofungin in the treatment of patients with documented *Aspergillus* or *Candida* infections.

This document focuses primarily on the development program for caspofungin for the treatment of invasive aspergillosis (IA) in patients who are refractory to or intolerant of other therapies. Because data in IA have been obtained from a noncomparative study, the objective in this specific setting was to demonstrate efficacy in patients with limited therapeutic alternatives in the context of a comparison to a historical control group treated with standard antifungal therapy.

The study results described in this document confirm that caspofungin is effective in the treatment of IA in patients who are refractory to or intolerant of other therapies. The benefit of caspofungin is unchanged when the results are compared to the efficacy of standard antifungal therapy in a historical control group. The overall safety and tolerability of caspofungin is favorable even in seriously ill patients.

This document is organized as follows:

Section 1. Introduction to the Document.

Section 2. Synopsis.

Section 3. Preclinical Pharmacotoxicology of Caspofungin. This section describes the preclinical studies of caspofungin.

Section 4. Preclinical Microbiology. This section outlines the *in vitro* and *in vivo* evaluation of caspofungin against a variety of fungal pathogens.

Section 5. Pharmacokinetics. This section describes the pharmacokinetic profile, metabolism, drug interaction and population pharmacokinetic results from preclinical studies and clinical studies in subjects and patients.

Section 6. Clinical Efficacy. This section details the data in patients with IA who are refractory to or intolerant of other therapies. Supportive efficacy in the treatment of documented fungal infections is also provided from the controlled Phase II studies in esophageal and oropharyngeal candidiasis. Rationale for Dose Selection for Phase III is also included within this section.

Section 7. Clinical Safety. This section details the general findings in the clinical pharmacology studies as well as in the noncomparative *Aspergillus* and controlled *Candida* Studies.

Section 8. Recommended Caspofungin Dosing Information.

Section 9. Summary of Benefits and Risks.

Section 10. Conclusions.

2. Synopsis

2.1 Introduction

Caspofungin (CANCIDAS™ [caspofungin acetate], MK-0991), an echinocandin, is a member of a new class of antifungals that demonstrates potent noncompetitive inhibition of the synthesis of $\beta(1,3)$ -D glucan, a critical component of the fungal cell wall. This mechanism of action is distinct from the currently available classes of antifungal agents (polyenes and azoles), which both act against the fungal cell membrane.

The ongoing development program for caspofungin includes studies designed to evaluate the efficacy and safety of caspofungin in documented *Aspergillus* and *Candida* infections as well as in empiric therapy of neutropenic patients. This document describes the results of the development program supporting the proposed indication for caspofungin:

“CANCIDAS™ is indicated for the treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.”

The recommended dose for this indication is 50 mg daily following one 70-mg dose on Day 1.

Invasive Aspergillosis (IA) is a serious disease which has been observed with increasing frequency in immunocompromised patients. The mortality rate due to invasive aspergillosis remains 40 to 90%, despite the introduction of itraconazole and the lipid formulations of amphotericin B. In addition, there are potential dose limiting toxicities associated with use of amphotericin B. Thus, there is a clear need for alternative therapies for treatment of this disease.

Due to the relative rarity of IA and the significant mortality associated with this disease, a noncomparative study design was chosen to evaluate the clinical efficacy and safety of caspofungin in patients with documented IA. In order to obtain the best interpretable data from such a study design, several features were included in the Noncomparative *Aspergillus* Study design. These included: use of strict definitions of disease (based on Mycoses Study Group [MSG] criteria), documentation of disease and outcome, and review of study data by an independent panel of experts. In addition, the efficacy results from the noncomparative trial were put into perspective by a predefined comparison to the results of an Historical Control Study (Protocol 028/029), conducted at many of the same sites enrolling patients in the Noncomparative *Aspergillus* Study.

Preliminary efficacy results from the Noncomparative *Aspergillus* Study (Protocol 019) together with a favorable safety profile demonstrated in both patients with IA and with localized *Candida* infections led to FDA concurrence with a “fast-track” designation for caspofungin. Subsequent results which have demonstrated a 41.3% overall favorable response rate in patients with IA who are refractory to or intolerant of other therapies strongly support the efficacy of caspofungin for use in this patient population. In addition, safety data from the IA patients as well as from patients in the completed, comparator-controlled and blinded *Candida* studies support the safety and tolerability of

casposfungin and show that the safety profile for casposfungin appears to be more favorable than Amphotericin B.

The purpose of this synopsis is to highlight the key conclusions from the casposfungin development program that are summarized in this document.

2.2 Preclinical Safety (Section 3)

The potential toxicity of casposfungin has been evaluated in an extensive series of in vitro and in vivo studies, including genetic toxicity studies, single dose toxicity studies in mice and rats, repeated dose toxicity studies in rats and rhesus monkeys (up to 27 weeks duration), and developmental and reproductive toxicity studies in rats and rabbits.

Casposfungin is not genotoxic or mutagenic. There were no findings in the developmental and reproductive toxicity studies that would indicate a significant risk for women of childbearing potential. The treatment-related changes which have been observed in the repeated dose toxicity studies are: mild elevations in serum transaminases observed only in monkeys; signs of histamine release with bolus injections (rats and monkey); and irritation and thrombosis at the site of injection (rats and monkeys). None of these findings represent a contraindication to the use of casposfungin in humans.

2.3 Preclinical Microbiology (Section 4)

Casposfungin exhibits activity against *Aspergillus* spp. and *Candida* spp. in vitro and in several animal models.

Determination of activity against *Aspergillus* spp. was initially demonstrated by showing a gross morphological change in *Aspergillus* hyphae in vitro after exposure to casposfungin (minimum effective concentration) that correlated with efficacy in animal models and subsequently correlated with a minimum inhibitory concentration (MIC) in standard microbroth dilution testing. The MIC₉₀ of casposfungin against *Aspergillus* spp. tested ranged from 0.20 to 0.50 µg/mL. Casposfungin was tested in several murine models of disseminated aspergillosis including C'5 deficient, granulocytopenic, and cyclophosphamide-treated pancytopenic mice. Casposfungin demonstrated efficacy comparable to amphotericin B as assessed by percent survival in all models tested. Due to the difficulties in developing and standardizing methodologies for testing this new class of agents, it remains uncertain as to whether casposfungin is fungistatic or fungicidal against *Aspergillus* spp.

Casposfungin exhibits activity against *Candida* spp, including non-albicans *Candida* spp., corroborating the antifungal activity of this drug. As might be expected based on its unique mechanism of action, casposfungin was active (with MIC values ≤2 µg/mL) against a panel of amphotericin B, flucytosine, and fluconazole-resistant isolates. Casposfungin was also effective against *Candida* infections in several murine models, including cyclophosphamide-treated pancytopenic mice, when endpoints of tissue sterilization and survival were used. The ability of casposfungin to sterilize tissues and prolong survival was comparable to amphotericin B, consistent with data from in vitro studies indicating that casposfungin is fungicidal against *Candida* spp.

2.4 Pharmacokinetics (Section 5)

Caspofungin is administered only by intravenous infusion. Metabolism and excretion are not the rate-controlling steps in the clearance of caspofungin from plasma. Plasma clearance for caspofungin is determined primarily by the rate of distribution of caspofungin from plasma into tissues.

The major metabolic pathways of caspofungin are peptide hydrolysis and *N*-acetylation. There is a low level of irreversible plasma protein binding (≤ 7 pmol/mg protein in humans) following a single dose administration of caspofungin. In vitro experiments suggest that the irreversible binding is caused by intermediates generated from spontaneous chemical degradation of caspofungin to a hydrolytic product, L-747969. Renal clearance of unchanged caspofungin constitutes a minor pathway of elimination.

The results from Phase I studies as well as population pharmacokinetics analyses showed that no dose adjustments are necessary in the elderly or on the basis of gender or race. No dosage adjustment is recommended for patients with mild to end-stage renal insufficiency and there is no need for a supplementary dose after dialysis since caspofungin is not cleared by dialysis. No dosage adjustment is recommended for patients with mild hepatic insufficiency. A dose reduction is recommended for moderate hepatic insufficiency from the standard 50 mg to 35 mg caspofungin daily, following a 70-mg loading dose on Day 1.

Caspofungin is a poor substrate for the cytochrome P450 (CYP) enzyme system and does not appear to inhibit the major CYP450 isozymes. Thus, drug interactions based on alterations in CYP-mediated metabolism are unlikely to occur with caspofungin. Itraconazole, tacrolimus, mycophenolate have no effect on the pharmacokinetics of caspofungin. Coadministration of cyclosporin A moderately increases plasma concentrations of caspofungin, most likely due to reduced tissue uptake of caspofungin. Caspofungin has no effect on the pharmacokinetics of itraconazole, amphotericin B, cyclosporin A and mycophenolic acid, the pharmacologically active metabolite of mycophenolate. Caspofungin slightly decreases whole blood concentrations of tacrolimus and therefore, for patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate dosage adjustments are recommended.

2.5 Clinical Efficacy (Section 6)

As noted above, the ongoing development program for caspofungin has been designed to evaluate the efficacy and safety of caspofungin in documented *Aspergillus* and *Candida* infections as well as in empiric therapy of neutropenic patients. This section focuses on the results of the evaluation of the efficacy of caspofungin in the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

Dose Selection for Phase IIb/III Studies

Preclinical MIC values for *Aspergillus* and *Candida* spp. suggested that a clinical dose that would maintain plasma concentrations above a target of 1 $\mu\text{g/mL}$ should be chosen. Dose ranging studies evaluating 35, 50, and 70 mg in patients with *Candida* esophagitis

demonstrated that all of these doses were effective and well tolerated. There were no dose-dependent toxicities. Since the efficacy for the 35-mg dose was numerically lower than that for the 50- and 70-mg doses and the 50-mg dose resulted in plasma concentration above the target concentration, this dose was used in Phase III *Aspergillus* and *Candida* studies. In order to assure that the target concentration of 1 µg/mL was achieved early in treatment, a dosing regimen including a single 70-mg dose followed by daily 50-mg doses of caspofungin was tested and found to be efficacious and well tolerated. This dosing regimen is thus recommended for treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

Efficacy in Invasive Aspergillosis

The efficacy of caspofungin in the treatment of invasive aspergillosis was evaluated in a multicenter, noncomparative study in patients with documented disease who were refractory to or intolerant of other therapies (Protocol 019, the Noncomparative *Aspergillus* Study). Refractory was defined as demonstrating progression of infection or failure to improve after a minimum of 7 days of therapeutic doses of effective antifungal therapy. Intolerance was defined as a doubling of creatinine or creatinine ≥ 2.5 mg/dL on standard therapy, creatinine ≥ 2.5 mg/dL due to another preexisting condition, or other significant intolerance to amphotericin B or lipid formulations of amphotericin B. The study was designed to include strict definitions for diagnosis (based on MSG criteria) and response to therapy. In addition, objective documentation of definite or probable disease including radiographic evidence, was required in all cases. All results obtained from patients who had documented disease and documented outcome and who had received at least one dose were included in the analyses of efficacy, regardless of duration of caspofungin therapy. An Expert Panel reviewed the data from this study to ensure consistency in assessments of both diagnoses and outcomes. A retrospective medical chart review of patients with IA (the Historical Control Study; Protocol 028/029) was conducted to provide an approximate comparator group of patients with IA treated with standard antifungal therapy. Patients enrolled in the Historical Control Study were identified through a process designed to yield, at each study site, a consecutive series of cases meeting eligibility criteria comparable to those of Protocol 019. The methods of comparison of data from the Historical Control Study and Noncomparative *Aspergillus* Study (by tabular display and by logistic regression) were predefined and included in the Historical Control Study data analysis plan. Further supportive data were collected from patients with IA enrolled in the Compassionate Use Study (Protocol 024/025).

Efficacy and safety information from 69 patients with IA were included in the original application. However, Expert Panel assessments were only available for 58 of the 69 patients at the time of the initial submission of the application. The Expert Panel determined that 54 of the 58 patients met diagnostic criteria for invasive aspergillosis, received at least one dose of caspofungin and had data on which to base an assessment of outcome. Due to the late cutoff date for final case report form data for 11 patients, Expert Panel Review was not available on these for the original application. Subsequent Expert Panel review of these patients has confirmed that 9 of the 11 patients met

diagnostic criteria for invasive aspergillosis, received at least one dose of caspofungin and had data on which to base an assessment of outcome. Thus, 63 of the 69 patients were evaluated by the Expert Panel for efficacy.

Data on the 63 patients with well-documented IA and a high prevalence of poor prognostic factors evaluated by the Expert Panel showed a response rate of 41.3%. Favorable responses (complete or partial) were seen in patients with disseminated disease, hematologic malignancies, allogeneic bone marrow transplant (BMT), and neutropenia. Most patients (84.1%) were refractory to initial antifungal therapies and overall, these refractory patients had a favorable response rate of 35.8%. The number of intolerant patients was small (N=10), but 7 of 10 had a favorable response. Of the 52 patients who received >7 days of caspofungin therapy, 25 (48.0%) had a favorable response.

Supportive data was obtained from 3 patients with IA in the Compassionate Use Study (Protocol 024/025). These patients were evaluated by the same Expert Panel and 2 of 3 were determined to have a favorable response, using the same definitions.

The favorable response rate observed in the Noncomparative *Aspergillus* Study (Protocol 019) was further strengthened by comparison to a historical control group treated with standard antifungal therapy. In this reference group a favorable response rate of only 17% was observed. After adjustment for bone marrow transplant, neutropenia, disseminated disease, and corticosteroid use in a logistic regression analysis, the odds ratio in favor of caspofungin was consistently above 3, with a lower bound of the 95% confidence interval >1, supporting the efficacy of caspofungin. This analysis demonstrated that caspofungin was at least as effective as standard antifungal therapy in the treatment of patients with invasive aspergillosis, thus supporting the overall efficacy of caspofungin.

Efficacy in Candida Infections

The antifungal activity of caspofungin has been corroborated in Phase II clinical studies examining the efficacy of caspofungin for the treatment of localized *Candida* infections. Results from the completed Phase III clinical study examining efficacy and safety of caspofungin in *Candida* esophagitis (Protocol 020) are not yet available.

2.6 Clinical Safety (Section 7)

Although the focus of this application is on the treatment of IA, blinded, comparator-controlled studies in patients with *Candida* infections provided an important supportive safety database for caspofungin, because these patients had less acute diseases than the patients with *Aspergillus* infections and fewer confounding acute background illnesses. In addition, *Candida* infections permitted evaluation in controlled studies providing a much larger safety database and an assessment of a higher dose of caspofungin (70 mg/day for up to 14 days).

Caspofungin has been administered to over 800 individuals with final safety data available on 625 patients or subjects receiving multiple doses from 15 to 70 mg daily. In

clinical pharmacology studies, a total of 274 subjects received caspofungin for up to 21 days, including 126 subjects receiving caspofungin at doses of ≥ 50 mg for >7 days. In Phase II/III studies of *Candida* or *Aspergillus* infections, 349 patients (277 with *Candida* infections and 72 with IA) received caspofungin for up to 26 and 162 days, respectively, with most patients receiving ≥ 50 mg daily. In all studies, caspofungin was generally well tolerated.

In the randomized, double-blind, controlled clinical studies of *Candida* infections, caspofungin was generally well tolerated at doses of 35, 50, and 70 mg. There were no dose-related toxicities reported. The most common clinical adverse experiences reported as drug related by the investigator were fever and phlebitis/infused vein complications. The most common drug-related laboratory adverse experiences were increased ALT, increased AST, decreased hemoglobin, and decreased hematocrit. The overall incidence of clinical and laboratory adverse experiences was generally comparable to fluconazole and better than that observed with amphotericin B. In these studies, there were no serious drug-related clinical or laboratory adverse experiences and very few discontinuations due to drug-related clinical or laboratory adverse experiences in patients treated with caspofungin. Of note, in a drug interaction study with cyclosporin A, volunteers who received both cyclosporin A and caspofungin experienced transient elevations in ALT and AST to 2- to 3-fold the upper limit of normal. Based on these transaminase elevations, cyclosporin A was generally excluded from Phase II/III clinical trials.

In the Noncomparative *Aspergillus* Study (Protocol 019), the adverse experiences classified as drug related were generally similar to those observed in the controlled clinical studies for *Candida* infections. In the *Aspergillus* study, there were no drug-related laboratory adverse experiences of increased ALT or AST or increased serum creatinine. The safety profile did not appear to change with extended therapy (beyond 28 days).

2.7 Summary of Benefits and Risks

Invasive Aspergillosis is a life-threatening disease. Despite the introduction of itraconazole and the lipid formulations of amphotericin B, mortality remains unacceptably high at 40 to 90%. There is a tremendous need for new antifungal agents to treat this serious disease. Caspofungin has a unique mechanism of action, which should result in a lack of cross-resistance with available polyene and azole antifungal agents. Caspofungin has shown compelling efficacy as salvage treatment for IA in patients refractory to or intolerant of standard antifungal therapy, a patient population with few therapeutic alternatives. In addition, caspofungin has been well tolerated, even in seriously ill patients. In the context of currently available treatment options, both the efficacy and safety profiles of caspofungin support the addition of caspofungin to the therapeutic armamentarium for invasive aspergillosis in patients who are refractory to or intolerant of standard antifungal therapy.

2.8 Conclusions

1. Caspofungin is a member of a new class of antifungals which inhibits the synthesis of 1,3 β D-glucan, a critical component of the fungal cell wall. The mechanism of action is distinct from that of other currently available antifungals and may be expected to result in a lower potential for cross-resistance with approved therapies.
2. Caspofungin is effective in the treatment of well documented invasive aspergillosis in patients refractory to or intolerant of other therapy.
3. Caspofungin is associated with favorable outcomes in patients with an expected poor prognosis, including those refractory to initial therapy, with disseminated disease, who are neutropenic or are recipients of allogeneic transplants or corticosteroids. Documented relapse is uncommon up to 4 weeks after the completion of caspofungin therapy.
4. Caspofungin is effective in the treatment of invasive aspergillosis when compared to a historical control group receiving standard therapy.
5. In Phase II studies, caspofungin at 35, 50, and 70 mg daily appears effective in the treatment of esophageal and oropharyngeal candidiasis.
6. The recommended dosage for treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies is 50 mg daily, after an initial 70 mg loading dose on Day 1.
7. Caspofungin is a poor substrate for the cytochrome P450 system and does not inhibit the major cytochrome P-450 isozymes at clinically relevant concentrations.
8. No dosage adjustments are necessary when caspofungin is coadministered with itraconazole, amphotericin B, mycophenolate mofetil, or tacrolimus. Standard monitoring of tacrolimus blood concentrations should be used to determine whether patients receiving concurrent caspofungin require dosage adjustments of tacrolimus.
9. No dose adjustments are necessary in the elderly or on the basis of gender or race.
10. No dosage adjustment is recommended for patients with mild to end-stage renal insufficiency. Caspofungin is not cleared by hemodialysis, so there is no need for a supplementary dose after dialysis.
11. No dosage adjustment is recommended for patients with mild hepatic insufficiency. Pending additional results from a multiple dose study, a dose reduction to 35 mg following the 70-mg loading dose is recommended for patients with moderate hepatic insufficiency.
12. Coadministration of cyclosporin A cannot be recommended until additional data regarding multiple dose administration in patients are available, due to the mild transient elevations in ALT and AST that were seen in some subjects in Phase I studies

Caspofungin Acetate
FDA Advisory Committee Meeting Background
Synopsis

-19-

13. Caspofungin 50 mg is generally well tolerated. There are few drug-related serious adverse experiences or discontinuations of therapy due to drug-related adverse experiences.
14. There is no evidence of dose related toxicities and the safety profile of caspofungin does not appear to change with extended therapy.

3. Preclinical Pharmacotoxicology of Caspofungin

3.1 Introduction

The potential toxicity of the diacetate salt of caspofungin (caspofungin acetate), has been extensively evaluated in laboratory animals and in in vitro systems. These studies included assessment of general toxicity in single-dose (acute) toxicity studies in mice, rats, and rabbits; repeated-dose (subacute and chronic) toxicity studies in rats and monkeys; toxicokinetic studies in rabbits and rats; reproductive toxicity studies in rats; and developmental (embryo-fetal/perinatal) studies in rats and rabbits; and in vitro and in vivo genetic toxicity studies. In addition, the local (dermal, ocular, and at the injection site) irritancy potential of caspofungin was investigated. Finally, a series of other toxicity studies were completed to evaluate the hepatic enzyme induction and hemolytic potential of the compound as well as the toxicity in pediatric rhesus monkeys. Preclinical studies were conducted using either a saline formulation of the compound, or a lyophilized formulation which is the proposed market formulation.

The 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 rhesus monkeys, and very slight elevations in serum transaminase values in monkeys with no consistent association with histologic changes in the liver. Caspofungin was not teratogenic in rats or rabbits at maximally tolerated doses. However, there were very slight decreases in fetal weights in rats that correlated with an increased incidence of fetuses with incomplete ossifications of the torso and/or skull at a maternally toxic dose of 5 mg/kg/day. Maternal toxicity in this study was due to histamine release in the first few days of dosing. The dose at which fetal changes occurred was approximately 3.5 times the single 70-mg loading dose proposed for patients.

3.2 Preclinical Safety Evaluation of Metabolites, Impurities, and Degradates

As discussed in section 5.3.3. of the Pharmacokinetics and Metabolism section of this document, all major metabolites of caspofungin detected in humans were also found in rats and monkeys, which were the preclinical species used to test the toxicity of caspofungin. In addition, impurities that are present in bulk material were qualified and quantified. It was determined that preclinical test species were exposed to impurities at levels that were similar to or exceed those at the maximum (70 mg) human dose of caspofungin.

Since new degradates, or higher levels of preexisting degradates are generated as a consequence of the lyophilization of caspofungin, preclinical studies were conducted using a thermally degraded, lyophilized formulation to increase degradate levels. These studies achieved exposures equal to or exceeding the exposure in humans expected with the market formulation at the minimum purity specification. These studies consisted of an acute study in female rats, genotoxicity studies (microbial mutagenesis assay, in vitro alkaline elution assay, and in vitro chromosomal aberration assay), a 5-week intravenous toxicity study in monkeys, and a full developmental and reproductive toxicity program. No toxicity was attributed to the degradates when the results of studies using thermally

degraded material were compared to the results of studies conducted with the nondegraded lyophilized or saline formulations.

3.3 Acute Toxicity Studies

The approximate intravenous LD₅₀ for the saline formulation of caspofungin was 19 mg/kg for female mice, 27 mg/kg for male mice, and 38 mg/kg for rats. In the acute intravenous toxicity study in rats with the lyophilized formulation of the compound containing degradates, an approximate LD₅₀ between 25 and 50 mg/kg was established which was considered to be equivalent to that for the saline formulation.

The approximate subcutaneous LD₅₀ for the saline formulation was 200 mg/kg for mice and 150 mg/kg for rats. The oral LD₅₀ in female mice was >2000 mg/kg.

3.4 Subacute and Chronic Toxicity Studies

Several treatment-related changes were seen in intravenous toxicity studies in the rat and rhesus monkey. The dosages used in these studies were as shown in Table 1:

Table 1

Caspofungin: Subacute and Chronic Toxicity Studies

Species, Formulation and Study Duration	Doses (mg/kg/day)
15-Day Exploratory in Rats (Saline)	2, 5
5 Weeks	
Rats (Saline)	0.5, 2, 5
Monkeys (Saline)	2, 5, 8
Monkeys (Lyo [†] with degradates [‡])	0.5, 2, 5
14 Weeks	
Rats (Saline)	0.5, 2, 5
Monkeys (Saline)	0.5, 2, 5
27 Weeks	
Rats (Lyo)	1.8, 3.6, 7.2
Monkeys (Lyo)	1.5, 3, 6
[†] Lyophilized formulation. [‡] Since degradates were known to be present in the lyophilized formulation, they (L-799717, L-747969 [a major metabolite of caspofungin], Dimer 1 and Dimer 2) were generated in the dosing material used in a 5-week study in rhesus monkeys at levels that equaled or exceeded the specifications established for the 5°C clinical formulation proposed for registration.	

The findings in the 5- to 27-week studies included signs of (a) histamine release in the rat, (b) irritation at the injection site in both species, and (c) increases in serum transaminase levels in the monkey, and are discussed in the following paragraphs.

3.4.1 Treatment-Related Findings

3.4.1.1 Signs of Histamine Release

It is well established that chemical agents containing particular characteristics in their structure have a tendency to cause histamine release [1]. Since caspofungin, as a lipopeptide, fits into the category of the basic polypeptides which are known to produce this effect, the fact that intravenous administration of the compound incites endogenous histamine release in the rhesus monkey and the rat is not unexpected.

Ancillary pharmacology studies established that the mechanism for these adverse effects (reddening and/or swelling of the snout, paws, and/or ears, and prostration) in the rat was release of endogenous histamine, since pretreatment with antihistaminic agents (cyproheptadine or diphenhydramine) significantly diminished these effects and prevented a lethal response. In the 5- and 14-week intravenous toxicity studies in rats using the saline formulation, signs of histamine release occurred in high-dosage group rats only (5 mg/kg/day) and signs no longer occurred after Drug Days 7 to 9 (presumably due to endogenous histamine depletion). The No-Observed-Effect-Level (NOEL) for this finding in these studies was 2 mg/kg/day. In the 27-week intravenous toxicity study in rats using the lyophilized formulation, signs of histamine release occurred in one 1.8-mg/kg/day dosage group animal (low-dosage group) on Drug Day 1 and in the 3.6- and 7.2-mg/kg/day dosage group animals on Drug Days 1 to 5. Overall, the NOEL for histamine release in rats is 0.5 mg/kg/day which is slightly less than the loading dose administered to patients. However, there have been no signs of histamine release in patients treated with caspofungin.

In rhesus monkeys, previously conducted ancillary pharmacology studies had established that bolus intravenous doses of caspofungin of 5 or 8 mg/kg produced signs of histamine release that were reversed upon injection of cyproheptadine using an infusion period of 20 minutes however, resulted in no adverse response at the 8 mg/kg dose. No signs of histamine release occurred in the 5- and 14-week intravenous toxicity studies in monkeys using the saline formulation or in the 27-week intravenous toxicity study in monkeys using the lyophilized formulation where 20-minute daily infusions of caspofungin were administered at doses of 2, 5, or 8 mg/kg/day; 0.5, 2, or 5 mg/kg/day; and 1.5, 3, and 6 mg/kg/day, respectively, nor did they occur in the 5-week study in monkeys using the lyophilized formulation containing degradates.

3.4.1.2 Injection Site Irritation

Clinical, gross, and histologic evidence of injection site irritation occurred in rats and monkeys in studies ranging from 5- to 27-weeks duration. The extent of damage at injection sites as assessed histologically was significant at higher doses and concentrations, and thrombosis was frequently present. It was established that use of meticulous venipuncture technique, and pre- and postdose flushing of catheter lines, decreased the incidence and severity of irritation. In the 27-week studies, a NOEL of 1.8 mg/kg/day (0.18 mg/mL) was established in rats, and a NOEL of 3 mg/kg/day (0.25 mg/mL) was established in monkeys. These NOEL dosages/concentrations are

similar to those proposed as a loading dose in patients (70 mg or approximately 1.4 mg/kg; approximately 0.26 mg/mL).

3.4.1.3 Elevations in Serum Transaminase Values

In the 5-week intravenous toxicity studies in monkeys that used caspofungin formulated in saline, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels were increased slightly as shown in Table 2:

Table 2

Caspofungin: 5-Week Intravenous Toxicity Study in Monkeys
 (TT #94-638-0)
 Average Values and % Increase in Transaminase Relative to Controls

Dose Group (mg/kg/day)	AST Values (U/L)				ALT Values (U/L)			
	Control	2	5	8	Control	2	5	8
Week 2 Average Values	41	41	56	74	33	33	70	96
% Increase			+37	+80			+112	+191
Week 4 Average Values	42	43	51	71	30	37	55	83
% Increase			+21	+69			+83	+177

Similar elevations in alanine aminotransferase levels occurred in the 14-week study in monkeys at the highest dose tested of 5 mg/kg/day (100% increase at 3 weeks, and 38% increase at 12 weeks, compared to concurrent controls). Elevations did not occur at 0.5 or 2 mg/kg/day in this study. It is important to note that there was a decreasing trend in the enzyme elevations during the course of both the 5- and 14-week studies with the saline formulation. In addition, determination of liver levels of caspofungin in these studies showed that there were no significant increases in the levels of caspofungin in the liver between 5 and 14 weeks of treatment. Microscopically, in the 5-week study, there were a few small scattered foci of subcapsular necrosis of the liver in 2 out of 8 mid-dosage group animals and 4 out of 8 high-dosage group animals, and in the 14-week study, there was very slight subcapsular hepatic scarring in 1 out of 8 high-dosage group animals.

In a 5-week intravenous toxicity bridging study in the rhesus monkey (0.5, 2, 5 mg/kg/day) using the lyophilized formulation containing degradates, there were increases in serum ALT levels in the 5-mg/kg/day dosage group animals. The elevations were similar in degree to that seen in previous 5- and 14-week intravenous toxicity monkey studies using the saline formulation at that dosage level. Very slight ALT

elevations in 4 out of 8 low-dosage group and 2 out of 8 mid-dosage group monkeys were considered to be of uncertain relationship to treatment and of no toxicological significance. It is important to note that a correlating histopathologic finding of subcapsular hepatic necrosis was not seen in any of the animals in this study.

In the 27-week intravenous toxicity study in monkeys using the lyophilized formulation (1.5, 3, and 6 mg/kg/day), ALT levels were increased slightly throughout the study (52 to 72% when compared to concurrent controls) in the 6-mg/kg/day dosage group. Histopathologic examination of the liver did not reveal a correlating histomorphologic change. The NOEL for increase in ALT levels in this study was 1.5 mg/kg/day based on very slight increases in ALT in one mid-dose animal in Drug Week 4 which was considered to be of uncertain relationship to treatment.

There were no serum biochemical or histologic changes indicative of hepatotoxicity in the 15-day, the 5- or the 14-week intravenous toxicity studies in rats at doses up to the highest dose tested (5 mg/kg/day), or in the 27-week intravenous toxicity study in rats at doses up to the highest dose tested (7.2 mg/kg/day).

Considered in total, the 5-, 14-, and 27-week intravenous studies in monkeys show that the very slight (and often transient) elevations in serum ALT levels seen in animals administered doses >1.5 mg/kg/day are not associated with reproducible histologic liver damage. A NOEL of 1.5 mg/kg/day was established in the 27-week study based on increases in ALT levels. In this study, there were no drug-related microscopic hepatic changes in animals administered up to 6 mg/kg/day, the maximum dosage tested. As discussed in Section 3.4.2 below, a 5-mg/kg/day dose in monkeys achieves exposure levels ($AUC_{2-24 \text{ hr}}$) approximately 4 times the levels present after a clinical loading dose (70 mg; $AUC_{0-24 \text{ hr}}$), and a 6-mg/kg/day dose for 6 months in the intravenous study in monkeys produced only mild elevations in transaminase levels and no correlating histopathologic change in the liver.

3.4.2 Pharmacokinetic/Toxicokinetic Data

The pharmacokinetics of caspofungin have been evaluated thoroughly in the animal species used for the Safety Assessment studies (see Section 5; Pharmacokinetics and Metabolism). In all species examined, caspofungin is eliminated very slowly ($CL_p \leq 0.5 \text{ mL/min/kg}$) and bound extensively (>95%) to plasma proteins. In rats that received an IV dose of [^3H]caspofungin, the radioactivity is distributed widely throughout the body, with the liver containing the highest level of radioactivity. The hepatic uptake of [^3H]caspofungin is a very slow process and the equilibration of the drug between blood and liver tissue is not rapid. Caspofungin is neither a substrate nor a potent inhibitor of P-glycoprotein-mediated transport. Following IV administration of [^3H]caspofungin to rats and monkeys, the radioactivity is excreted almost equally into the urine and feces. Less than 5% of the dose is excreted as unchanged drug in the urine. Qualitatively, the metabolism of [^3H]caspofungin is similar in rats, monkeys, and humans. In all species, L-747969, a peptide hydrolysis product of the parent drug, is the major metabolite found in plasma, while urine contains primarily the polar hydrolytic metabolites. Caspofungin is a poor substrate for CYP isozymes, and at clinically-relevant plasma concentrations, both

caspofungin and L-747969 do not inhibit major human CYP isozymes. Thus, drug-drug interactions via CYP-mediated metabolism are considered unlikely. The similarity of disposition and metabolism properties between animals and humans validates the usage of the animal models selected for the toxicity studies of caspofungin.

Analyses of blood levels of caspofungin in monkeys (5-week intravenous toxicity study) demonstrated that the 28-day AUC_{2-24 hr} (141.1 µg•hr/mL) at the NOEL for elevations in serum transaminase levels (2 mg/kg/day) slightly exceeded those seen in humans administered a 70-mg dose for 14 days (137 µg•hr/mL). Clearance of the drug from the plasma appeared to decrease after repeated dosing in the monkey, as demonstrated by an increase in half-life and trough values between Drug Days 1 and 28. In a 6-month study in monkeys using dosages of 1.5, 3.0, and 6.0 mg/kg/day, 1.5 mg/kg/day produced no treatment-related changes. In rats (5-week intravenous toxicity study), the NOEL for treatment-related effect was 2 mg/kg/day, where the mean 28-day AUC_{2-24 hr} was 122.1 µg•hr/mL. These data are shown in Table 3:

Table 3

Caspofungin AUC Data (µg•hr/mL)

Rat (2 to 24 Hr; 28 Days)		Monkey (2 to 24 Hr; 28 Days)		Human (0 to 24 Hr; 14 Days)			
Dose (mg/kg/day)	Mean	Dose (mg/kg/day)	Mean	Dose (mg)	Mean	Range	n
0.5	20.8	2.0	141.1	35	55	49-62	5
2.0	122.1	5.0	496.0	50	88	71-108	8
5.0	175.8	8.0	920.4	70	137	97-173	16

3.4.3 Irreversible Plasma Protein Binding

As described in Section 4.3.3, Metabolism and Excretion, there is a low level of irreversible binding to plasma proteins in both monkeys and humans. Following administration of a single IV dose of [³H]caspofungin to monkeys (5 mg/kg) and humans (70 mg), a prolonged half-life of radioactivity in plasma was observed. Further examination of plasma samples collected from humans and monkeys during the terminal elimination phase (Day 5 to 20) revealed that approximately half of the radioactivity could not be removed from plasma proteins after exhaustive extraction of the protein pellets with strong acid and various organic solvents, suggesting that part of the caspofungin-derived radioactivity in plasma was bound irreversibly to proteins. The level of irreversible binding was low (≤33 pmol/mg protein in monkeys and ≤7 pmol/mg protein in humans) at these late time points, and declined with time. Thus, at comparable time points after IV administration, the extent of irreversible binding in monkeys was about 3 to 5 times higher than that in humans. There is no evidence that the presence of long-lived metabolites was associated with significant adverse effects in preclinical safety assessment studies.

3.5 Reproductive Toxicology and Embryo-Fetal/Perinatal Toxicology

The developmental and reproductive toxic potential of caspofungin has been tested in a series of intravenous studies in rabbits and rats. The studies were conducted using the lyophilized formulation of caspofungin. Since small amounts of degradates (L-799717, L-747969 [a major metabolite of caspofungin], Dimer 1 and Dimer 2) were found to be present in the lyophilized formulation of caspofungin, levels of these degradates that equaled or exceeded the specifications established by Pharmaceutical Research and Development (Merck Research Laboratories) for these agents in the clinical formulation were tested in these studies.

3.5.1 Reproductive Toxicology

In an intravenous fertility study in female rats, dosages up to 5 mg/kg/day of caspofungin produced no drug-related effects on mating performance or embryonic survival; therefore, the NOEL for female fertility and general reproductive performance is >5 mg/kg/day. In an intravenous fertility study in male rats, the NOEL for effects on male fertility was >5 mg/kg/day (the highest dosage tested). The NOEL for effects on fertility were therefore established at a dose at least 3 to 4 times that proposed as a loading dose in humans (70 mg).

3.5.2 Embryo-Fetal and Perinatal Toxicology

In a developmental toxicity study in pregnant rabbits, NOELs of 3 mg/kg/day for maternal toxicity (minimal decreases in average maternal body weight gain and food consumption) and ≥ 6 mg/kg/day (the highest dose administered) for developmental toxicity were established.

In the intravenous developmental toxicity study in pregnant rats with fetal evaluation, there were slight nonsignificant ($p > 0.05$) decreases in mean fetal body weights at 5 mg/kg/day (highest dose tested) that were considered to be drug related since the values were close to or below the lowest mean values for historical controls. There was also a drug-related increase in the incidence of fetuses with incomplete ossifications of the torso and/or skull in the 5-mg/kg/day group. The increased incidence of incomplete ossifications is considered to be secondary to drug-related decreases in fetal body weights (which occurred coincidentally with maternal toxicity due to histamine release) and not due to a direct effect of caspofungin on fetal ossification. In addition, there was a drug-related increase in the incidence of fetuses with cervical rib at the maternally toxic dose of 5 mg/kg/day. Based on these findings, the NOEL for maternal (excluding signs of histamine release) and developmental toxicity in rats is 2 mg/kg/day. Therefore, the NOEL for these effects is slightly greater than the proposed loading dose in patients.

In an intravenous developmental toxicity study in rats with postweaning evaluation, the NOEL for maternal (excluding physical signs of drug-related histamine release) and developmental toxicity in rats, as assessed following natural delivery, was >5 mg/kg/day (the highest dose tested).

Toxicokinetic studies in pregnant rabbits and rats at a dose of 5 mg/kg/day indicated that although the placenta of the rabbit and rat, and the mammary gland of the rat, act as partial barriers to drug entry into the fetus and/or neonate, significant fetal exposure occurs at the no-effect-dose for developmental toxicity in rabbits (>6 mg/kg/day) and at the maximum dose tested (5 mg/kg/day) in rats. Following IV administration of 5 mg/kg/day, the mean fetal plasma concentrations of caspofungin in rabbits and rats, determined on Gestational Day 20, were 29 and 18% of the maternal plasma values, respectively, at 24 hours after dosing. Caspofungin also was secreted into milk in rats after IV administration of 5 mg/kg/day. On Lactation Day 14, the drug concentration in milk was about 13% of the maternal plasma value. There are no studies of caspofungin in pregnant women, therefore, it should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. In addition, since it is not known whether caspofungin is excreted in human milk, women receiving CANCIDAS™ should not breast-feed.

3.6 Genetic Toxicology

Caspofungin was evaluated in a series of in vitro and in vivo genotoxicity assays. The compound was found to be neither genotoxic nor mutagenic.

Caspofungin was negative in multiple microbial mutagenesis and in replicate mammalian cell (V-79, Chinese hamster lung cell system) mutagenesis assays. Caspofungin was tested in duplicate assays for DNA strand breakage (the in vitro alkaline elution/rat hepatocyte assay) up to 42 µM, and was considered not to be genotoxic.

In duplicate in vitro chromosomal aberration assays in Chinese hamster ovary cells, caspofungin was negative for chromosomal aberrations. Caspofungin was also negative in the in vivo chromosome aberration assay in mouse bone marrow in female mice at doses up to 12.5 mg/kg. Only one sex of mice was used since there was no marked sex difference in acute toxicity in mice. The highest dose was limited by compound toxicity in female mice.

In conclusion, caspofungin has been demonstrated to be neither genotoxic nor mutagenic in a series of duplicate in vitro assays. Further, caspofungin was determined not to be genotoxic in an in vivo assay for chromosomal aberrations in mouse bone marrow at doses up to 12.5 mg/kg intravenously.

3.7 Carcinogenic Potential

Assessment of carcinogenicity was not performed since the duration of dosing planned for the target clinical population is expected to be generally <3 months. In addition, there was no evidence of carcinogenic potential based on the lack of genotoxicity, and the lack of histologic changes (other than irritation at the injection site) in the 27-week toxicity studies in rats and monkeys.

3.8 Local Tolerance

Caspofungin was evaluated in dermal and ocular studies to determine the local tolerance to the bulk drug substance and in a 15-day intravenous toxicity study in rhesus monkeys

to determine a no-effect-dosage level for local irritation of the saline formulation of the compound. Caspofungin was found to be potentially severely irritating in the bovine corneal opacity and permeability (BCOP) assay at a 20% w/v concentration for 4 hours, and mildly irritating to the skin of rabbits at a dose of 500 mg/site for 24 hours. The intravenous irritation study in rhesus monkeys established that 2 weeks of daily intravenous infusion of 5 mL/kg of a 0.1 mg/mL solution (0.5 mg/kg/day) of caspofungin did not produce irritation or thrombosis at the injection site (see Section 3.4.1.2). These results demonstrate that direct exposure of tissue to solutions containing caspofungin may cause irritation, and that appropriate handling techniques should be employed during manufacture and administration of the compound.

3.9 Other Information

Caspofungin was evaluated in a series of other toxicity studies to evaluate the potential to produce hemolysis, induce hepatic enzymes, and produce toxicity in neonatal rhesus monkeys.

Hemolysis occurred in ex vivo human (0.45 to 1.8 mg/mL), rat (0.9 to 1.8 mg/mL), and monkey (0.9 to 1.8 mg/mL) washed red cells after 30 minutes of incubation. No hemolysis was observed for the compound in any species tested (rat, monkey, and human) at any time point in the whole blood hemolytic assay. Intravenous toxicity studies of up to 27 weeks duration in rats and monkeys have not shown evidence of in vivo hemolysis.

In the enzyme induction studies, caspofungin did not induce EFCOD (7-ethoxy-4-trifluoromethylcoumarin-O-deethylase) or FACO (fatty acid acyl CoA oxidase) in the livers of CD-1 mice after 4 days of treatment at 5 mg/kg/day, nor did it cause induction of FACO activity in isolated rat hepatocytes.

In the 5-week intravenous toxicity study in neonatal rhesus monkeys, there were no treatment-related effects at dosages of 2 and 5 mg/kg/day, and toxicokinetic parameters were consistent with a previous study in young adult rhesus monkeys. Therefore, there is no contraindication against use of caspofungin in pediatric populations based on preclinical results in neonatal monkeys.

3.10 Conclusions

1. The NOELs for elevations in serum transaminase values after intravenous treatment with caspofungin for 27 weeks are 1.5 mg/kg/day in rhesus monkeys and >7.2 mg/kg/day in rats.
2. Since one rat dosed with 1.8 mg/kg showed signs of histamine release on Day 1 of the 27-week intravenous toxicity study, the overall NOEL for signs of histamine release in rats is 0.5 mg/kg/day.
3. Although injection site irritation was seen in rats and monkeys at lower dosages and concentrations, it was not seen in the high-dosage group (5.0 mg/kg/day; 0.625 mg/mL) in the 5-week intravenous toxicity study in monkeys administered the lyophilized formulation containing degradates.

Caspofungin Acetate
FDA Advisory Committee Meeting Background
Preclinical Pharmacotoxicology of Caspofungin

-29-

4. In the definitive developmental toxicity studies in the rat and rabbit, the sole treatment-related developmental or reproductive findings occurred at a maternally toxic dose (due to histamine release), and consisted of a decrease in mean fetal body weight in the rat (with secondary very slight increases in incomplete ossification of the torso and/or skull) and an increase in cervical rib formation, both with a NOEL of 2 mg/kg/day.
5. In a postweaning evaluation study in rats, the NOEL for effects on the F₁ and F₂ generation was >5 mg/kg/day.
6. The NOEL for fertility and general performance in the fertility studies in male and female rats was >5 mg/kg/day.
7. In toxicokinetic studies using a dose of 5 mg/kg/day in rats and rabbits, the maternal exposure levels were slightly greater than the human plasma AUC of approximately 137 µg•hr/mL. In rats and rabbits, the placenta acted as a barrier to drug entry into the fetus to some degree; however, significant fetal exposure did occur at the NOEL dose for developmental toxicity of >6 mg/kg/day for rabbits and at the highest dose tested in the developmental toxicity studies in rats (5 mg/kg/day). In rats, the drug concentrations in milk indicated a transfer of drug from the plasma to the milk. In both the rat and rabbit, plasma elimination was slower in the fetus than in the dam.
8. Based upon the results of the studies discussed above, with the establishment of no-effect dosage levels for all drug-related findings, the available preclinical data support the conclusion that caspofungin may be safely administered to humans for the treatment of disseminated aspergillosis infection.

4. Microbiology

4.1 Introduction

Caspofungin (caspofungin acetate, CANCIDAS™, MK-0991, L-743872) is a semisynthetic derivative of pneumocandin Bo, a lipopeptide fermentation product derived from the fungus *Glarea lozoyensis*. It is a member of the echinocandin family of antibiotics.

Extensive microbiological studies have been conducted with caspofungin to characterize its *in vitro* and *in vivo* antifungal activity. Information from these studies is summarized below, beginning with a brief description of caspofungin's mechanism of action. The *in vitro* and *in vivo* activity of caspofungin against *Aspergillus* spp. is then reviewed, followed by studies with *Candida* species. Activity against other filamentous and dimorphic fungi and studies addressing combination studies with other antifungals are also discussed.

Preclinical studies conducted with caspofungin demonstrate that it is a potent antifungal agent with activity against a number of clinically important fungi including *Aspergillus* and *Candida* species. Due to its novel mechanism of action, it retains activity against *Candida* isolates resistant to currently used antifungal agents including amphotericin B (AmB), fluconazole (FCZ), and flucytosine (5-FC). Caspofungin also has potent efficacy, comparable to AmB, in immunocompetent and immunosuppressed animal models of disseminated *Aspergillus* and *Candida* infections and pulmonary aspergillosis.

4.2 Mechanism of Action

Caspofungin is a potent noncompetitive inhibitor of the synthesis of β (1,3)-D-glucan, an essential component of the cell wall of many pathogenic fungi. Inhibition of β (1,3)-D-glucan formation results in osmotic fragility and cell lysis of susceptible fungi. It is important to note that mammalian cells do not produce β (1,3)-D-glucan, allowing caspofungin to be targeted specifically at fungal cells. Using membrane preparations from *Candida albicans* and *Aspergillus fumigatus*, caspofungin 50% inhibitory concentrations (IC₅₀) for β (1,3)-D-glucan synthesis of 0.6 nM and 9.6 nM were determined, respectively. *Cryptococcus neoformans* β (1,3)-D-glucan synthesis is much less sensitive to caspofungin (IC₅₀ to 2.5 μ M) and other echinocandins which explains the insensitivity of this organism to caspofungin.

The molecular target of the echinocandins has been identified via genetic studies in *Saccharomyces cerevisiae*, *C. albicans*, and *A. fumigatus* as an essential gene identified as *fks1*. The protein product of this gene, FKS1, has been shown to be part of the membrane protein complex responsible for β (1,3)-D-glucan synthesis. Laboratory induced mutations in *S. cerevisiae* and *C. albicans* *fks1* results in reduced sensitivity of β (1,3)-D-glucan synthesis to the echinocandins and correlates with increases in MIC values.

4.3 In Vitro Activity of Caspofungin on *Aspergillus* spp.

The initial observation demonstrating in vitro activity of caspofungin against *Aspergillus* was induction of dramatic morphological changes in hyphal elements following in vitro incubation with caspofungin. Filaments became distorted and blunted. Similar observations have been made for other compounds in the echinocandin class. The concentration of drug required to induce these morphological effects has been termed the minimal effective concentration (MEC). Supporting the biological significance of the MEC is the observation that the MEC for different echinocandins was predictive of efficacy in rodent models of aspergillosis.

Additional studies were conducted to better characterize the effect of caspofungin on *Aspergillus* isolates. Standard broth microdilution methods to define minimal inhibitory concentrations (MIC) demonstrated that caspofungin substantially inhibited *Aspergillus* growth, but complete inhibition of visible growth was generally not observed. This is a common phenomenon in the susceptibility testing of filamentous fungi. Therefore, the National Committee for Clinical Laboratory Standards (NCCLS) reference method for testing filamentous fungi, which recommends a microbroth dilution assay endpoint of "substantial inhibition" (ranging from 50 to 80% inhibition of visual growth) has been utilized. Studies in the laboratories of Dr. Espinel-Ingroff (Medical College of Virginia/Virginia Commonwealth University) and Dr. Rex (University of Texas Medical School, Houston, Texas) have demonstrated that this in vitro value of substantial growth inhibition also correlates well with the MEC of caspofungin across a number of *Aspergillus* isolates.

Standard quantitative culture experiments were also conducted to assess the effect of caspofungin on the viability of *Aspergillus* isolates. Unlike results involving *Candida* spp., in which a >99% reduction in viable organisms was demonstrated (see Section 4.7, In Vitro effects of Caspofungin on *Candida* spp.), reductions in *Aspergillus* colony counts were not consistently found. These studies are limited by technical difficulties in the quantitative culture of hyphal organisms where disruption and subsequent growth of multiple colonies from a single hyphae may make quantitation inaccurate. In addition, caspofungin treatment of severely immunocompromised rodents demonstrates a sustained antifungal effect, even after cessation of therapy in the setting of continued immunosuppression (see Section 4.5). Thus, standard techniques may not fully characterize the in vitro activity of caspofungin against *Aspergillus* isolates.

To further explore the in vitro activity of caspofungin, specific fluorescent dyes were used to determine the status of *A. fumigatus* hyphae after exposure to caspofungin, AmB and itraconazole (ITZ). One dye, 5,6 carboxyfluorescein diacetate (CFDA) was used to determine which hyphal cells were viable and the other DiBAC₄(3) (bis-(1,3-dibutylbarbituric acid) trimethane oxonol) was used to identify dead cells. CFDA penetrates all cells whether they are viable or dead but only gets converted to fluorescent 5,6 carboxyfluorescein in live cells due to esterase activity. DiBAC₄(3) cannot enter viable cells due to the membrane potential, so it selectively enters dead cells and complexes with phospholipids to form a fluorescent complex.

In studies using a microscope equipped with Nomarski optics and fluorescent detection capabilities, substantial killing (based on patterns of viability and mortality stain fluorescence) of *A. fumigatus* hyphal cells, particularly at the branch points and at the leading edge of growth, can be observed after exposure to 0.3 µg/mL of caspofungin for 6 hours (Figure 1 and Figure 2). Also, cells at the tips of the hyphae, where new growth would be expected, are observed to actually rupture releasing the cytosolic contents. However, there are cells in the center of the caspofungin-treated *A. fumigatus* fungal mass which appear viable based on fluorescence staining. Such observations are consistent with a cell-wall active agent where more dramatic effects are expected in cells with more rapid growth and cell wall synthesis. Similar studies using currently licensed antifungal agents with different mechanisms of action were also performed for comparison. A minimal amount of killing is seen with ITZ at 2.5 µg/mL. Near complete killing is seen with AmB at 0.15 µg/mL; this would be expected based on AmB's mechanism of action in which the cell membrane is disrupted.

4.4 In Vitro Susceptibility Testing of Caspofungin Against *Aspergillus* spp.

In vitro susceptibility testing to caspofungin has been examined in collections of *Aspergillus* clinical isolates as well as in the pathogens isolated from patients enrolled in caspofungin clinical studies.

4.4.1 Laboratory Clinical Isolates

Based on NCCLS guidelines and the demonstrated relationship between the MEC of caspofungin and drug concentrations producing substantial inhibition of growth in *Aspergillus* isolates, routine susceptibility testing of *Aspergillus* species has focused on the MIC value. Because standard methods and conditions for the echinocandin class have not yet been established, a range of conditions and culture media have also been evaluated.

Testing of caspofungin against laboratory collections of clinical *Aspergillus* isolates has been conducted primarily in the laboratories of Dr Espinel-Ingroff and Dr. Rex. The MIC values for 90% of the isolates (MIC₉₀) ranged from 0.2 to 0.5 µg/mL in the Espinel-Ingroff laboratory (103 isolates) and Geometric Mean MIC values ranged from 0.4 to 2.7 µg/mL in the Rex laboratory (80 isolates). The spectrum of activity of caspofungin in the *Aspergillus* species appears to be quite broad with comparable MIC values for all species. It should be noted that these MIC values have not as yet been validated with in vivo efficacy correlates.

Table 4

Susceptibility of *Aspergillus* Isolates to Caspofungin[†]

Organism	Espinel-Ingroff			
	n	MIC ₉₀ [‡] (µg/mL)	Geometric Mean MIC (µg/mL)	MIC Range (µg/mL)
<i>Aspergillus fumigatus</i>	56	0.5	0.25	0.12 to 4
<i>Aspergillus flavus</i>	13	0.2	0.2	0.06 to 2
<i>Aspergillus nidulans</i>	13	0.5	0.44	0.2 to 4
<i>Aspergillus niger</i>	10	0.23	0.14	0.06 to 0.5
<i>Aspergillus terreus</i>	11	0.2	0.12	0.06 to 0.2
Organism	Rex			
	n	MIC ₉₀ [‡] (µg/mL)	Geometric Mean MIC (µg/mL)	MIC Range (µg/mL)
<i>Aspergillus fumigatus</i>	26	ND [§]	0.7	0.25 to >16
<i>Aspergillus flavus</i>	27	ND	2.7	0.25 to >16
<i>Aspergillus nidulans</i>	3	ND	0.6	0.5 to 1
<i>Aspergillus niger</i>	17	ND	0.4	0.25 to 1
<i>Aspergillus terreus</i>	9	ND	0.5	0.5

[†] NCCLS M-38P protocol using RPMI-1640 medium (24 hour read, 35°C, MIC read as 50% inhibition of growth for Espinel-Ingroff; 24 hour read except *A. nidulans* which was read at 48 hours, 35°C, MIC read as 80% inhibition of growth for Rex).
[‡] MIC values for 90% of the isolates tested.
[§] ND = not determined.

4.4.2 Aspergillus Isolates From Caspofungin Clinical Trials

Similar methodology as described for laboratory collections of clinical isolates was utilized to assess the susceptibility of *Aspergillus* isolates obtained from patients in MRL clinical studies with caspofungin. In the MRL clinical laboratory, the NCCLS "substantial inhibition" endpoint was defined as an 80% inhibition of fungal growth (MIC-80). In a preliminary step to establish a standardized method for caspofungin susceptibility testing, the NCCLS protocol M38-P was employed with both the recommended Medium RPMI-1640 and an exploratory media, AM-3. The latter media was evaluated because AM3 has been useful in distinguishing AmB-resistant *Candida* isolates when evaluating susceptibility by this same method.

A total of 29 *Aspergillus* isolates recovered from 29 patients were received and identified; the MIC for 50% or 90% (MIC₅₀, MIC₉₀) of isolates and geometric mean MIC (GM-MIC) values are shown in Table 5. These results are consistent with susceptibility results for caspofungin against other *Aspergillus* isolates. An exploration of the relationship between these susceptibility tests and clinical response is summarized in the description of clinical results (Section 6.3).

Table 5

Caspofungin Susceptibility Data Against *Aspergillus* Clinical Isolates
 Determined in RPMI-1640 and AM-3 Media

	RPMI-1640 ($\mu\text{g/mL}$)	AM-3 ($\mu\text{g/mL}$)
<i>Aspergillus</i> isolates (29)		
Range	≤ 0.03 to >64.0	≤ 0.03 to >64.0
MIC ₅₀	0.125	≤ 0.03
MIC ₉₀	0.5	0.125
Geometric mean	0.22	0.07
<i>Aspergillus fumigatus</i> (22)		
Range	≤ 0.03 to 2.0	≤ 0.03 to 64.0
MIC ₅₀	0.125	≤ 0.03
MIC ₉₀	0.25	≤ 0.03
Geometric mean	0.14	0.04
<i>Aspergillus flavus</i> (7)		
Range	≤ 0.03 to >64.0	≤ 0.03 to >64.0
MIC ₅₀	0.125	≤ 0.03
MIC ₉₀	ND [‡]	ND
Geometric mean	0.90	0.40
[†] Microdilution broth method (NCCLS Document: M38-P); RPMI-1640 (Biowhittaker) medium or Antibiotic Medium No. 3 (Difco) + 2% glucose; inoculum 1 to 5×10^4 CFU/mL; incubation at 35°C for 24 hours. MIC was defined as the lowest concentration of caspofungin showing $\geq 80\%$ inhibition of growth (MIC-80). For geometric mean, when the MIC-80 value was ≤ 0.03 $\mu\text{g/mL}$, a value of 0.03 $\mu\text{g/mL}$ was used in the geometric mean calculation. When the MIC-80 value was >64 $\mu\text{g/mL}$, a value of 128 $\mu\text{g/mL}$ was used for the geometric mean calculation. [‡] ND = Not determined. The MIC of 90% (MIC ₉₀) of isolates could not be determined because there were <10 isolates.		

4.5 In Vivo Activity of Caspofungin Against *A. fumigatus*

As noted earlier, a reliable method for measuring organ burdens of filamentous fungi has not been established. Therefore, the in vivo efficacy of caspofungin was assessed by changes in survival in otherwise fatal *A. fumigatus* infection models in rodents. These models utilized increasingly severe immunosuppressive conditions and often incorporated a delay between the *Aspergillus* challenge and the initiation of treatment to increase the therapeutic challenge and more closely mimic human infection; amphotericin treatment groups were included as a positive control. Under these conditions, even in persistently immunosuppressed animals, caspofungin was very effective at increasing survival and was always at least comparable to AmB.

In the sections which follow, results from animal models will be presented as percent survival at the end of the study period. In some experiments, these survival results are expressed as the dose calculated to achieve 50% survival (survival ED₅₀) following a lethal challenge utilizing survival data across a dose range. The ED₅₀ is used to normalize the results between experiments and to appropriately compare different treatments.

4.5.1. Disseminated Aspergillosis in Complement-Deficient and Neutropenic Mice

Caspofungin and AmB significantly protect DBA/2N (C5' complement deficient) mice from a lethal *A. fumigatus* challenge with 5 days (twice daily or once daily administration) of treatment. Caspofungin at doses of approximately 0.1 mg/kg/dose achieved about 50% survival with almost complete protection from the lethal challenge observed at doses of 0.4 mg/kg/dose. These results were similar to those observed with an amphotericin control group (0.046 mg/kg/dose and 0.2 mg/kg/dose to achieve 50% and full protection, respectively).

An additional series of experiments evaluated caspofungin and amphotericin in a murine neutropenia model of disseminated aspergillosis. C3H/HeN mice were rendered neutropenic with a neutrophil depleting monoclonal antibody in an *A. fumigatus* challenge-treatment experiment to determine the efficacy of caspofungin in the setting of neutropenia. Caspofungin or AmB were injected I.P., q.d. for 5 days immediately after challenge. The 50% survival (ED₅₀) values at multiple time points were comparable for both compounds (Table 6). Mice were confirmed to be neutropenic for up to 6 days postchallenge by differential counts. At Days 10 and 20 postinfection, neutrophil counts equaled or exceeded normal levels.

Table 6

Efficacy of Caspofungin and Amphotericin B Against a Disseminated *A. fumigatus* MF5668 Infection[†] in Monoclonal Antibody Induced-Granulocytopenic[‡] C3H/HeN mice[§]

Compound [§]	ED ₅₀ Value (mg/kg/dose) [95% Confidence Interval] Days Post Challenge		
	7	14	21
Caspofungin	0.63 [0.43, 0.93]	1.05 [0.73, 1.51]	1.05 [0.73, 1.51]
Amphotericin B	0.65 [0.46, 0.90]	0.85 [0.61, 1.19]	0.85 [0.61, 1.19]

[†] Granulocytopenic (mAb-induced) C3H/HeN mice challenged IV with 1.0 to 8.0 x 10⁴ conidia/mouse *A. fumigatus* MF5668.
[‡] C3H/HeN mice were made granulocytopenic by the IP administration of 500 µg RB6-8C5 mAb 1 day prior to infection and then 250 µg RB6-8C5 on Days 2 and 4 post challenge.
[§] Mice treated IP, q.d. x 5 days. Mice received first treatment immediately following infection. Data from 3 studies (10 mice per treatment group per study or 30 total).
^{||} ED₅₀ values calculated using ED50.BAS Apl Program based on the Knudson and Curtis method.

4.5.2 Disseminated Aspergillosis in Pancytopenic Mice

Because patients with *Aspergillus* infection frequently have broad immune impairment which may persist for long periods of time, a more stringent animal model of aspergillosis in which to assess the efficacy of caspofungin was sought. Efforts focused on a murine model in which pancytopenia was induced by Cytoxan administration prior to and during therapy. Therapy was also delayed until 24 hours after *Aspergillus fumigatus* challenge to allow the infection to be established. Initial experiments evaluated caspofungin and amphotericin in this model under conditions in which Cytoxan-induced pancytopenia was allowed to resolve approximately at completion of antifungal therapy. In order to establish an even more rigorous test and to evaluate the ability of caspofungin to produce a sustained antifungal effect in the setting of continued immunosuppression, a second series of experiments maintained Cytoxan-induced pancytopenia for at least 2 weeks beyond the completion of caspofungin therapy. Results from both sets of experiments are described below.

Aspergillosis Model With Pancytopenia During Therapy

Outbred ICR mice were rendered pancytopenic by the administration of Cytoxan every 3 days from 3 days prior to challenge to 10 days postchallenge. The mice were challenged with a lethal *A. fumigatus* infection. Treatment (q.d. for 14 days) with

casposfungin, AmB or ABELCET™ (Amphotericin B Lipid Complex Injection, The Liposome Company, Inc.), was initiated 24 hours postchallenge to model treating an established infection. Survival was measured 28 days after therapy was initiated.

As shown in Table 7, the calculated survival ED₅₀ value for casposfungin in this model was 0.245 mg/kg/day and was comparable to AmB. A casposfungin dose of 1 mg/kg/day was associated with a 90% survival.

Table 7

Efficacy (Survival ED₅₀) against Disseminated
Aspergillosis in Cytoxin-Treated Mice[†]

Treatment (24-hr Delay) (I.P., q.d. x 14 Days)	Day 28 Survival ED ₅₀ (mg/kg/dose)
Caspofungin	0.245
AmB	0.264
ABELCET™	1.438

[†] Infected IV with 1.6×10^4 *A. fumigatus* conidia per mouse. 10 mice/group. All infected, sham treated control mice were dead by Day 8.

Aspergillosis Model With Pancytopenia Maintained After Therapy

Outbred ICR mice were rendered chronically pancytopenic by the administration of Cytoxin every 3 days from 3 days prior to a lethal *A. fumigatus* challenge to 25 days postchallenge. This maintains suppression for out to 28 days. Treatment with casposfungin or AmB (I.P., q.d., 7 days) was initiated 24 hours after challenge to model treating an established infection. Survival was measured 28 days after initiation of therapy. The survival associated with Cytoxin treatment in the absence of *Aspergillus* infection was $\geq 95\%$, indicating that mortality is attributable to *Aspergillus* infection.

Caspofungin and AmB had comparable 28 day survival ED₅₀ values in 3 independent experiments (not shown). Actual survival data obtained in each of the experiments and at specific doses is shown in Table 8.

Table 8

Disseminated Aspergillosis in Chronically Pancytopenic ICR Mice
 Day 28 Survival following Caspofungin or AmB Therapy

Treatment (24 hr Delay) (IP, q.d. x 7 Days)	Percent Survival		
	Exp. #1 [†]	Exp. #2 [†]	Exp. #3 [‡]
Infected/Sham-treated	10	10	22
Caspofungin			
1 mg/kg	80	50	92
0.5 mg/kg	80	100	90
0.25 mg/kg	40	30	86
Amphotericin B			
1 mg/kg	80	50	90
0.5 mg/kg	40	70	80
0.25 mg/kg	30	30	56
† N = 10 for each treatment group.			
‡ N = 50 for each treatment group.			

Caspofungin doses of >0.5 mg/kg/day were generally associated with at least 80% survival. These survival results, particularly in the setting of pancytopenia maintained after completion of therapy, provide strong evidence that caspofungin exerts a potent and sustained antifungal effect in aspergillosis.

4.5.3 Pulmonary Aspergillosis in Immune Compromised Rats

In 2 studies conducted at Memorial Sloan-Kettering Cancer Center, NY, male Sprague-Dawley rats were treated with cortisone and tetracycline while on a low-protein diet throughout the study starting at 2 weeks prior to infection. After intratracheal inoculation with 1×10^6 *A. fumigatus* conidia, the rats developed a progressive, rapidly fatal bronchopneumonia.

In the prophylaxis study, rats were treated 2 hours prior to infection with a single dose of saline, caspofungin, or AmB. Survival at Day 7 postinfection was 40% among controls, while it was 60, 90, and 100% in groups that received a single dose of 0.5, 2 mg/kg, and 8 mg/kg of caspofungin, respectively. One hundred percent (100%) survival was seen in the 4 mg/kg AmB group (Table 9).

In another study, rats received daily I.P. therapy starting at the time of infection and continuing for 7 days postchallenge. Survival at Day 7 was 30% among controls, while it was 80, 100, and 100% in the 0.5, 2, and 8 mg/kg caspofungin groups, respectively. One hundred percent (100%) survival was seen in the 4 mg/kg AmB group (Table 9). The results from these studies demonstrate that caspofungin is highly effective in the

treatment and prevention of pulmonary aspergillosis in this animal model which mimics pulmonary aspergillosis in humans.

Table 9

Survival Study—Pulmonary Aspergillosis in Dexamethasone Treated Sprague-Dawley Rats—Treatment and Prophylaxis[†]

	Percent Survival (Day 7)	
	Prophylaxis	Treatment
Control	40	30
Caspofungin		
8 mg/kg	100	100
2 mg/kg	90	100
0.5 mg/kg	60	80
Amphotericin B		
4 mg/kg	100	100
[†] Spraque-Dawley rats were infected via the trachea with 1×10^6 <i>A. fumigatus</i> conidia, 10 rats/group.		

4.6 Conclusions—Activity of Caspofungin Against *Aspergillus* spp.

1. Caspofungin has activity against a range of *Aspergillus* spp. as measured by the induction of morphological changes and in vitro susceptibility testing.
2. Inhibition of cell wall synthesis by caspofungin causes death and lysis of *fumigatus* growing hyphal tips and branching segments as assessed by specific fluorescent stains.
3. The in vitro activity of caspofungin is consistent with in vivo activity observed in immunosuppressed animal models of disseminated and pulmonary aspergillosis. Caspofungin exerts a potent and sustained antifungal effect in these models, similar to efficacy observed with amphotericin.

4.7 In Vitro Activity of Caspofungin Against *Candida* spp.

A range of in vitro and in vivo preclinical studies have examined the activity of caspofungin against *Candida* spp. These studies have demonstrated that caspofungin has potent activity against a wide range of *Candida* isolates, including isolates with inherent or acquired resistance to other licensed antifungals. In vitro susceptibility testing shows 100% growth inhibition for most isolates within clinically achievable concentrations and quantitative kill curves demonstrate that caspofungin is fungicidal against all *Candida* isolates tested.

4.7.1 Evaluation of Caspofungin Against Laboratory Yeast Isolates

A panel of clinical yeast isolates (199) were evaluated for susceptibility using the NCCLS reference method M27-A against caspofungin and AmB. The MIC was defined as that concentration resulting in 100% growth inhibition after 48 hours of incubation in RPMI-1640. The M-27-A method was developed for azole and AmB susceptibility testing and its utility for echinocandins has not been characterized. Susceptibility testing using other conditions has also been explored.

Caspofungin demonstrated potent broad spectrum activity against *Candida* species with MIC₉₀ values for laboratory isolates ranging from 0.5 to 2.0 µg/mL (Table 10). Caspofungin had weak activity (MIC values 16 to 32 µg/mL) against clinical isolates of *Cryptococcus neoformans*. When comparing MIC₉₀ values, caspofungin was comparable in activity to amphotericin with MIC₉₀ values not differing by more than 2-fold against *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. kefyr*, and *C. tropicalis*.

Table 10

Susceptibility (MIC₉₀) of Clinical Isolates to Caspofungin

	MIC ₉₀ (µg/mL)	
	Caspofungin	Amphotericin B
<i>Candida albicans</i> (n=40)	0.5	0.25
<i>Candida glabrata</i> (n=20)	1	0.5
<i>Candida guilliermondii</i> (n=20)	2	0.25
<i>Candida pseudotropicalis</i> (n=20)	0.5	0.5
<i>Candida krusei</i> (n=20)	2	0.5
<i>Candida lusitaniae</i> (n=20)	0.5	2
<i>Candida parapsilosis</i> (n=20)	0.5	1
<i>Candida tropicalis</i> (n=20)	1	0.5
<i>Cryptococcus neoformans</i> (n=19)	32	0.5

NCCLS M27-A, RPMI-1640, inoculum 0.5 to 2.5 x 10³ CFU/mL; incubation at 35°C for 48 hr. MIC for caspofungin and AmB defined as lowest concentration of antifungal inhibiting visible growth

4.7.2 Evaluation Against *Candida* spp. Clinical Trial Isolates

The in vitro susceptibility of *Candida* spp. to caspofungin has also been evaluated against over 950 clinical yeast isolates from 407 patients in the caspofungin clinical trials for localized *Candida* infections. There were 218 unique baseline *Candida* isolates from patients treated with caspofungin. Of these isolates a high proportion across a range of species have MICs <2 µg/mL to caspofungin (Table 11).

A trailing endpoint phenomena is often seen for *C. guilliermondii* and *C. parapsilosis* when tested in RPMI-1640 medium using NCCLS M27-A methodology, which makes

endpoint determinations difficult to interpret. However, this trailing is much less prominent when AM3 media is used instead of RPMI. MICs to caspofungin also tend to be generally lower in the presence of AM3 (Table 11). This difference may be due to the higher osmolality of RPMI which would tend to protect cell wall defective organisms from lysis. Identification of the susceptibility testing methodology with the greatest clinical utility will ultimately depend on the correlation of various testing method results to clinical outcome.

Table 11

Caspofungin Susceptibility (MIC₅₀ and MIC₉₀) of *Candida* Clinical Trial Baseline Isolates Determined in RPMI-1640 and AM-3 Media Medium[†]

(Number of Isolates)	RPMI-1640 MIC ₅₀	RPMI-1640 MIC ₉₀	AM-3 MIC ₅₀	AM-3 MIC ₉₀
<i>C. albicans</i> (180)	0.5	1	0.06	0.125
<i>C. guilliermondii</i> (12)	>8	>8	0.5	>2
<i>C. glabrata</i> (8)	1	ND	0.06	ND
<i>C. krusei</i> (8)	1	ND	0.25	ND
<i>C. parapsilosis</i> (5)	2	ND	0.5	ND
<i>C. tropicalis</i> (4)	0.25	ND	0.06	ND
<i>C. keyfr</i> (1)	0.5 [‡]	ND	ND	ND
Total <i>Candida</i> spp. (218)	0.5	2	0.06	0.125
[†] The MIC was defined as 100% growth inhibition after 48 hours of incubation in RPMI-1640 medium or 24 hours in AM-3 medium. [‡] Represents result of a single isolate. ND = Not determinable; MIC90 calculation requires at least 10 isolates.				

4.7.3 Time-Kill Curve Studies Against *Candida* spp.

In vitro time-kill curve studies were conducted to further characterize the activity of caspofungin against *Candida* isolates. The results of these studies with both *C. albicans* and *C. tropicalis* demonstrate that caspofungin is fungicidal with a 2 log reduction in viable organisms. As shown in (Table 12), the in vitro kill rate for caspofungin versus *C. albicans* was concentration independent and slower than that seen for AmB as determined by the smaller log reductions in colony forming units (CFU) per unit time. A slower kill rate is anticipated for a cell wall synthesis inhibitor in comparison to a compound such as amphotericin which directly disrupts the fungal cell membrane.

Table 12

In Vitro Killing Rates Against *C. Albicans*

Compound	Concentration X MFC [§]	Kill Rate	Time (h) to Reach	Log CFU Reduction
	(µg/mL)	(Log CFU/h)	99% Reduction	@ 9 Hours
Caspofungin	4 X (1.0)	0.29	7	2 [†]
	2 X (0.5)	0.34	5.6	2 [†]
	1 X (0.25)	0.23	7	2 [†]
	0.5 X (0.125)	0.21	8.5	2 [†]
	0.25 X (0.06)	0.23	7.6	2 [†]
Amphotericin B	1 X	1.33	1.3	4 [‡]
Fluconazole	1 X MIC			0
Untreated				-2

[†] Log CFU decreases linearly versus time.
[‡] Reaches four log reduction after 3 hours and then plateaus.
[§] MFC = minimum fungicidal concentration.

4.7.4 Susceptibility of Antifungal-Resistant Isolates to Caspofungin

Based on its distinct mechanism of action, it was anticipated that *Candida* isolates with acquired resistance to currently available antifungals would remain susceptible to caspofungin. As shown in Table 13, testing of clinical laboratory isolates resistant to fluconazole, 5-fluorocytosine and/or amphotericin confirm that MICs to caspofungin remain low despite decreased susceptibility to these other agents.

Table 13

Susceptibility (MIC) of Selected Antifungal-Resistant Clinical Laboratory Yeast Isolates[†]

<i>Candida</i> species [resistant to]	MIC (µg/mL)			
	Caspofungin	AmB	FCZ	5-FC
<i>Candida albicans</i> [5-FC, FCZ, AmB] (N=9) [‡]	0.125 to 1	0.50 to 4	0.5 to >32	0.06 to >32
<i>Candida tropicalis</i> [FCZ] (N=1)	0.125	1	>32	0.06
<i>Candida glabrata</i> [5-FC] (N=2)	0.50	0.50 to 1	>32	0.03 to >32
<i>Candida lusitanae</i> [AmB] (N=2)	1 to 2	8	0.125 to 0.5	≤0.01 to >32

[†] NCCLS broth microdilution method (M27-A), RPMI-1640 media, 1-5 x 10³ CFU/mL inocula, incubation 24 to 48 hr at 35 to 37°C.
[‡] Four (4) Isolates were resistant to fluconazole, 1 to amphotericin B, 2 to 5-flucytosine, and 1 to both 5-flucytosine and fluconazole.

4.8 Animal Models of Infections With *Candida* spp.

Various mouse studies were conducted with *Candida* infections to determine if the in vitro activity of caspofungin translated to in vivo efficacy. Unlike *Aspergillus* studies, several parameters can be used to determine efficacy with yeasts. For systemic infections, tissue burdens can be measured to determine the percent reduction in CFU (colony forming units)/gm of tissue relative to untreated controls. In addition, the same CFU measurement can be used to determine apparent sterilization of a particular organ, although it is limited by the detection limits of CFU determinations (50 CFUs/gram of tissue). Finally, survival can also be determined following a lethal infection, much like in the aspergillosis studies.

A number of experiments using a range of animal models have demonstrated the in vivo efficacy of caspofungin in *Candida* infections based on both survival and tissue sterilization. This summary focuses on studies utilizing a pancytopenic mouse model analogous to those described in studies of caspofungin in *Aspergillus* infection (Section 4.5.2). This model in immunosuppressed animals represents the most rigorous therapeutic challenge for evaluating the efficacy of caspofungin in animals models of disseminated candidiasis.

Outbred ICR mice were maintained pancytopenic by dosing with Cytosan every 3 days starting 3 days prior to infecting with *C. albicans* to the end of the study at 25 days postinfection. Mice received 7 days (I.P., q.d.) of treatment with caspofungin or AmB starting at 24 hr postinfection. As shown in Table 14, all doses of caspofungin tested (0.25 to 1 mg/kg) resulted in a >3 log₁₀ reduction in CFU/gm of kidneys compared to sham-treated controls as determined at Days 14 and 28 postinfection. The reduction in

CFU/gm of kidneys was similar in mice treated with comparable doses of AmB. In contrast, FCZ substantially reduced the CFU/gm kidneys based on the Day 14 time point, but showed recrudescence of the infection by Day 28 postinfection, where there was less reduction in kidney burden relative to controls.

Table 14

Disseminated Candidiasis in Chronically Pancytopenic ICR Mice
 Log₁₀ Reduction of Kidney Fungal Burden

Treatment (24 hr Delay) (I.P., q.d. x 7 Days)	Dose (mg/kg)	Mean Log ₁₀ Change in CFU/gm Kidney [†]	
		Day 14 Postinfection [‡]	Day 28 Postinfection [‡]
Caspofungin	1	-4.19	-4.84
	0.5	-4.20	-4.83
	0.25	-3.48	-3.13
Amphotericin B	1	-3.80	-3.52
	0.5	-3.33	-2.79
	0.25	-2.18	-2.49
Fluconazole	80	-1.89 ⁵	-0.92 ⁵
	40	-0.91 ⁵	-0.76 ⁵
	20	-1.04 ⁵	+0.75 ¹

[†] Log₁₀ reductions are based on reduction in CFU/g kidneys of treated groups compared to sham-treated control animals. Absolute mean log₁₀ CFU/g kidney in sham-treated controls was 6.26 at Day 14 (n=8) and 6.93 at Day 28 (n=2).

[‡] Mice were challenged IV with *C. albicans* MY1055 at 5.6 x 10⁴ CFU/mouse and 1.22 x 10⁵ CFU/mouse. Kidneys aseptically collected at Days 14 and 28 after challenge. Mean log₁₀ CFU/g at time points after challenge for paired kidneys. Ten mice per group unless indicated by superscript number.

It is valuable to express the results of these experiments in terms of the proportion of animals in which kidney tissue has been sterilized. Table 15 shows the percentage of mice in which there are no detectable CFU's in the kidney tissue (limit of detection of 50 CFU/gm kidney). Caspofungin was found to sterilize the kidneys of 70 to 100% of the mice at the 0.5 to 1.0 mg/kg dose and was at least comparable to AmB in this regard. Fluconazole resulted in only a minimal number of mice free of kidney infections.

Table 15

Disseminated Candidiasis in Chronically Pancytopenic ICR Mice
 Percentage of Mice With Kidney Tissue Sterilization

Treatment (24 hr Delay) (I.P., q.d. x 7 Days)	Dose (mg/kg)	% Mice With no Detectable CFUs in Kidneys (Sterilized) †	
		Day 14 Postinfection‡	Day 28 Postinfection‡
Caspofungin	1	70	100
	0.5	100	90
	0.25	60	40
Amphotericin B	1	60	80
	0.5	50	40
	0.25	10	50
Fluconazole	80	0 ⁵	20 ⁵
	40	0 ⁵	20 ⁵
	20	0 ⁵	0 ¹
Sham-treated§		6.26 (0) ⁸	6.93 (0) ²

† Percent reductions are based on reduction in CFU/g kidneys of treated groups compared to sham-treated control animals. Percent sterilization indicates the number of mice with no detectable yeast where the limit of detection was 50 yeast cells per gram of kidneys.

‡ Mice were challenged IV with *C. albicans* MY1055 at 5.6 x 10⁴ CFU/mouse and 1.22 x 10⁵ CFU/mouse. Kidneys aseptically collected at Days 14 and 28 after challenge. Mean log₁₀ CFU/g at time points after challenge for paired kidneys. Ten mice per group unless indicated by superscript number.

§ Sham treated data listed as log₁₀ CFU/gm kidney and (% sterilization). Number of remaining mice of the 10 is shown in the numbered superscript.

When 28 day survival data were compared, percent survival with caspofungin at doses of 0.25, 0.5, and 1 mg/kg were between 80 and 95%. Similar survival rates were observed for AmB at doses of 0.25, 0.50, and 1 mg/kg. Percent survival with fluconazole at doses of 20, 40, and 80 mg/kg was 10, 30, and 50%, respectively. All infected, sham treated control mice were dead by Days 16 to 25 postinfection.

These results demonstrate that caspofungin is highly effective in immunosuppressed mice even with delayed therapy after a lethal *C. albicans* challenge. The high proportion of animals achieving tissue sterilization provides strong support for the fungicidal activity of caspofungin against *Candida*, even in the setting of impaired host response.

4.9 Conclusions—Activity of Caspofungin Against *Candida* spp.

1. Caspofungin has potent in vitro activity against a wide range of *Candida* spp., including isolates that are resistant to currently available antifungal agents.

2. Based on in vitro kill curve studies and tissue sterilization in animal models, caspofungin is fungicidal against *Candida spp.*
3. The in vivo efficacy of caspofungin has been demonstrated in several immunosuppressed rodent models of disseminated candidiasis as measured both by improved survival and as tissue sterilization. The efficacy of caspofungin in these models has been at least as effective as amphotericin B.

4.10 Resistance to Caspofungin

Twenty serial passages of a typical *C. albicans* isolate on subinhibitory concentrations of caspofungin did not substantially increase its initial MIC value (initial MIC of 0.06 versus final MIC of 0.125). Echinocandin-resistance is a very rare laboratory event, occurring at a rate of 1 in 10⁸ in *C. albicans*. Laboratory-generated mutations that allow growth on inhibitory levels of a caspofungin analog mapped to a single locus in *C. albicans*, the *FKSI* gene, the putative catalytic component of glucan synthase. Spontaneous mutants derived in the laboratory were sensitive to AmB, both in vitro and in animal models of candidiasis. In animal models, *FKSI* mutants remained virulent, but responded to treatment with 4-fold higher doses of caspofungin. Laboratory generation of *Aspergillus* resistance to caspofungin has not been performed and no clinical *Aspergillus* isolates with acquired resistance to caspofungin have been identified.

4.11 Drug Combination Studies

Because caspofungin exerts its antifungal activity through a mechanism of action distinct from other agents, the potential utility of caspofungin in combination with other available antifungal compounds was investigated. In vitro studies evaluated caspofungin in combination with AmB against *C. albicans*, *Cryptococcus neoformans*, and *A. fumigatus*. The results of these studies were indicative of additive or indifferent activity; the evidence for synergy was inconclusive. No evidence of antagonism was observed.

Combination therapy including caspofungin was also evaluated in vivo using animal models. Because high doses of either caspofungin or AmB alone achieve high efficacy rates, in vivo studies of combination therapy have focused on lower doses of each agent used together. Against *C. albicans*, caspofungin doses of 0.03 mg/kg and lower plus 0.03 mg/kg and lower of AmB appeared more efficacious than either agent administered alone at these doses, suggesting a potential additive or synergistic effect. However, the evidence for synergy was inconclusive. Combination therapy of caspofungin with FCZ showed similar results with no indication of synergy or antagonism. Against *A. fumigatus*, some improvement in survival was seen with caspofungin at 0.008 to 0.031 mg/kg combined with AmB at 0.031 to 0.125 mg/kg over the compounds administered alone (Table 16).

Table 16

Efficacy Against a Disseminated *A. fumigatus* Infection[†] in DBA/2N Mice
 Comparison of Therapy With Caspofungin Alone and in Combination With AmB[‡]

Percent Survival at 28 Days Postchallenge					
Caspofungin (mg/kg/dose)	AmB (mg/kg/dose)				
	0	0.5	0.125	0.031	0.008
0	0	80	40	10	30
2.0	80	90	100	90	50
0.5	90	100	70	80	50
0.125	70	70	90	50	80
0.031	50	80	80	50	50
0.008	0	90	90	50	0

[†] DBA/2N mice were infected IV with 1.0×10^6 conidia/mouse.
[‡] Mice were treated I.P., q.d. x 5 days. Mice received first treatment within 15 min after challenge. Ten mice/treatment group.

Thus, both in vitro and in vivo studies suggest that combinations of caspofungin with AmB or FCZ have the potential for additive or synergistic activity but results are not definitive. Importantly, no evidence of antagonism was observed.

4.12 In Vitro Activity of Caspofungin Against Other Filamentous and Dimorphic Fungi

Investigators from several laboratories using microbroth dilution assays have evaluated the in vitro activity of caspofungin against other filamentous (Table 17) and dimorphic fungi (Table 18). The potential clinical significance of these findings is difficult to determine in the absence of reproducible animal models.

Table 17

Susceptibility of Other Filamentous Fungi to Caspofungin

Organism (Number of Isolates)	Geometric MIC Value (µg/mL)
<i>Alternaria</i> spp. (n=1)	≤0.09
<i>Bipolaris</i> spp. (n=6)	1.7
<i>Cladophilophora bantiana</i> (n=5)	3.6
<i>Curvularia lunata</i> (n=4)	0.38
<i>Exophiala jeanselmei</i> (n=2)	1.1
<i>Fonsecaea pedrosoi</i> (n=4)	0.13
<i>Fusarium oxysporum</i> (n=5)	75.8
<i>Fusarium solani</i> (n=5)	59.5
<i>Paecilomyces lilacinus</i> (n=5)	50
<i>Paecilomyces variotti</i> (n=2)	≤0.09
<i>Phialophora</i> spp. (n=5)	2.8
<i>Pseudallescheria boydii</i> (n=6)	1.3
<i>Rhizopus arrhizus</i> (n=5)	>100
<i>Scedosporium apiospermum</i> (n=4)	0.38
<i>Scedosporium prolificans</i> (n=2)	8.8

Table 18

Susceptibility of Other Dimorphic Fungi Sensitive to Caspofungin

Organism (Number of Isolates)	Geometric MIC Value (µg/mL)
<i>Blastomyces dermatitidis</i> (n=5),	2.0
<i>Histoplasma capsulatum</i> (n=5),	1.3
<i>Sporothrix schenckii</i> (n=5),	5.4

4.13 Conclusions

1. Caspofungin prevents the synthesis of β (1,3)-D-glucan, an essential cell wall component in many pathogenic fungi.
2. Caspofungin has in vitro activity against *Aspergillus* isolates using the NCCLS proposed M38-P microbroth dilution protocol with either RPMI-1640 or AM-3 medium. The M38-P MIC endpoint of substantial (50 to 80%) inhibition of growth correlates well with the caspofungin concentration which induces morphological changes in *Aspergillus* isolates.

3. Caspofungin causes death and lysis of the growing hyphal tips and branching segments of *A. fumigatus* based on fluorescent stains designed to distinguish viable from dead cells. In regions of less active growth, the hyphae appeared to be viable.
4. Caspofungin is highly efficacious in animal survival models of disseminated aspergillosis and was also efficacious in a pulmonary aspergillosis survival model in rats as a therapeutic or prophylactic agent. In all in vivo studies, the efficacy of caspofungin was comparable to that achieved with AmB.
5. Caspofungin has potent in vitro activity in broth microdilution assays against a wide range of *Candida* spp. including isolates that are resistant to azole antifungals, flucytosine or AmB.
6. Caspofungin is fungicidal against *Candida* spp. based on growth inhibition kinetic studies and tissue sterilization in animal models of disseminated candidiasis.
7. Caspofungin resistance is a very rare event in the laboratory occurring at a rate of approximately 1 in 10⁸ when selected on agar plates with *C. albicans*.
8. Caspofungin has potent in vivo efficacy in a range of animal models of disseminated candidiasis in both immunocompetent and immunosuppressed mice. Caspofungin also sterilizes kidneys in mouse models of disseminated candidiasis even in the setting of impaired host response. The efficacy of caspofungin is similar to that of AmB.
9. Results from in vitro and in vivo tests of caspofungin in combination with AmB against *Aspergillus*, *Candida*, and *Cryptococcus* isolates suggest that this combination is additive or indifferent compared to each compound alone; no evidence of antagonism has been observed. In vivo studies examining the efficacy of caspofungin in combination with FCZ against *C. albicans* show no antagonism.

5. Pharmacokinetics and Metabolism

5.1 Overview

The pharmacokinetics of caspofungin were evaluated in Phase I studies in healthy volunteers and in population pharmacokinetics analyses conducted using data obtained in patients enrolled in the efficacy studies. Various preclinical and in vitro studies were conducted to provide supportive information. This overview focuses on results in humans. Similar pharmacokinetic results were seen in preclinical species.

Metabolism and excretion of caspofungin are very slow processes. In contrast to many drugs, these processes are not the rate-controlling step that determines the clearance of caspofungin from plasma. Rather, plasma clearance, and therefore the plasma concentration-time profile, is determined primarily by the rate of distribution of caspofungin from plasma into tissues. Thus, any factor such as concomitant medication which affects plasma pharmacokinetics is most likely exerting its influence on the distribution of caspofungin from plasma into tissues, rather than metabolism or excretion.

Approximately 75% of radioactivity is recovered in urine and feces over 27 days following a single dose of radiolabeled caspofungin. The major metabolic pathways are peptide hydrolysis and *N*-acetylation and the major circulating metabolite appears to be formed by spontaneous chemical decomposition. Caspofungin is a poor substrate for the major cytochrome P-450 (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 radiolabeled caspofungin. Renal clearance of unchanged caspofungin constitutes a minor pathway of elimination.

Average concentrations at 24 hours postdose following single 70 or 100 mg doses are above a target concentration of 1 µg/mL, which was determined from in vitro susceptibility testing of clinically relevant fungal isolates. This comparison, as well as a relatively long β -phase half-life, support the investigation of once daily dosing regimens. Average concentrations from a 50 mg daily regimen are above the target concentration at steady-state and the use of a 70 mg loading dose on Day 1 of that regimen maintains average concentrations above target throughout therapy.

Race and underlying disease or condition (HIV infection, hematologic malignancy, transplant recipient) are not significant determinants of caspofungin pharmacokinetics. Modest, but clinically unimportant, elevations in plasma concentrations are seen in women, the elderly, subjects with varying degrees of renal insufficiency and subjects with mild hepatic insufficiency. Results from a single dose study in patients with moderate hepatic insufficiency suggest that clinically meaningful increases in plasma concentrations may occur. A proposed dose reduction for patients with moderate hepatic insufficiency is being evaluated in an ongoing study.

Results from in vitro testing and clinical drug interaction studies indicate that drug interactions based on alterations in cytochrome P-450 (CYP) mediated metabolism are unlikely to occur with caspofungin. Itraconazole, tacrolimus, mycophenolate and

probably amphotericin B have no effect on the pharmacokinetics of caspofungin. Coadministration of cyclosporin A moderately increases plasma concentrations of caspofungin, most likely due to reduced tissue uptake of caspofungin. Caspofungin has no effect on the pharmacokinetics of itraconazole, amphotericin B, cyclosporin A and mycophenolic acid, the pharmacologically active metabolite of mycophenolate. Caspofungin slightly decreases whole blood concentrations of tacrolimus. Population pharmacokinetic screening of caspofungin concentrations in patients suggests that coadministration of agents known to induce drug metabolism may reduce caspofungin plasma concentrations. However, the mechanism mediating a possible effect of inducers is more likely to be at the level of drug transport. Further studies with rifampin and nelfinavir are ongoing to investigate this observation in a controlled setting.

5.2 Drug Formulation

Caspofungin acetate has a molecular weight of 1213.42. It is freely water soluble, with a solubility of >400 mg/mL in distilled water at 23°C. Caspofungin for Injection is a lyophilized product which is reconstituted and diluted prior to infusion. Drug supplies for early clinical studies were formulated as frozen solutions of caspofungin acetate.

5.3 Nonclinical Pharmacokinetics

5.3.1 Disposition Kinetics

Following administration of a single IV dose, the elimination of caspofungin in rats and monkeys was very slow, as evidenced by low plasma clearance (CL_p) of 0.5 mL/min/kg in the rat and 0.25 mL/min/kg in the monkey. The area under the concentration-time curve (AUC) increased in a roughly proportional fashion over a dose range of 0.5 to 5 mg/kg in both species, indicating linear pharmacokinetics. The plasma concentrations of caspofungin declined polyphasicly with a long terminal $t_{1/2}$ (>36 hours). Because the drug concentrations in the terminal phase were far below the minimum inhibitory concentration against *C. albicans* (MIC_{90} ; 0.5 μ g/mL), a pharmacologically-relevant $t_{1/2}$ (effective $t_{1/2}$) was calculated using the plasma concentrations that exceeded the MIC_{90} . After IV doses of 0.5, 2, and 5 mg/kg, the effective $t_{1/2}$ values were 6.1, 6.3, and 8.5 hours for rats, and 4.3, 6.3, and 7.9 hours for monkeys, respectively. The apparent volume of distribution at steady-state ($V_{d_{ss}}$) was about 0.6 L/kg for rats and 0.3 L/kg for monkeys. Oral absorption of caspofungin was very poor in rats. Following a single oral dose of 50 mg/kg, the bioavailability of caspofungin was <0.2%.

5.3.2 Distribution

[3 H]Caspofungin was bound extensively to rat, monkey, and human plasma proteins. The free fraction was 4.1% for rats, 1.3% for monkeys, and 3.5% for humans, and the extent of binding was concentration-independent up to 100 μ g/mL. The blood/plasma partition ratio of [3 H]caspofungin for rats, monkeys, and humans was about 0.7.

Following IV administration of [3 H]caspofungin (2 mg/kg) to rats, radioactivity at 0.5 hour postdose was distributed widely into tissues with the highest levels of radioactivity in kidney, lung, liver, and spleen. With the exception of the liver, the concentration of

radioactivity peaked within 2 hours in most tissues and declined with time thereafter. In the liver, the amount of radioactivity peaked at 24 hours postdose at ~35% of the administered dose and consisted predominantly of unchanged drug. Once in the liver, radioactivity declined very slowly; about 3% of the administered dose remained in the liver at Day 12. These results suggest that the processes of hepatic uptake and elimination of caspofungin are very slow, and that the equilibration of drug between blood and liver tissue is not rapid. Results from an in situ rat liver perfusion preparation were consistent with the hypothesis that the hepatic uptake of caspofungin is a two-step process involving an initial rapid binding of the drug to the cell surface that is followed by a slow, as yet unknown, mechanism of transport into the cell.

The potential of caspofungin to act as a substrate of P-glycoprotein (P-gp) was assessed in vivo using P-gp-deficient CF-1 mice (*mdr 1a* (-/-)) and in vitro cell lines (L-*mdr 1a*, L-MDR1, Caco-2, and KB-V1) which over-express mouse and human P-gp. Both in vivo and in vitro data suggest that caspofungin is a poor substrate for P-gp-mediated transport. Caspofungin also was shown not to be a significant P-gp inhibitor and the IC₅₀ value, determined in KB-V1 cells using [³H]vinblastine as a marker substrate, was >100 μM. Thus, drug-drug interactions at the level of P-gp-mediated transport are considered unlikely.

Caspofungin was able to cross the placenta in rabbits and rats. Caspofungin also was secreted into milk in lactating rats after IV administration (See Section 3.4.2 of Preclinical Pharmacotoxicology for details).

5.3.3 Metabolism and Excretion

When [³H]caspofungin (2 mg/kg) was administered intravenously to rats, about 42% of the dose was excreted into urine and 29% into feces over a 12-day collection period. The unchanged drug was detected only in the initial urine samples (<5% of dose), while polar metabolites were the predominant components in the later (>2 days) urine samples. In bile duct-cannulated rats, about 3% of the dose was excreted into the bile within 24 hours, primarily as unchanged drug. Similarly, when monkeys received an intravenous dose (5 mg/kg) of [³H]caspofungin, the radioactivity was excreted almost equally into urine (45%) and feces (36%) over a collection period of 28 days. Again, the unchanged drug (<5% of the dose) was detected only in the initial (Day 1) urine samples.

Qualitatively, all major metabolites of caspofungin detected in humans also were found in rats and monkeys. At approximately 24 hours postdose, caspofungin was the major component of rat, monkey, and human plasma extracts with a trace amount of a peptide hydrolysis product, L-747969. For plasma collected at later time points (> Day 3), the relative proportion of caspofungin decreased and that of L-747969 increased in all species. The majority of the radioactivity in the initial 0 to 24 hr urine of all species was in the form of unchanged drug. At later time points (> Day 2), the major fraction of the radioactivity in urine consisted of predominantly polar metabolites (dihydroxyhomotyrosine, its N-acetyl derivative, and an unidentified minor metabolite).

In vitro studies with rat and human liver microsomes revealed that caspofungin is a poor substrate for the major human cytochrome P450 (CYP) isozymes. At clinically-relevant concentrations (C_{max} of 11 μ M in humans following a 1-hour IV infusion of 70 mg), the inhibitory effect of caspofungin on the major human CYP isozymes was minimal and the IC_{50} values were $>67 \mu$ M for CYP1A2, 2A6, 2C9, 2C19, 2D6, and 3A4. Thus, inhibition by caspofungin of the CYP-mediated metabolism of coadministered drugs is considered to be unlikely in humans.

Following IV administration of [3 H]caspofungin to monkeys (5 mg/kg) and humans (70 mg), low levels of irreversible protein binding of caspofungin-derived radioactivity was detected in plasma. In humans, the extent of the irreversible binding decreased from 7 pmol/mg protein on Day 5/6 to 3 pmol/mg protein on Day 19/20. At comparable time points, the level of irreversible binding in monkeys was about 3 to 5 times higher than that in humans. To elucidate the mechanism(s) responsible for the irreversible binding, a series of mechanistic experiments were conducted with nucleophilic trapping agents glutathione (GSH) and methoxylamine, as well as $H_2^{18}O$. The results from these in vitro studies suggest that during the spontaneous chemical degradation of caspofungin to L-747969, 2 potentially reactive intermediates are generated nonenzymatically which bind irreversibly to plasma proteins. Once bound to plasma proteins, these intermediates are no longer reactive.

5.4 Pharmacokinetics in Healthy Subjects

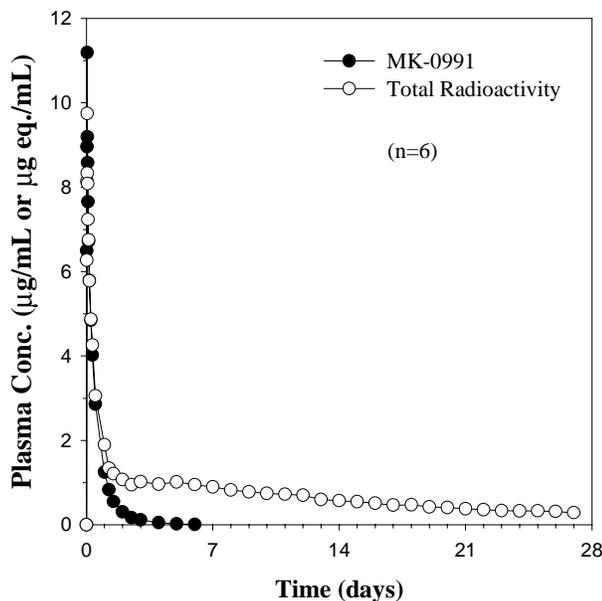
5.4.1 In Vivo Fate of [3 H]Caspofungin

The disposition of caspofungin in man was investigated in an open-label study in which plasma, urine, and feces were collected over 27 days following a single 1-hour infusion of a 70-mg (200 μ Ci) dose of [3 H]caspofungin. An average of 75.4% of the radioactive dose was recovered (40.7% in urine and 34.4% in feces). Plasma concentrations of total radioactivity were roughly comparable to caspofungin concentrations for the first day or 2 postdose, after which parent drug levels fell more rapidly than total radioactivity (Figure 3). Radioactivity remained quantifiable in plasma throughout the 27-day study in all subjects. A long terminal phase with a harmonic mean half-life of 12 days characterized much of the plasma profile of total radioactivity. Parent drug comprised 17% of the total radioactivity in plasma. Plasma concentrations of caspofungin declined in a polyphasic manner following the 1-hour infusion.

The next 3 sections discuss the implications of these findings and related results with regards to distribution, metabolism, and elimination of caspofungin. Absorption is not relevant to the pharmacokinetics of the proposed intravenous treatment regimen.

Figure 3

Mean Plasma Profiles of Caspofungin and Total Radioactivity Following Administration of a Single 70-mg (200- μ Ci) Dose of [3 H]Caspofungin to Healthy Male Subjects



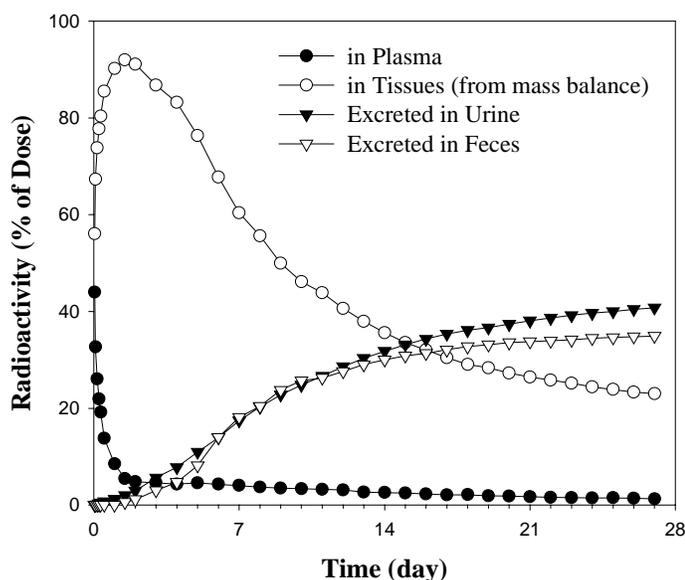
5.4.1.1 Distribution

Distribution plays a prominent role in caspofungin plasma pharmacokinetics and is the rate-controlling step in both the α - and β -disposition phases evident following single doses. The short α -phase apparent for 1 to 2 hours immediately postinfusion is a distribution phase during which the initial distribution volume of ~ 4 L increases to ~ 8 to 10 L, as estimated by compartmental modeling. This result suggests that the expansion of distribution volume occurring during the α -phase is roughly from plasma space to extracellular fluid space (i.e., plasma and interstitial fluid).

The plasma profile of caspofungin is dominated by a prominent β -phase exhibiting log-linear behavior over a period of ~ 6 to ~ 48 hours postdose, during which plasma concentrations drop by approximately an order of magnitude. Little excretion or biotransformation of caspofungin is seen at 24 to 30 hours postdose, implying that distribution is the rate-controlling step during this phase. Caspofungin is likely distributing into the tissues during this phase. In the clinical disposition study, the mass balance indicates that radioactivity in tissues peaks at $\sim 92\%$ of dose at 1.5 to 2 days postdose following administration of a single dose of [3 H] caspofungin (Figure 4).

Figure 4

Mean Distribution and Excretion Profiles of Radioactivity Following Administration of a Single 70-mg (200- μ Ci) Dose of [3 H]Caspofungin to Healthy Male Subjects (n=6)



Animal tissue distribution studies provide some insight into the nature of this tissue distribution. Given the similarity of pharmacokinetics and radiolabeled disposition results in animals and humans, similar mechanisms likely underlie caspofungin disposition across the species. Results from studies in rats and monkeys (Section 3.4.2) are consistent with the uptake of caspofungin into hepatocytes being mediated, at least in part, by an active transport process. This interpretation is also consistent with the fact that most of the caspofungin plasma AUC is associated with the α - and β -distribution phases, even though little excretion or biotransformation of caspofungin occurs during these phases. Active transport of caspofungin into hepatocytes may act as a mechanism of plasma clearance, since the return of caspofungin to plasma would be expected to be mediated by passive diffusion across the cell membranes of the hepatocytes, and therefore would be very slow. The identity of the proposed transport mechanism mediating hepatocyte uptake of caspofungin is currently unknown. It is clear, however, that it is not p-glycoprotein mediated since caspofungin is neither a substrate for nor an inhibitor of the P-glycoprotein transporter.

5.4.1.2 Metabolism

The major metabolic pathways of caspofungin involve peptide hydrolysis and *N*-acetylation, and not oxidative metabolism. Caspofungin degrades chemically to L-747969, a ring-opened peptide, which is the major component of extractable radioactivity in plasma at later time points (beyond 5 days) following single doses. This process is spontaneous, and thus it is expected to occur throughout the body at sites to which caspofungin distributes. In vitro incubation experiments suggest that 2 potentially reactive intermediates are formed during the degradation of caspofungin to L-747969, and that these form covalent adducts to protein. Low levels of irreversible binding to plasma proteins (3 to 7 pmol/mg protein, or 0.6 to 1.3% of administered dose) were seen in vivo during later time points (Days 5 to 20) in the clinical disposition study, as well as in monkey studies where levels 3 to 5 times higher were obtained. Additional metabolism of caspofungin appears to involve the hydrolysis of this hexapeptide into its constitutive amino acids or their degradates. The metabolites M1 and M2 were identified as the synthetic amino acid, dihydroxyhomotyrosine, and its *N*-acetyl derivative, respectively. These metabolites were only seen in urine.

The metabolism of caspofungin is very slow. Caspofungin was the major component of radioactivity in plasma and urine at 24 to 30 hours postdose in the clinical disposition study (Protocol 010), indicating that little biotransformation occurs during the first 2 days postdose. Results from extensive in vitro metabolism studies of [³H] caspofungin using tissue slices, hepatocytes, cellular fractions (S9 and microsomes), recombinant CYP isozymes, and commercially available hydrolytic enzymes indicate that caspofungin is a poor substrate for the major CYP isozymes and the various hydrolytic enzymes tested.

5.4.1.3 Excretion

Radioactivity comprised of caspofungin and its metabolites was excreted very slowly in the clinical disposition study. Caspofungin was excreted unchanged at low levels in urine (1.44% of dose). Renal clearance of caspofungin is very slow, averaging 0.15 to 0.16 mL/min. A striking feature of the radioactivity recovery in the clinical disposition study was that little excretion of drug-related material occurred during the first few days postdose and that the rate of recovery did not peak until 6 to 7 days postdose for both urine and feces. This finding is consistent with there being a series of slow disposition steps occurring prior to the major pathway(s) of excretion, including slow but extensive uptake of caspofungin into the liver, extensive binding to liver tissue, and slow degradation of caspofungin to L-747969, as well as slow formation of M1 and M2.

5.4.2 Single-Dose Pharmacokinetics in Healthy Subjects

In all the clinical studies, caspofungin was administered as a constant-rate, 1-hour intravenous infusion. Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour IV infusions. A short α -phase is seen immediately postinfusion. A dominant β -phase characterizes much of the profile and exhibits clear log-linear behavior from ~6 to ~48 hours postdose. At higher doses, an additional longer half-life phase, γ -phase, is evident. Most of the AUC is accounted for by the β -phase,

which has a half-life of 9 to 11 hours. Plasma clearance is very slow, averaging 10 to 12 mL/min. Plasma concentrations were dose proportional following single doses ranging from 5 to 100 mg. Geometric mean $C_{24 \text{ hr}}$, following single doses of 70 and 100 mg, was above a target concentration of 1 $\mu\text{g/mL}$, which was determined from in vitro susceptibility testing of clinically relevant fungal isolates. This comparison, as well as the relatively long β -phase half-life, supported the investigation of daily dosing regimens.

5.4.3 Multiple-Dose Pharmacokinetics in Healthy Subjects

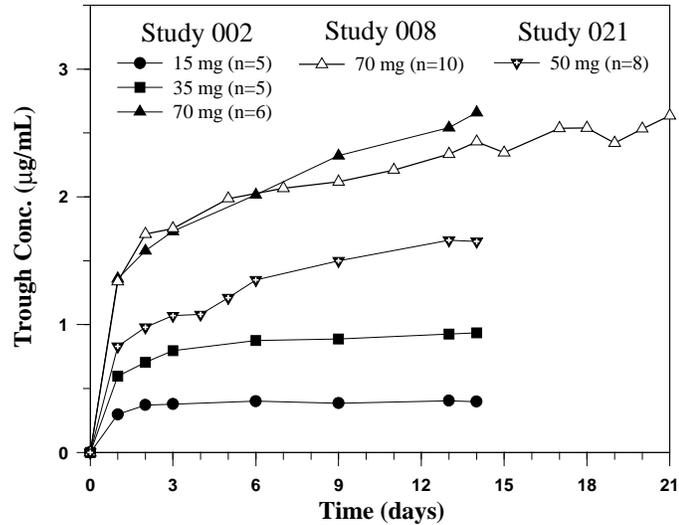
In all multiple-dose studies, caspofungin was administered using a daily dosing regimen. Following daily IV infusion, caspofungin plasma profiles demonstrated moderate accumulation (Table 19). Accumulation was greatest for $C_{24 \text{ hr}}$ and least for $C_{1 \text{ hr}}$. The accumulation data indicate that caspofungin pharmacokinetics are modestly nonlinear. The degree of accumulation of both $\text{AUC}_{0-24 \text{ hr}}$ and $C_{24 \text{ hr}}$, but not $C_{1 \text{ hr}}$, increased with dose in these studies.

5.4.3.1 Steady State

The time course of trough accumulation also indicates a dose dependency in the time to reach steady state (Figure 5). Steady state was obtained within 4 days at 15 mg daily and was not obtained by Day 14 at 50 or 70 mg daily. Slight but continued accumulation was seen during the third week of 70-mg daily administration. Additional data regarding the approach to steady state, obtained in aspergillosis patients (Protocol 019) on long-term (>28 days) therapy, found no continued slow accumulation of caspofungin with long-term therapy.

Figure 5

Mean Trough Concentrations of Caspofungin Following Multiple Daily 1-Hour Intravenous Infusions of 15 to 70 mg to Healthy Men



Protocol 002—Initial, Multiple-Dose Study
Protocol 008—Three-Week Study
Protocol 021—Multiobjective Pharmacokinetic Study

Table 19

Geometric Mean (90% CI) Plasma Pharmacokinetics of Caspofungin Following Daily 1-Hour Infusions to Young Healthy Men

Protocol	Dose (mg/day)	N	Day	AUC _{0-24 hr} (µg•hr/mL)	AUC _{0-24 hr} Ratio [†]	C _{1 hr} (µg/mL)	C _{1 hr} Ratio [†]	C _{24 hr} (µg/mL)	C _{24 hr} Ratio [†]	t _{½ β} (hr)	
002	15	5	1	19.66 (17.94, 21.55)	-	2.47 (2.20, 2.78)		0.29 (0.24, 0.34)			
			14	24.37 (21.45, 27.69)	1.24 (1.15, 1.33)	2.79 (2.51, 3.10)	1.13 (1.04, 1.23)	0.38 (0.31, 0.47)	1.31 (1.17, 1.46)	8.60 (0.89) [‡]	
	35	5	1	41.18 (37.57, 45.14)	-	5.22 (4.65, 5.88)		0.59 (0.50, 0.70)			
			14	54.90 (48.32, 62.38)	1.33 (1.24, 1.43)	5.97 (5.38, 6.63)	1.14 (1.05, 1.24)	0.92 (0.75, 1.13)	1.56 (1.40, 1.74)	9.51 (1.21) [‡]	
	70	6	1	96.01 (88.29, 104.40)	-	12.31 (11.06, 13.70)		1.33 (1.14, 1.56)			
			14	144.27 (128.40, 162.10)	1.50 (1.41, 1.60)	15.42 (14.00, 16.97)	1.25 (1.16, 1.35)	2.61 (2.15, 3.15)	1.96 (1.77, 2.17)	10.70 (1.22) [‡]	
008	70	10	1	93.47 (86.34, 101.20)		12.14 (11.50, 12.81)		1.30 (1.11, 1.51)			
			14	129.61 (117.91, 142.47)	1.39 (1.35, 1.43)	14.03 (13.26, 14.86)	1.16 (1.12, 1.19)	2.37 (2.07, 2.72)	1.83 (1.77, 1.89)		
			21	137.29 (126.03, 149.55)	1.47 (1.43, 1.51)	14.03 (13.47, 15.10)	1.17 (1.14, 1.21)	2.57 (2.23, 2.96)	1.98 (1.85, 2.12)	11.16 (1.20) [‡]	
021	50	8	1	57.57 (NA)		7.64 (NA)		0.76 (NA)			
			14	86.90 (NA)	1.51 (1.43, 1.59)	8.74 (NA)	1.14 (1.07, 1.22)	1.59 (NA)	2.09 (1.82, 2.40)	10.09 (1.58) [‡]	

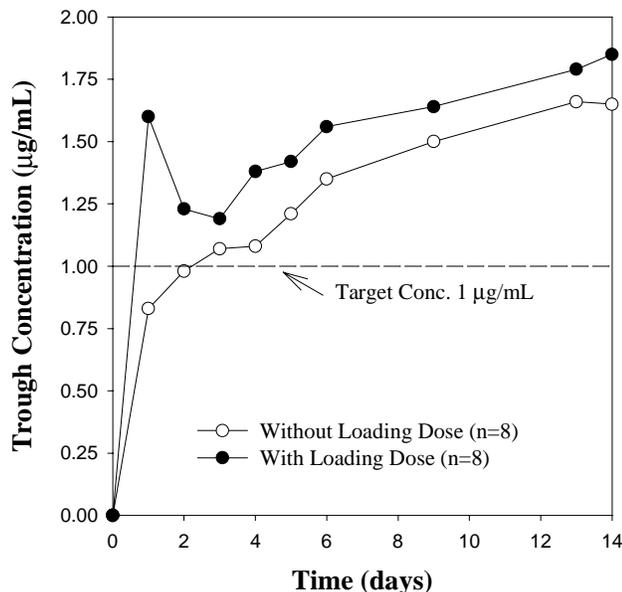
[†] Accumulation ratio relative to Day 1.
[‡] Harmonic mean (jack-knife standard deviation).
 NA = Not available.

5.4.3.2 Loading Dose

A 70-mg loading dose on Day 1 was added to the 50-mg daily regimen used in the studies of invasive aspergillosis and candidiasis, since pharmacokinetic model simulations had suggested that this would allow steady-state concentrations of caspofungin to be reached sooner. A subsequent pharmacokinetic evaluation indicated that the loading dose regimen maintained mean concentrations above the 1- $\mu\text{g}/\text{mL}$ target throughout the 14-day study, while concentrations were below target at trough during the first 2 days of the 50-mg daily regimen without a loading dose (Figure 6). These results confirmed the pharmacokinetic advantage of using the loading dose for life-threatening infections requiring early effective treatment.

Figure 6

Mean Trough Concentrations in Men Receiving 50 mg Caspofungin Daily With or Without a 70-mg Loading Dose on Day 1



5.5 Pharmacokinetics in Patients With Fungal Infections

In a formal pharmacokinetic study, trough concentrations were above a target concentration of 1 $\mu\text{g}/\text{mL}$ on Days 9 and 14 in all *Candida* esophagitis patients receiving caspofungin 50 or 70 mg daily. Moderate accumulation was seen with a dose dependency in the degree of accumulation. On Day 14 at the 50-mg dose, the accumulation of $\text{AUC}_{0-24 \text{ hr}}$ and $\text{C}_{24 \text{ hr}}$ was 38% and 49%, respectively. On Day 14 at the 70-mg dose, the accumulation of $\text{AUC}_{0-24 \text{ hr}}$ and $\text{C}_{24 \text{ hr}}$ was 78% and 124%, respectively. Changes to CANCIDAS™ Advisory Committee Background from Drug Metabolism/

Clinical Pharmacology. Pharmacokinetic steady state in plasma was achieved in these patients by Day 9 at both doses.

Additional data in patients were obtained through population PK/PD analyses of pharmacokinetic data from patients with localized candidiasis (Protocols 003, 004, and 007) and aspergillosis (Protocol 019). The pharmacokinetics in patients and healthy subjects were similar with a tendency for higher variability in the patients relative to healthy subjects. Modest but statistically significant reductions (17 to 26%) in $C_{1\text{ hr}}$ were seen in patients relative to healthy subjects. The alteration in $C_{1\text{ hr}}$ is unlikely to be clinically important.

5.5.1 Definition of a Clinically Significant Alteration in Caspofungin Pharmacokinetics

The population pharmacokinetic data obtained in patients was used to explore the relationship between caspofungin pharmacokinetics and treatment outcome or the occurrence of adverse experiences. These analyses are presented in greater detail later in this document in Section 6.5 (Concentration-Effect Relationship for Treatment Outcome) and Section 7.12 (Concentration-Effect Relationship for Adverse Experiences). In this section, the implication of these analyses regarding the quantitative limits defining a clinically significant alteration in caspofungin pharmacokinetics is discussed.

The population pharmacokinetic analysis for localized candidiasis patients receiving daily doses of 35, 50, or 70 mg identified an association of reduced efficacy with lower trough concentrations and possibly also AUC. No association of increased caspofungin concentrations and increased risk of dose-limiting toxicities were identified. Based on these results, the interval (0.7, 1.5) was selected to define a clinically significant alteration in caspofungin AUC. The lower bound of 0.7 is supported by data suggesting an association of reduced efficacy with reductions in AUC or trough concentration of >30%. No association between an increased risk of a dose-limiting adverse event or laboratory abnormality and increases in AUC of >50% was found. Rather, the 1.5-fold limit was obtained from the ratio of the mean plasma concentrations at the highest dose studied under multiple dosing relative to the recommended dose (i.e., 70 mg daily relative to 50 mg daily). In patients with proven or potentially life-threatening fungal infections, caution indicates that dosing decisions should err on the side of assuring that effective drug concentrations are achieved. Given the absence of clear dose-limiting toxicities related to high plasma concentrations, decisions on whether a dose adjustment should be recommended will be made with an emphasis on assuring that effective caspofungin concentrations are maintained. In cases where the upper bound of a 90% confidence interval (CI) characterizing the effect of a characteristic or condition exceeds 1.5, a dose reduction will only be recommended if the lower bound of that 90% CI substantially exceeds 1. In this way, the risk of reducing caspofungin concentrations relative to patients without that characteristic or condition when the dose adjustment is applied will be small. It should also be noted that this upper limit could be increased in the future, if additional clinical experience at higher exposures is obtained and indicates acceptable tolerability. For $C_{24\text{ hr}}$, there is no reason to suppose that an increase in $C_{24\text{ hr}}$ alone would

be associated with an increase in the risk of adverse experiences. Therefore, $C_{24\text{ hr}}$ is not an appropriate parameter from which to judge clinically meaningful elevations in caspofungin concentrations. The concentration-effect analyses of treatment outcome and adverse experiences suggest that $C_{1\text{ hr}}$ is not an appropriate parameter from which to judge clinically meaningful alterations in caspofungin pharmacokinetics.

5.6 Special Populations

This section examines the effect of various demographic characteristics or underlying organ dysfunctions on caspofungin pharmacokinetics. The interval (0.7, 1.5) will be used throughout this summary to judge whether an alteration in AUC may be clinically meaningful. Table 20 summarizes the results from the special population studies.

Table 20

Summary of Results From Special Population Studies
 of Caspofungin Pharmacokinetics

Population	Protocol	Comparison	N1/N2	AUC GMR (90% CI) [†]
Elderly	022	Healthy Elderly (≥65 years)/Controls	12/12	1.28 (1.08, 1.50)
Gender	021	Young Women/Young Men	8/8	1.22 (1.01, 1.47)
	022	Elderly Women/Elderly Men	6/6	1.18 (0.92, 1.52)
Renal Insufficiency (RI)	011	Mild RI (CR_{CL} 50 to 80 mL/min)/Controls	5/12	0.96 (0.78, 1.17)
		Moderate RI (CR_{CL} 31 to 49 mL/min)/Controls	5/12	1.31 (1.07, 1.62)
		Advanced RI (CR_{CL} 5 to 30 mL/min)/Controls	8/12	1.49 (1.24, 1.79)
		End-Stage RI (CR_{CL} <10 mL/min, dialysis)/Controls	9/12	1.30 (1.09, 1.56)
Hepatic Insufficiency (HI)	009	Mild HI (Child-Pugh 5 to 6)/Controls	8/24	1.55 (1.32, 1.86)
		Moderate HI (Child-Pugh 7 to 9)/Controls	8/24	1.76 (1.51, 2.06)
	030	Mild HI (Child-Pugh 5 to 6)/Controls	8/8	1.19 (1.03, 1.37)
		Moderate HI (Child-Pugh 7 to 9) receiving reduced dose [‡] /Controls	8/8	1.07 (0.90, 1.28)

[†] Geometric Mean Ratio (GMR) for $AUC_{0-\infty}$ following single 70-mg doses (Protocols 022, 011 and 009) or Day 14 $AUC_{0-24\text{ hr}}$ following 50 mg daily with a 70-mg loading dose on Day 1 (Protocols 021 and 030).

[‡] Moderate hepatic insufficiency patients in Protocol 030 received 35 mg daily with a 70-mg loading dose on Day 1 and were compared to healthy controls receiving 50 mg daily with a 70-mg loading dose on Day 1.

CR_{CL} = creatinine clearance.

Note: Effect of race as evaluated in the population pharmacokinetic studies (see Section 5.6.4).

5.6.1. Effect of Age and Gender

Following single doses, caspofungin plasma concentrations in healthy elderly subjects (65 years of age or older) were modestly elevated relative to those obtained in healthy young adults (Table 20). In the covariate analyses of the population pharmacokinetic data, age was found not to be a significant determinant of $AUC_{0-24\text{ hr}}$, $C_{1\text{ hr}}$, or $C_{24\text{ hr}}$. The modest increase in caspofungin plasma concentrations in elderly subjects identified in the Phase I study is judged not sufficient to warrant a dose adjustment in the elderly in view

of the interval defining a clinically significant alteration in pharmacokinetics and the lack of effect of age in patients.

Caspofungin plasma concentrations were unaltered by gender on Day 1, but were modestly elevated on Day 14 (Table 20) in young women relative to young men receiving multiple daily doses, due to somewhat greater accumulation in women relative to men. In elderly men and women, caspofungin pharmacokinetics following single doses were similar (Table 20) with a slight, nonsignificant trend toward higher plasma concentrations in women. In the population pharmacokinetic studies of patients, modest (17 to 38%), statistically significant increases in plasma concentrations in women relative to men were identified. The modest effect of gender on pharmacokinetics of caspofungin is judged not sufficient to warrant different dosing recommendations between men and women.

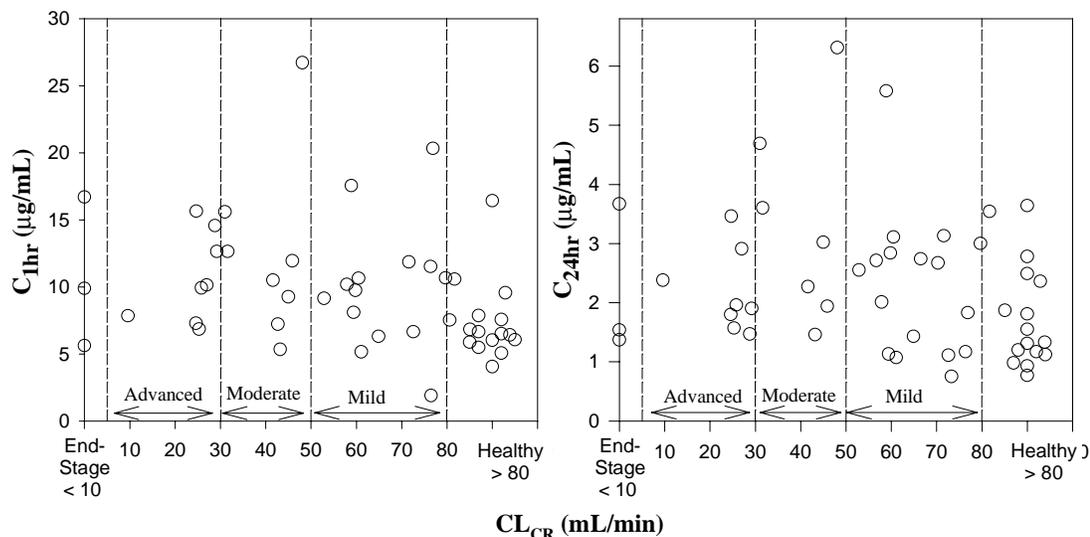
5.6.2 Renal Insufficiency

In a single-dose Phase I study, mild renal insufficiency had no effect and moderate, advanced, and end-stage renal dysfunction were found to have a moderate effect on the pharmacokinetics of caspofungin (Table 20). At study entry in the aspergillosis study (Protocol 019), there were 3 patients with end-stage renal insufficiency and roughly equal proportions of patients with advanced, moderate, and mild dysfunction, and normal renal function. Renal status was found not to be a significant determinant of either $C_{1\text{ hr}}$ or $C_{24\text{ hr}}$ in that study (Figure 7).

No dose adjustment is recommended in patients with mild, moderate, advanced, or end-stage renal insufficiency. The absence of statistically significant differences in plasma concentrations with renal status in patients with fungal disease supports the conclusion that no dosage adjustment is necessary. Caspofungin is not cleared by hemodialysis. No supplementary dose is necessary following dialysis.

Figure 7

Individual Pharmacokinetic Values Versus Estimated Creatinine Clearance in Aspergillosis Patients Receiving 70 mg on Day 1 Followed by 50 mg Daily



5.6.3 Hepatic Insufficiency

Following single doses, hepatic insufficiency was found to moderately increase caspofungin plasma concentrations relative to historical control data (Protocol 009). The effect of hepatic insufficiency was somewhat more pronounced in patients with moderate dysfunction (Child-Pugh 7 to 9) than with mild dysfunction (Child-Pugh 5 to 6) (Table 20). Preliminary results from a more definitive 14-day multiple-dose pharmacokinetic study (Protocol 030) suggest that the effect of mild hepatic insufficiency on caspofungin pharmacokinetics is of smaller magnitude than that observed in the single-dose study. In patients with mild hepatic insufficiency, caspofungin plasma concentrations were modestly increased relative to healthy control subjects matched for age, gender, and weight (Table 20). Recently, preliminary results, not yet reviewed by the agency, have become available from an amendment to the multiple dose study (Protocol 030) designed to test a proposed dose reduction for moderate hepatic insufficiency to 35 mg daily following the 70-mg Day 1 loading dose. The AUC obtained on Day 14 in moderate hepatic insufficiency patients receiving the dose reduction was similar to that obtained in matched healthy control subjects receiving the standard regimen of 50 mg daily following the 70-mg Day 1 loading dose (Table 20).

A reduced rate of metabolism in the setting of hepatic dysfunction cannot account for the alterations in caspofungin pharmacokinetics observed, since little biotransformation of

casposfungin is seen in the first day or 2 postdose even in the absence of hepatic insufficiency. The lengthening of the β -phase half-life following single doses suggests that the rate of uptake into tissues is slowed in patients with hepatic insufficiency.

Based on the preliminary results from the multiple-dose hepatic insufficiency study, no dose adjustment is recommended for mild hepatic insufficiency, and a dose reduction to 35 mg daily following the 70-mg Day 1 loading dose is recommended for moderate hepatic insufficiency.

5.6.4 Other Covariates From Population Pharmacokinetic Studies

Population pharmacokinetics in patients with localized candidiasis and invasive aspergillosis were used to screen for patient characteristics (covariates) which may have an unanticipated effect on casposfungin pharmacokinetics. Low serum albumin was found to be associated with modest reductions in $C_{1\text{ hr}}$ that are unlikely to be clinically meaningful.

Results from both analyses of patient pharmacokinetics, as well as an additional covariate analysis conducted using the pooled healthy subject data, indicate that casposfungin plasma concentrations are higher and more variable in lighter patients/subjects. $C_{1\text{ hr}}$ is affected the most by weight, and $C_{24\text{ hr}}$ is affected the least, if at all. No decrease in dose for patients with low body weight is recommended, given that the clearest association of pharmacokinetics with body weight is for $C_{1\text{ hr}}$, which has no clear association with efficacy or safety, that the association of $C_{24\text{ hr}}$ with body weight is not consistent across the studies, and that adjusting dose on the basis of body weight would likely result in some patients with inadequate $C_{24\text{ hr}}$ values. In the 3 data sets examined (localized candidiasis, aspergillosis, and healthy subjects), there was insufficient information to draw any conclusions regarding the effect of greater than average weight on casposfungin pharmacokinetics. In the limited data available, the lower end of the range of pharmacokinetic parameter values obtained in patients/subjects weighing >90 kg does not appear to be reduced relative to that obtained in patients of average weight (60 to 80 kg), and thus there is no rationale for an increased dose in patients with high body weight.

No clinically meaningful alterations in casposfungin pharmacokinetics with race were identified in the patients from either analysis. In the covariate analysis of patients with localized candidiasis, there were sufficient numbers of Black, Caucasian, Hispanic, and Mestizo patients to provide a meaningful comparison for these races. The patients in the aspergillosis analysis were largely Caucasian.

Underlying disease or condition (HIV infection, hematologic malignancy, transplant recipient) had no significant effect on the pharmacokinetics of casposfungin in patients with fungal infections.

5.7 Drug-Drug Interactions

The drug interaction program for casposfungin addressed both the effect of casposfungin on the pharmacokinetics of other drugs and the effect of other drugs on casposfungin pharmacokinetics. The potential for casposfungin to cause clinically significant inhibition

of cytochrome P-450 enzymes was considered to be low based on in vitro studies with human and rat microsomes, which indicated that caspofungin and its major circulating metabolite, L-747969, would not inhibit the major CYP pathways at clinically relevant concentrations. As discussed in the metabolism section, caspofungin is a poor substrate for cytochrome P-450 enzymes and therefore is unlikely to be subject to CYP-based alterations in its pharmacokinetics. The Phase I drug interaction program focused on 2 classes of drugs: antifungal drugs likely to be coadministered or sequentially administered with caspofungin and immunosuppressants used in transplant recipients, a patient population subject to invasive fungal infections due to their immunosuppression. As in the previous section on special populations, the interval (0.7, 1.5) will be used throughout this summary to judge whether an alteration in caspofungin AUC may be clinically meaningful. Table 21 summarizes the results from the drug interaction studies.

Table 21

Summary of Results From Drug Interaction Studies

Coadministered Drug	Protocol	Dosing Regimens	N ₁ /N ₂ /N ₃ [†]	AUC GMR (90% CI) [‡]	
				Caspofungin	Coadministered Drug
Itraconazole	021	Caspofungin 50 mg q.d. with a 70-mg Day 1 loading dose, Itraconazole 200 mg oral q.d.	7/8/7	1.03 (0.85, 1.25)	0.97 (0.76, 1.24)
Amphotericin B (AmB)	016	Caspofungin 50 mg q.d., AmB—single 0.25-mg/kg dose	6/6/6	0.81 (0.61, 1.09)	0.96 (0.64, 1.42)
Cyclosporin A (CsA)	013	Caspofungin 70 mg q.d., CsA—single 4-mg/kg dose	8/5/5	1.34 (1.17, 1.54)	1.00 (0.87, 1.15)
	017	Caspofungin 70 mg q.d., CsA—two 3-mg/kg doses given 12 hr apart	4/5	1.35 (1.21, 1.49)	1.02 (0.93, 1.11)
Tacrolimus (FK-506)	017	Caspofungin 70 mg q.d., FK-506—two 0.1-mg/kg doses given 12 hr apart	12/5	1.00 (0.96, 1.04)	0.80 (0.72, 0.89)
		Caspofungin 50 mg q.d., FK-506—two 0.1-mg/kg doses given 12 hr apart	8/7	1.05 (0.96, 1.15)	---
Mycophenolate	023	Caspofungin 50 mg q.d., Mycophenolate—single 1.5-g dose	12/6	1.04 (1.00, 1.08)	1.02 (0.95, 1.10) [§]

[†] N₁ = number receiving combination, N₂ = number receiving caspofungin alone and N₃ = number receiving other drug alone. (Note: If no N₃ is given, subjects randomized to the combination group also received comparator drug alone in a 2-period crossover design.)

[‡] Geometric Mean Ratio (coadministration/administration alone) for AUC_{0-∞} or AUC_{0-τ} on the day of coadministration (Protocols 013, 016, 017 and 023) or for AUC_{0-24hr} on the 14th day of multiple-dose coadministration (Protocols 021).

[§] Effect on the active metabolite, mycophenolic acid.

5.7.1 Itraconazole

Coadministration of itraconazole had no significant effect on caspofungin pharmacokinetics (Table 21). Itraconazole is a potent inhibitor of cytochrome P-450 3A4 (CYP3A4). The lack of significant effect of itraconazole coadministration on

casprofungin pharmacokinetics indicates that casprofungin is not subject to drug interactions based on CYP3A4 inhibition. This result confirms the in vitro metabolism results which indicate that casprofungin is a poor substrate for CYP3A4. Coadministration of casprofungin did not alter the pharmacokinetics of itraconazole (Table 21) or 2-hydroxy-itraconazole, a pharmacologically active metabolite of itraconazole. No dosage adjustment for casprofungin or itraconazole is recommended when coadministered.

5.7.2 Amphotericin B

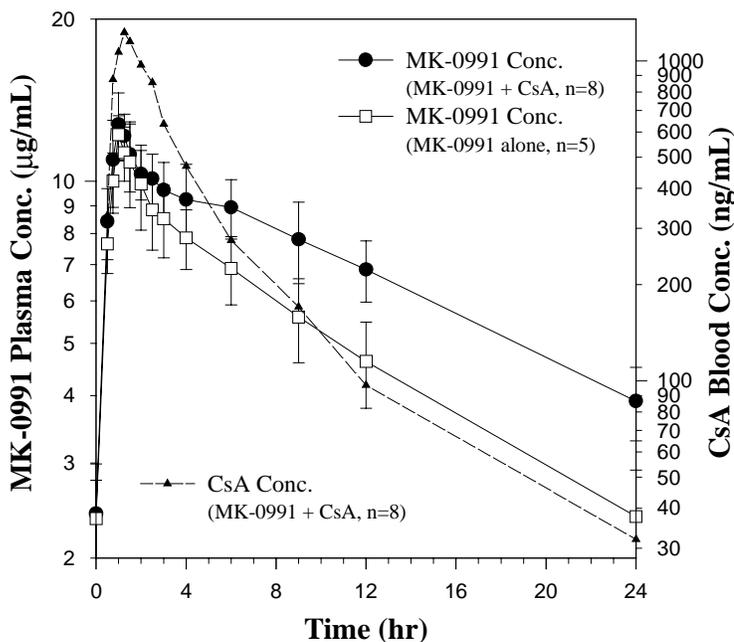
It is likely that amphotericin B has little or no effect on the pharmacokinetics of casprofungin, even though the CI for the effect of amphotericin B on casprofungin AUC extends below 0.7 (Table 21), since most of the difference in pharmacokinetics between the parallel groups appears to be present prior to the coadministration of amphotericin B or placebo. Amphotericin B pharmacokinetics do not appear to have been meaningfully altered by coadministration of casprofungin (Table 21). No dosage adjustment for casprofungin or amphotericin B is recommended if the drugs were coadministered.

5.7.3 Cyclosporin A

Caspofungin plasma concentrations were moderately elevated by coadministration of cyclosporin A (Table 21). The shape of the plasma profile obtained with coadministration suggests that cyclosporin A has a reversible inhibitory effect on casprofungin disposition (Figure 8). Whole blood concentrations of cyclosporin A were essentially unaltered by coadministration of casprofungin (Table 21). The lack of effect of casprofungin on cyclosporin A pharmacokinetics indicates that casprofungin does not significantly inhibit or induce CYP3A4. Elevations in liver transaminases (up to 3 times the upper limit of normal) were observed following coadministration in some subjects. This safety finding is discussed in more detail in Section 7.8 (Drug-Drug Interactions in Clinical Pharmacology Studies).

Figure 8

Mean (SD) Plasma Concentration Profiles From
10th Day of 70-mg Caspofungin (MK-0991) Daily Alone or
Coadministered With a Single Dose (4 mg/kg) of Cyclosporin A (CsA)



The caspofungin disposition process inhibited by cyclosporin A is unlikely to be a metabolic process, since the effect is evident rapidly after coadministration. The lack of effect of itraconazole, a more potent CYP3A4 inhibitor, on caspofungin further supports this conclusion. Cyclosporin A is a potent inhibitor of P-glycoprotein; however, caspofungin has been shown not to be a substrate for this efflux transporter. Furthermore, excretion of caspofungin is a slow process and reduced rate of excretion could not account for the rapid manifestation of the effect observed. The primary alterations in the caspofungin profile following coadministration occurred in the β distribution phase, suggesting that distribution of caspofungin into tissues was altered by cyclosporin A. A rat model of the drug interaction was developed which demonstrated that caspofungin and total radioactivity levels in the liver are reduced by coadministration of cyclosporin A, but that liver tissue binding of caspofungin is unaffected by cyclosporin A. This finding suggests that cyclosporin A inhibits the uptake of caspofungin into the liver. This mechanism does not explain the elevations of liver enzymes noted to occur with caspofungin in combination with cyclosporin A.

The decision whether a dosage adjustment is warranted must be based on an integrated assessment of both the pharmacokinetic and safety interaction. Therefore, it is planned to further evaluate the interaction between these 2 drugs in the setting of concurrent multiple-dose therapy by allowing the enrollment of patients on cyclosporin A in the efficacy trials when the benefit/risk balance is appropriate. In this evaluation, a dosage reduction of caspofungin to 35 mg will be used, because of the increases in ALT (up to 3-fold upper limit of normal) seen in some subjects administered in the combination in Phase I studies. Based upon the pharmacokinetic effect observed in the Phase I studies, administration of caspofungin 35 mg daily with concomitant cyclosporin A should maintain adequate exposure.

5.7.4 Tacrolimus

The pharmacokinetics of caspofungin were unaltered by coadministration of tacrolimus (Table 21). In contrast, the whole blood pharmacokinetics of tacrolimus appear to be slightly reduced in the presence of caspofungin (Table 21). These small reductions may be clinically significant, since tacrolimus has a narrow therapeutic index. Standard monitoring of tacrolimus blood concentrations, as recommended in the product circular for tacrolimus for all patients, will be useful in determining whether any patients receiving concurrent caspofungin therapy require tacrolimus dose adjustments.

5.7.5 Mycophenolate

Mycophenolate had no clinically significant effect on the pharmacokinetics of caspofungin (Table 21). Mycophenolate is a prodrug. Coadministration of caspofungin had no effect on the pharmacokinetics of mycophenolic acid, the active metabolite (Table 21), or mycophenolic acid glucuronide. No dosage adjustment for caspofungin or mycophenolate is recommended when coadministered.

5.7.6 Other Concomitant Medications in Population Pharmacokinetic Studies

Screening for unanticipated drug interactions was conducted in the population pharmacokinetic analyses. It is important not to overinterpret the findings from these drug interaction screens since many factors (small numbers, multiplicity of statistical analysis, overlapping administrations, potential correlations with underlying conditions) confound clear interpretation.

The results of the drug interaction screens indicate that elevations in caspofungin concentrations as a result of drug interactions are not common. Statistically significant reductions in AUC and C₂₄ hr associated with the use of inducers or nelfinavir were of sufficient magnitude that they could be clinically meaningful and were consistent with a plausible mechanism. Although caspofungin has not been shown to undergo oxidative metabolism, an unknown minor oxidative pathway could become a major pathway if induced, or it is possible that a transport mechanism that contributes to caspofungin clearance may be induced. The inducer category included in the localized candidiasis analysis was composed of drugs known to induce CYP3A4 (efavirenz, nevirapine, rifampin, dexamethasone, phenytoin, and carbamazepine), but many of these drugs induce drug disposition processes more broadly than just CYP3A4. While nelfinavir is

known to be a net inhibitor of CYP3A4, available pharmacokinetic data for nelfinavir suggest that this HIV protease inhibitor may also induce other drug disposition process(es) [1-3]. In the aspergillosis analysis, omeprazole, an inducer of CYP1A2, was shown to have no effect on the pharmacokinetics of caspofungin. Reduced caspofungin concentrations associated with the use of other drugs/groups were smaller in magnitude than the associations seen with inducers and nelfinavir, and/or were judged to be more likely due to overlapping administration with inducers or nelfinavir.

A further study of the potential for drug interactions with rifampin and nelfinavir is planned to test the hypothesis that coadministration of inducers or mixed inducer/inhibitors may lead to clinically meaningful reductions.

5.8 Conclusions: Pharmacokinetics and Metabolism

1. Distribution, rather than excretion or biotransformation, is the predominant mechanism controlling caspofungin plasma clearance. Biotransformation of caspofungin is slow. The major metabolic pathways are peptide hydrolysis and *N*-acetylation.
2. Following IV administration of [³H]caspofungin, the radioactivity is distributed widely throughout the body of rats. Liver contains the highest level of radioactivity and hepatic uptake is very slow. Kinetically, the equilibration of the drug between blood and liver tissue is not established rapidly (>24 hours).
3. There is a low level of irreversible binding of radioactivity (3 to 7 pmol/mg protein) in plasma following single dose administration of [³H]caspofungin. In vitro experiments suggest that the chemical degradation of caspofungin to L-747969 involves the formation of 2 potentially reactive intermediates which appear to bind irreversibly to plasma proteins.
4. The radiolabeled dose is excreted almost equally into the urine and feces after IV dosing in rats, monkeys, and humans. Less than 5% of the dose is excreted as unchanged drug in the urine.
5. Caspofungin is not a substrate for P-glycoprotein, nor is it a potent inhibitor of P-glycoprotein. Caspofungin is a poor substrate for CYP isozymes. At clinically relevant concentrations, caspofungin does not inhibit major human CYP isozymes.
6. Administration of a 70-mg loading dose on Day 1 followed by 50 mg caspofungin daily maintains mean caspofungin plasma concentrations above a 1-μg/mL target throughout treatment.
7. No clinically meaningful effects on caspofungin pharmacokinetics were observed for age, gender, race, renal insufficiency, mild hepatic insufficiency, and underlying disease or condition. Pending additional results from a multiple dose study, a dose reduction to 35 mg following the 70-mg loading dose is recommended for patients with moderate hepatic insufficiency.
8. Itraconazole, tacrolimus, mycophenolate, and probably amphotericin B have no effect on the pharmacokinetics of caspofungin. Coadministration of a single dose or 2 doses

Caspofungin Acetate
FDA Advisory Committee Meeting Background
Pharmacokinetics

-71-

of cyclosporin A moderately increases (~35% for AUC) plasma concentrations of caspofungin.

9. Caspofungin has no effect on the pharmacokinetics of itraconazole, amphotericin B, cyclosporin A and mycophenolic acid, the pharmacologically active metabolite of mycophenolate. Caspofungin slightly decreases (~20% for AUC) whole blood concentrations of tacrolimus.

6. Clinical Efficacy

6.1 Overview of the Caspofungin Clinical Development Program

Caspofungin, an echinocandin antifungal, has been shown in vitro to be a potent noncompetitive inhibitor of the synthesis of $\beta(1,3)$ -D glucan, an essential component of the cell wall of a number of pathogenic fungi, including *Aspergillus* and *Candida* spp. This mechanism of action is distinct from the currently available classes of antifungal agents (polyenes and azoles), which both act against the fungal cell membrane. The unique mechanism of action should result in a lack of cross-resistance with approved agents. The safety profile of glucan synthesis inhibitors may also be different from, and potentially superior to, currently approved antifungal agents.

The ongoing development program for caspofungin examines the efficacy and safety of caspofungin in the treatment of documented invasive aspergillosis and localized and invasive *Candida* infections. This section describes the clinical data supporting the efficacy of caspofungin in the treatment of invasive aspergillosis and the rationale for dose selection for Phase III. Data obtained concurrently in *Candida* infections are presented to provide supportive evidence of the efficacy of caspofungin in documented fungal infections. Phase III efficacy studies in *Candida* Esophagitis (Protocol 020—enrollment completed) and Invasive Candidiasis (Protocol 014—ongoing) will provide the basis for determining the efficacy of caspofungin in the treatment of *Candida* infections and will be the subject of a supplemental application. In addition, a Phase III study was recently initiated to assess the empirical treatment of fever and neutropenia, comparing caspofungin to AMBISOME™ (Protocol 026). A clinical pharmacology study has also recently been initiated in pediatric patients to provide pharmacokinetic data to support further studies in the pediatric population. A brief outline of each of the clinical studies in the caspofungin development program is provided in Table 22.

The purpose of this overview is to describe the structure of the clinical program designed to support the efficacy of caspofungin in the treatment of invasive aspergillosis and to highlight the key design issues encountered and addressed across studies. A brief summary of the design and objectives of the completed studies in Esophageal and Oropharyngeal Candidiasis is also provided.

Caspofungin Acetate
 FDA Advisory Committee Meeting Background
 Clinical Efficacy

-73-

Table 22

Clinical Studies Supporting Caspofungin Efficacy

Protocol/ (Short Title)	Phase	Major Entry Criteria	Treatment Daily Doses (mg)/Duration	Primary Efficacy Endpoints
Efficacy in Invasive Aspergillosis				
019 Noncomparative <i>Aspergillus</i> Study	I Ib	Definite or probable <i>Aspergillus</i> infection, and refractory to or intolerant of standard antifungal therapy	MK-0991 70 mg x 1 day, then 50 mg daily/variable	Resolution or clinically meaningful improvement in attributable symptoms, signs, and radiographic or bronchoscopic abnormalities, if present at study enrollment.
024/025 Compassionate Use Protocol	III	Definite or probable <i>Aspergillus</i> infections; documented invasive candidiasis, oropharyngeal candidiasis, or <i>Candida</i> esophagitis and refractory or intolerant of standard antifungal therapy	MK-0991 70 mg x 1 day, then 50 mg daily/variable	Resolution or clinically meaningful improvement in attributable symptoms, signs, and radiographic or bronchoscopic abnormalities, if present at study enrollment.
028/029 Historical Control Study	NA	Definite or probable <i>Aspergillus</i> infection treated between 1995 to 1998 with at least 7 days of therapeutic doses of standard antifungal therapy.	Minimum of 7 days of therapeutic doses of standard antifungal therapy	Resolution or clinically meaningful improvement in attributable symptoms, signs, and radiographic or bronchoscopic abnormalities, if present at study enrollment.
Efficacy in Candidiasis—Studies Completed				
003 Pilot <i>Candida</i> Esophagitis Study	I Ia	Microbiologically documented <i>Candida</i> esophagitis	MK-0991 50, 70 mg daily, or amphotericin B 0.5 mg/kg daily/14 days	Evaluation of symptoms and endoscopy.
007 <i>Candida</i> Esophagitis Pharmacokinetics Study	I Ia	Microbiologically documented <i>Candida</i> esophagitis	MK-0991 50 mg, 70 mg daily/14 days	Pharmacokinetics of MK-0991 in patients with fungal infections.
004 Dose-Response Oropharyngeal or Esophageal Candidiasis Study	I Ib	Microbiologically documented oropharyngeal candidiasis or esophageal candidiasis	MK-0991 35 mg, 50 mg, 70 mg daily, amphotericin B 0.5 mg/kg daily/10 to 14 days	Evaluation of symptoms and oropharyngeal exam or endoscopy.
020 [†] Phase III <i>Candida</i> Esophagitis Study	III	Microbiologically or histopathologically documented diagnosis of esophageal candidiasis	MK-0991 50 mg daily or 200 mg Fluconazole daily/7 to 28 days	Evaluation of symptoms and endoscopy.

Table 22 (Cont.)

Clinical Studies Supporting Caspofungin Efficacy

Protocol/ (Short Title)	Phase	Major Entry Criteria	Treatment Daily Doses (mg)/Duration	Primary Efficacy Endpoints
Ongoing Blinded Studies[†]				
014 Invasive Candidiasis Study	III	Documented diagnosis of invasive candidiasis	MK-0991 70 mg x 1 day, then 50 mg daily, or amphotericin B 0.6 to 1.0 mg/kg daily/14 days after the last + blood culture or deep tissue culture and clinical improvement	Clinical and microbiological response
026 Empirical Therapy Study	III	Febrile neutropenia	MK-0991 70 mg x 1 day, then 50 mg daily, or AmBisome 3 mg/kg daily/until patient's ANC is at least 500 and for up to 72 hours later.	Survival, resolution of fever during period of neutropenia, outcome of baseline fungal infections, breakthrough fungal infection, and discontinuation of study drug because of drug-related toxicity or lack of efficacy
[†] Efficacy data are not yet available; final safety data included. [‡] No efficacy data available; safety limited to blinded, serious adverse experiences.				

Invasive Aspergillosis

The primary efficacy study for caspofungin in the treatment of invasive aspergillosis is a noncomparative study of patients with invasive aspergillosis who are refractory to or intolerant of other therapies (Protocol 019). Consideration was given to conducting a randomized, comparative trial of caspofungin in patients with Invasive Aspergillosis. However, IA is a rare disease with high mortality, and it has not been possible to complete a randomized, comparative trial in patients with this disease. The efficacy data on caspofungin in the treatment of IA were therefore obtained in a noncomparative study using strict definitions of disease and outcome (Protocol 019) with supportive data from a compassionate use study (Protocol 024/025). An approximate comparator group was identified in a retrospective chart review (Protocol 028/029, Historical Control Study) of patients with invasive aspergillosis treated with standard antifungal therapy. The Historical Control Study was designed to identify a patient population that closely resembled the patients in the Noncomparative *Aspergillus* Study (Protocol 019) using the same definitions for diagnosis and response to therapy. The approach of using a

historical control is consistent with what has been used to evaluate the efficacy of other antifungals for the treatment of invasive aspergillosis.

A literature review was also conducted to provide an estimate of Case Fatality Rate (CFR) and an assessment of potential prognostic factors in patients with IA in a time frame contemporary to Protocol 019. While a systematic literature review can often provide useful general information, the applicability of such a review for direct comparison with the results from Protocol 019 was anticipated to be limited. There were inherent limitations in identifying comparable data based on similarly strict diagnostic and outcome criteria in the published reports. In addition, information in published reports is often presented in aggregate, making it difficult to determine outcome by relevant risk category.

Recognizing the limitations of noncomparative studies, every effort was made in the design of the *Aspergillus* studies (Noncomparative *Aspergillus* Study, Compassionate Use, Historical Control Study) to enhance the interpretability of the data obtained. Several specific interventions were made, and a summary of the distinctive features of the caspofungin *Aspergillus* program is provided. The principal goal was to ensure stringent and consistent interpretation of diagnoses and outcomes.

Key Features of Study Design in Invasive Aspergillosis Studies

Definitions for Diagnosis and Outcome

Strict entry and outcome criteria were applied consistently across the *Aspergillus* studies. Definitions of disease were modeled after Mycoses Study Group (MSG) criteria and are consistent with the new joint recommendations of the MSG and the European Organization on Research and Treatment of Cancer (EORTC). In all studies (Protocols 019, 024/025, and 028/029), patients were required to have definite extrapulmonary aspergillosis or probable or definite pulmonary aspergillosis. Less well-documented cases (possible disease) were excluded. In addition, probable pulmonary aspergillosis was defined as requiring supportive data from culture or antigen detection; appropriate clinical and radiographic abnormalities were necessary, but not sufficient, for diagnosis.

The definitions of refractory and intolerant in the Noncomparative *Aspergillus* Study (Protocol 019) were consistent with those used in studies of other antifungals, but documentation supporting the status of infection at diagnosis and study entry was required for all refractory patients. This information provided a basis for confirming progression of infection or failure to respond to initial antifungal therapy. In the Historical Control Study (Protocol 028/029), patients were required to have received at least 7 days of therapeutic doses of standard antifungal therapy to be considered for chart abstraction. This was intended to exclude patients who would not have survived long enough to meet minimum eligibility criteria for entry into the Noncomparative *Aspergillus* Study (Protocol 019).

In all 3 studies (Protocols 019, 024/025, and 028/029), a favorable outcome was defined as complete or partial response, consistent with MSG criteria, but all favorable responses

required significant improvement or resolution of attributable radiographic findings in addition to improvement in signs and symptoms of infection. Documentation of this improvement was required; copies of official radiographic reports and actual films were collected from all patients in the Noncomparative *Aspergillus* Study (Protocol 019) and the Compassionate Use Study (Protocol 024/025). Official reports and radiographs were not collected for patients in the Historical Control Study (Protocol 028/029), but sites were instructed to transcribe interpretations from official radiographic reports in the medical record onto the case report forms.

In the Noncomparative *Aspergillus* Study (Protocol 019), the primary assessment of outcome included all patients with the appropriate diagnosis who received at least one dose of caspofungin therapy and had any data on which to base an assessment of outcome. Patients who received short courses of therapy were not censored from the primary analysis of efficacy. Because studies in invasive aspergillosis have frequently presented outcome data limited to patients who receive some minimum course of therapy (typically at least 7 days), outcomes in the noncomparative *Aspergillus* study (Protocol 019) are also presented for patients who received >7 days of therapy. This outcome assessment is intended to be supportive of the primary analysis.

Expert Panel

The data from the Noncomparative *Aspergillus* Study (Protocol 019) were strengthened by the independent expert evaluation of cases. A 3-member panel of mycologists, expert in invasive aspergillosis, reviewed all cases enrolled into the study. The objectives of the panel were to provide consistent and authoritative assessments of diagnosis, determine whether patients were refractory to or intolerant of standard therapy, and evaluate outcome after caspofungin treatment. The panel was provided with case report form summaries; copies of official reports of radiographs, procedures, and autopsies; and actual radiographs. The Expert Panel assessments are considered primary and are the results presented in this document. The 3 patients in the Compassionate Use Study (Protocol 024/025) with invasive aspergillosis were also reviewed by the same Expert Panel as for Protocol 019 and outcome is based on Expert Panel assessments for these patients.

Invasive Aspergillosis Studies

There were three studies supporting the efficacy of caspofungin in the treatment of invasive aspergillosis: the Noncomparative *Aspergillus* Study (Protocol 019), the Historical Control Study (Protocol 028/029), and the Compassionate Use Study (Protocol 024/025).

Noncomparative Aspergillus Study (Protocol 019)

Protocol 019, the primary efficacy trial for invasive aspergillosis, was an open-label, noncomparative study of well-documented cases of IA using stringent criteria, and data on 69 patients are included. Although all patients have been reviewed by the Expert Panel, only assessments on the initial 58 patients were available at the time of the submission of the application. Final data on the additional 11 patients were included in

the application, but the efficacy was based on investigator assessments. These 11 patients have subsequently been reviewed by the Expert Panel and the assessments of the Expert Panel for these 11 patients are also described in this document. Of note, there were no differences in final diagnosis or outcome (favorable or unfavorable) between the Expert Panel and investigator assessments for these 11 patients.

The Primary Efficacy analysis included all patients who met diagnostic criteria for invasive aspergillosis, received at least one dose of caspofungin and had data on which to base an assessment of outcome. Sixty three of the 69 patients (54 + 9) enrolled were included in the efficacy analysis and an accounting of patients is in Figure 9 in Section 6.3.1.

Compassionate Use Study (Protocol 024/025)

The compassionate use study used the same definitions of disease and outcome as Protocol 019, but captured more limited efficacy data; it was designed to allow patients access to caspofungin in a compassionate use setting and to provide supportive evidence of the efficacy of caspofungin in the treatment of IA. Three patients with definite IA were evaluated for efficacy by the same Expert Panel as those in Protocol 019.

Historical Control Study (Protocol 028/029)

The Historical Control Study was a retrospective medical chart review of patients with IA who were treated from 1995 to 1998 with standard antifungal therapy at 9 U.S. sites (Protocol 028) and 1 European site (Protocol 029). The characteristics of the population enrolled in the Noncomparative *Aspergillus* Study (Protocol 019) and the rigorous criteria used for diagnosis and outcome make it difficult to compare the results to published studies of other agents. Although there are well-recognized limitations to historical comparisons, Protocol 028/029 was designed to identify a population that was approximately comparable to the patients enrolled in Protocol 019. As described, the Historical Control Study included patients who met the same diagnostic criteria for IA and definitions of outcomes as the patients in Protocol 019. Eligible cases were enrolled starting at 31-Dec-1998 and working backward in time until data collection for this study ended or until 01-Jan-1995 was reached. This process was designed to yield, at each site, a consecutive series of cases meeting eligibility criteria comparable to those of Protocol 019, with enrollment ending just prior to the start date of Protocol 019. All patients in Protocol 028/029 received a minimum of 7 days of therapeutic doses of standard antifungals. This mirrored the minimum duration of initial therapy that patients had to receive before becoming eligible for enrollment into Protocol 019. Patients in Protocol 028/029 were relatively contemporary with patients in Protocol 019 (1995 to 1998 versus 1998 to 2000, respectively) and treated at similar sites. In fact, a majority of patients in each study were entered from the same 4 investigator sites. This overlap in investigator sites was done to ensure that medical practices were consistent across studies.

One relevant factor that could not be accounted for in a historical control group was the difference between salvage and primary therapy. There was also the tendency to bias

patient selection towards the sickest patients in Protocol 019. Despite the inherent difference in the study populations, a comparison does provide useful information about the effectiveness of the new drug.

The comparison of Protocol 019 to Protocol 028/029 was performed by tabular displays. To further account for potential differences between the 2 study populations in the relevant baseline characteristics which could influence outcome, a more formal quantitative comparison between populations was prospectively defined. A small set of prognostic factors that were clinically relevant predictors of clinical outcomes were identified in the Historical Control Study population by stepwise logistic regression. The comparison of outcomes between Protocol 019 and Protocol 028/029 was then made by logistic regression adjusting for potential imbalances in prognostic factors between the 2 study populations. In addition to the primary comparison, several models were used to ensure that the conclusions were robust to the specific analytical methods used.

Esophageal and Oropharyngeal Candidiasis

As previously stated, studies in patients with documented *Candida* infections were conducted concurrently. Additional supportive data on the efficacy of caspofungin in the treatment of documented fungal infections are provided by the completed Phase II *Candida* studies (Protocols 003 [Phase IIa *Candida* esophagitis study, 004 [oropharyngeal and esophageal candidiasis study], and 007 [noncomparative pharmacokinetic *Candida* esophagitis study]). These studies were designed to demonstrate that caspofungin was effective in the treatment of oropharyngeal and esophageal candidiasis, based on resolution of symptoms and reduction in endoscopic or oropharyngeal lesions in patients with microbiologically confirmed infections. These studies were also used to select the dose of caspofungin for further evaluation in Phase III studies. Two randomized, double-blind, comparative studies (Protocols 003 and 004) compared the effects of 2 and 3 doses of caspofungin, respectively, to amphotericin B. One noncomparative, open-label study (Protocol 007) explored the pharmacokinetics, safety, and efficacy of 2 doses of caspofungin in patients with *Candida* esophagitis. A total of 282 patients were enrolled in the Phase II *Candida* studies, and 193 received caspofungin. Of note, efficacy data from the Phase III *Candida* esophagitis study (Protocol 020) are not yet available.

Organization of the Efficacy Section

As outlined, this section describes the efficacy data on caspofungin from studies in invasive aspergillosis and supportive data in esophageal and oropharyngeal candidiasis. The section is organized as follows: 1) Rationale for Dose Selection for Phase IIb/III studies; 2) Efficacy in Invasive Aspergillosis; and 3) Results of Phase II Studies in Esophageal and Oropharyngeal Candidiasis.

6.2. Rationale for Dose Selection for Phase IIb/III Studies

The selection of the dose of a new chemical entity for the treatment of IA is complex. Typical dose-ranging studies are not feasible for this rare disease associated with a high mortality. In addition, because mortality is high early in treatment, it is important to ensure that effective drug levels are achieved rapidly. The selection of the caspofungin dose of 50 mg IV daily, after a 70-mg loading dose on Day 1, for the treatment of IA is based on the integration of data from in vitro and in vivo preclinical studies in IA, human pharmacokinetics, and safety and efficacy data from less serious fungal infections such as esophageal candidiasis, as outlined below.

Dose selection for caspofungin was based in part on preclinical data that demonstrated activity against *Aspergillus* and *Candida* spp. There is currently no standardized method for testing in vitro susceptibility to glucan synthesis inhibitors. Thus, the initial in vitro evaluation of caspofungin against *Aspergillus* was based on identifying a concentration of drug that produced morphological alterations in the growing tips of *Aspergillus* hyphae. The concentration of drug that produced microscopic morphological changes (MEC), ranged from 0.008 to 0.5 µg/mL for the *Aspergillus* species tested and was found to correlate with activity in animal models and with an endpoint using standard microbroth dilution (MIC). Based on NCCLS method M38P at 24 hours in RPMI-1640 medium, the MEC was found to correlate with an MIC-80, the concentration of caspofungin that produced substantial inhibition of visible fungal growth. Therefore, the MIC-80 was selected as the appropriate endpoint for the initial determination of in vitro susceptibility. Subsequent testing of several *Aspergillus* spp. using this endpoint demonstrated a minimum inhibitory concentration for 90% of isolates tested (MIC₉₀) that was consistently ≤1 µg/mL. These results supported the hypothesis that caspofungin had activity against *Aspergillus*.

Caspofungin was tested in several murine models of disseminated aspergillosis to confirm that the morphological changes seen in vitro resulted in biologically relevant effects in animals. In the most stringent model studied, delaying the initial treatment of disseminated aspergillosis in chronically pancytopenic mice for 24 hours, caspofungin treatment at a dose of 1 mg/kg resulted in prolonged survival, as compared to results in untreated controls. Survival at 28 days was comparable to that seen with 1 mg/kg doses of amphotericin B. These data correlated the morphological changes, observed in vitro after exposure of *Aspergillus* hyphae to caspofungin, with in vivo efficacy in murine models. Preclinical studies in *Candida*, performed concurrently with the studies on *Aspergillus*, demonstrated that the MIC₉₀ of caspofungin for *Candida* spp. was also ≤1 µg/mL and that there was in vivo efficacy in several animal models, including a chronically pancytopenic murine model of disseminated candidiasis.

Although the specific PK/PD relationships for glucan synthesis inhibitors were unknown, it was clear from the in vivo animal studies that the response was dependent on the dose of caspofungin. Furthermore, even doses of caspofungin that yielded C_{24 hr} plasma concentrations less than the MIC₉₀ for *Aspergillus* produced efficacy results similar to those seen with amphotericin B. However, results from preclinical animal efficacy

models may not directly translate to comparable dosing in humans. In the absence of a more clearly defined PK/PD relationship, a conservative strategy was adopted to identify a clinical dose that maintained plasma concentrations above the target of 1 µg/mL, the MIC₉₀ for most *Candida* and *Aspergillus* spp., for the entire dosing interval.

Single-dose administration of caspofungin to healthy men demonstrated the β-phase half-life of IV caspofungin, administered as single doses of 5 to 100 mg to be 9 to 11 hours. The geometric mean C_{24 hr} following single doses of 70 and 100 mg was above the target concentration of 1 µg/mL. This comparison, as well as the relatively long β-phase half-life, supported the investigation of once daily dosing regimens. Multiple-dose studies in healthy volunteers showed that caspofungin doses of 50 mg daily resulted in a C_{24 hr} >1 µg/mL.

The initial clinical evaluation of caspofungin was for the treatment of esophageal candidiasis. This infection was selected because diagnosis and outcome could be reliably documented; conduct of a randomized, blinded, comparative trial was possible; and there was minimal risk to patients if the doses selected were subtherapeutic. Based on the in vitro susceptibility and PK data from Phase I, the doses of caspofungin selected for the Phase IIa study in *Candida* esophagitis (Protocol 003) were 50 and 70 mg IV daily. The 50-mg dose was expected to provide caspofungin levels above the predicted MIC₉₀ for the entire 24-hour dosing interval. The 70-mg dose was included to allow evaluation of a dose that would result in higher levels for a greater portion of the dosing interval. In this randomized, comparative Phase II study of caspofungin versus amphotericin B, both doses of caspofungin were effective, well tolerated, and appeared at least as effective as amphotericin B. This study supported the hypothesis that once-daily dosing was appropriate, and that caspofungin at doses of 50 and 70 mg daily was effective in treating infections due to *Candida*.

Because Protocol 003 did not determine a minimum dose associated with efficacy, a second trial (Protocol 004) was conducted in oropharyngeal and esophageal candidiasis. This study was designed not only to repeat the evaluation of the 50- and 70-mg doses but also to assess a lower 35-mg dose; a comparison to amphotericin B was included as well. In this 140-patient Phase II study, all 3 doses of caspofungin appeared at least as effective as amphotericin B. There was no evidence of dose-related toxicity across the range of caspofungin doses tested (35 to 70 mg). In the formal analysis of dose response, no dose response was demonstrated. However, the response rate at 35 mg was numerically lower than at 50 or 70 mg. This was consistent with a population pharmacokinetics analysis of this study showing that a lower caspofungin C_{24 hr} was more commonly associated with an unfavorable outcome. There was no apparent increase in efficacy at 70 mg, as compared to 50 mg. Based on these findings, the dose of caspofungin selected for evaluation in Phase III studies was 50 mg daily.

Pharmacokinetic evaluation of multiple doses of 50 mg caspofungin in patients and healthy volunteers demonstrated that the mean C_{24 hr} early in treatment was <1 µg/mL. While a slightly lower trough level early in therapy did not appear to influence outcome in patients with *Candida* esophagitis, low trough levels were considered a potentially

critical issue early in the treatment of invasive infections. As a result, a formal comparison of the pharmacokinetics of the 50-mg daily regimen versus the 50-mg daily regimen with a 70-mg loading dose on Day 1 was conducted. The loading-dose regimen maintained mean concentrations above the 1 µg/mL target throughout the study, while concentrations were below this target during the first 2 days of the 50-mg daily regimen without a loading dose. For invasive infections, the dosage regimen of caspofungin selected was 50 mg daily IV, after a 70-mg loading dose on Day 1.

Although the Phase II studies had evaluated patients with locally invasive *Candida* infections, the same dosing regimen was felt to be appropriate for IA. The patterns of in vitro susceptibility and results from in vivo animal models were similar in *Candida* and *Aspergillus*. Dose-ranging studies in *Candida* esophagitis (Protocols 003, 004, and 007) supported the efficacy of caspofungin in documented fungal infections. Pharmacokinetics in patients and volunteers showed that 50 mg daily IV, after a 70-mg loading dose on Day 1, would provide caspofungin levels above 1 µg/mL throughout therapy. Therefore, the caspofungin dosing regimen selected for the treatment of invasive aspergillosis was 50 mg daily IV, after a 70-mg loading dose on Day 1.

6.3. Invasive Aspergillosis Studies

Caspofungin's efficacy in the treatment of invasive aspergillosis was evaluated primarily in the Noncomparative *Aspergillus* Study (Protocol 019) with supportive data from the Compassionate Use Study (Protocol 024/025). The results from the noncomparative *Aspergillus* study were compared to a historical control group treated with standard antifungal therapy that was identified in a retrospective chart review (Protocol 028/029). The design of each study and major efficacy results are summarized in this section.

6.3.1 Efficacy of Caspofungin in Patients With *Aspergillus* Infections Who Are Refractory to or Intolerant of Standard Therapies (Protocol 019)

Study Design

Protocol 019 is a multicenter, open, noncomparative study of patients with well-documented IA using stringent criteria. Only patients with definite extrapulmonary aspergillosis and definite or probable pulmonary aspergillosis were eligible. Definite disease was defined as positive culture or histopathology from an invasive procedure plus appropriate clinical and radiographic findings. Probable pulmonary aspergillosis required an appropriate clinical setting, radiographic abnormalities consistent with IA, and either positive cultures from sputum or bronchoalveolar lavage or repeatedly positive tests for the detection of antigen (galactomannan ELISA) or DNA polymerase chain reaction (PCR). These definitions of infection are modeled after the Mycoses Study Group (MSG) criteria [1] and are consistent with the new joint recommendations regarding the definitions for invasive fungal infections that have been developed by the MSG and the European Organization on Research and Treatment of Cancer (EORTC) [13].

Patients were required to be refractory to or intolerant of other antifungal therapy. Refractory was defined as demonstrating progression of infection or failure to improve after a minimum of 7 days of therapeutic doses of effective antifungal therapy.

Intolerance was defined as a doubling of creatinine or creatinine ≥ 2.5 mg/dL on standard therapy, creatinine ≥ 2.5 mg/dL due to another preexisting condition, or other significant intolerance to amphotericin B or lipid formulations of amphotericin B. Documentation supporting response to initial antifungal therapy was required. All systemic antifungal therapy was to be discontinued prior to study entry.

Efficacy Endpoints

The primary endpoint for the evaluation of IA was the overall clinical and radiographic response, assessed primarily at the end of IV therapy. A favorable response was defined as either a complete response (resolution of all attributable clinical and radiographic findings of infection) or a partial response (clinically significant improvement in attributable clinical and radiographic findings). Documentation supporting significant improvement or resolution of attributable radiographic abnormalities was required for a patient to be classified as having had a favorable response. The interpretation of findings from pertinent radiographs was documented in the case report form and copies of official radiographic reports and films were forwarded to Merck Research Laboratories (MRL) for review by the Expert Panel.

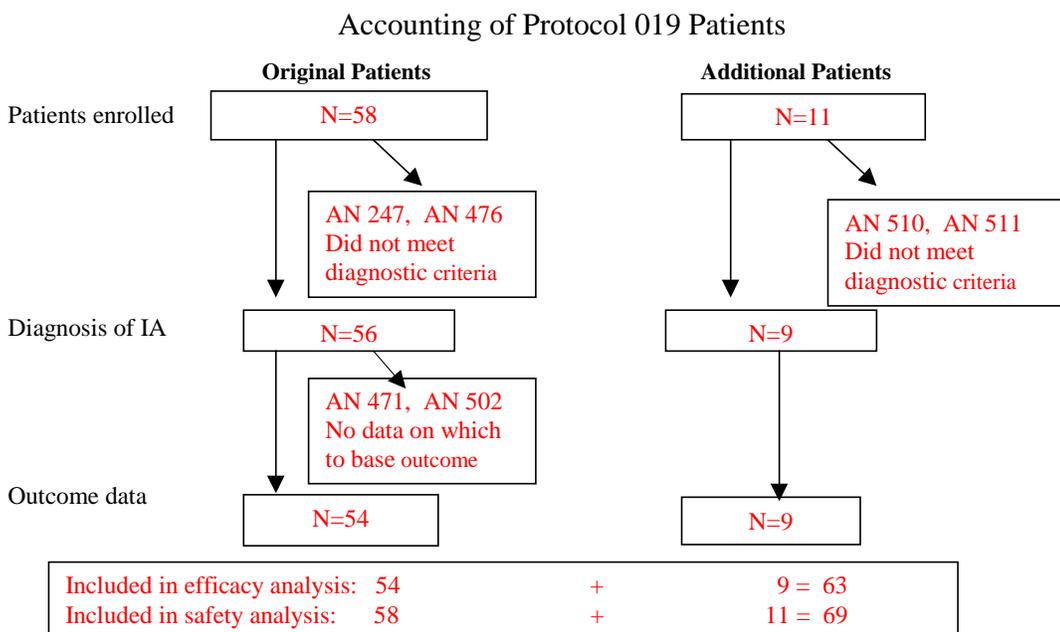
Patients were also evaluated for evidence of relapse (recurrence of infection after a favorable response at end of IV therapy) at a follow-up visit 4 weeks after discontinuation of IV therapy. Microbiologic outcome was a secondary endpoint and was assessed for all patients for whom the diagnosis was based on culture.

Independent Expert Panel

Because of the complexities involved in determining the diagnosis of IA and assessing outcome after treatment, an independent Expert Panel reviewed the data on patients enrolled in Protocol 019. The panel was comprised of 3 mycologists noted to be international experts on aspergillosis (Drs. Thomas Walsh, David Denning, and Thomas Patterson). The Expert Panel was provided with case report form data and official reports of radiographs, relevant procedures, and autopsies, as appropriate. Radiographic films were available for review. Each case was reviewed independently by each panel member. Based on the data provided, each member defined the diagnosis of infection, determined whether each patient was refractory to or intolerant of initial therapy, and determined the outcome after caspofungin therapy. Any disagreements were discussed and resolved at a face-to-face meeting with all three members present. At the meeting, case details and radiographs were reviewed and, after a discussion of the discrepancies, the panel voted. The experts were unanimous among themselves in their assessments of diagnosis in all but 2 assessments of outcome. As predefined, in the few cases in which there was disagreement among experts, the majority vote was considered final. In most cases, the final assessments of the Expert Panel also agreed with investigator assessments of diagnosis, status as refractory or intolerant, and outcome. However, the Expert Panel assessments were somewhat more conservative and the overall response rate was slightly lower by Expert Panel than by investigator assessment. Discrepancies between the Expert Panel and Investigator assessments are summarized in Appendix 1. The patients were included in the evaluation of efficacy by the Expert Panel if they were considered to

have met the criteria for diagnosis and had data on which to base an assessment of response. Sixty-three of the 69 patients enrolled met these requirements as displayed in Figure 9.

Figure 9



As described earlier, the Expert Panel assessments of the first 58 patients enrolled were included in the application. Data from the investigator assessments were available at the time of the submission on 11 additional patients and were summarized in the application. The Expert Panel has subsequently completed their review of the 11 additional patients and the Expert Panel assessments of these patients are also provided. The efficacy data from Protocol 019 are summarized in 3 parts based on Expert Panel assessments: (1) original 58 patients; (2) 11 additional patients; (3) overall summary of all 69 patients enrolled.

6.3.2 Demographics and Baseline Characteristics of Patients Enrolled in the Noncomparative Aspergillus Study (Protocol 019)

The baseline demographic characteristics of patients enrolled in the Noncomparative *Aspergillus* Study (Protocol 019) are in Table 23. In the Noncomparative *Aspergillus* Study (Protocol 019), the original 58 enrolled patients were between 20 and 71 years of age. The mean duration of caspofungin treatment was 31.1 days (range 1 to 162 days; median: 23 days). The majority of the original 58 patients (~60%) with IA treated with

casposfungin in the Noncomparative *Aspergillus* Study were men with a mean age of ~48 years. Most patients were Caucasian (94.8%). There was a high prevalence of poor prognostic factors in the study population. Almost all patients had significant underlying immunosuppression. The most common underlying disease was hematologic malignancy (67.2%); acute myelogenous leukemia was the malignancy most frequently reported. Forty-one percent of patients included in the category of hematologic malignancies had undergone allogeneic bone marrow (BMT) or peripheral stem cell transplants (PSCT). Most other patients were also immunocompromised, and predisposing conditions included solid organ transplants (13.8%), solid tumors (3.4%), and high dose corticosteroid use (6.8%). Approximately 5% had other risk factors for IA, including, in 1 patient each, methotrexate use, skull trauma, and prior pulmonary mycobacterial infection. No clear risk was identified in 2 patients, both of whom had definite extrapulmonary infections. Approximately 22% were neutropenic (absolute neutrophil count [ANC] <500/ μ L), and 39.3% had been receiving high-dose corticosteroid therapy (defined as \geq 20 mg prednisolone-equivalents/day) at study entry. Of note, 82.1% of patients were enrolled as refractory to standard therapies, and 17.9% of patients were enrolled as intolerant of standard therapies.

The additional 11 patients had similar baseline characteristics as shown in Table 23.

Secondary Diagnoses

All patients had one or more secondary diagnoses. The most common secondary diagnoses included: edema/swelling, cytomegalovirus infection, abdominal pain, septicemia, hypertension, diarrhea, nausea, diabetes mellitus, anemia, acute myelogenous leukemia, thrombocytopenia, bone marrow transplantation, graft-versus-host disease, pneumonia, and renal insufficiency.

Prior Therapies

All patients received one or more prior therapies. The most common prior therapies included: acyclovir, amphotericin B formulations, itraconazole, meropenem, vancomycin, human red blood cells (RBCs), platelet concentrate, acetaminophen, meperidine hydrochloride, morphine, propacetamol, furosemide, omeprazole, hydrocortisone, insulin, methylprednisolone, tacrolimus, and albuterol .

Concomitant Therapies

The most common concomitant therapies were acyclovir, sulfamethoxazole and/or trimethoprim, vancomycin hydrochloride, human RBCs, platelet concentrate, filgrastim, acetaminophen, fentanyl citrate, lorazepam, morphine, propacetamol, furosemide, omeprazole, ranitidine, hydrocortisone, insulin, methylprednisolone, tacrolimus, albuterol, and ipratropium bromide.

Caspofungin Acetate
 FDA Advisory Committee Meeting Background
 Clinical Efficacy

-85-

Table 23

Baseline Patient Characteristics for Patients Enrolled in the
 Noncomparative *Aspergillus* Study (Protocol 019)

	Protocol 019 Caspofungin		
	N=58	Additional Patients N=11	Total N=69
	n (%)	n (%)	n (%)
Gender			
Male	35 (60.3)	11 (100.0)	46 (66.7)
Female	23 (39.7)	0 (0.0)	23 (33.3)
Race			
Caucasian	55 (94.8)	10 (90.9)	65 (94.2)
Hispanic	2 (3.4)	1 (9.1)	3 (4.3)
Black	1 (1.7)	0 (0.0)	1 (1.5)
Age (Years)			
<18	0	1	1
18 to 25	4	3	7
26 to 40	13	1	14
41 to 65	33	5	38
>65	8	1	9
Mean	48.4	42.2	47.4
Standard deviation	13.3	21.0	14.8
Median	51.0	49.0	51
Range	20 to 71	15 to 71	15 to 71
Site of <i>Aspergillus</i> Infection (Final Diagnosis)			
	N=56 With IA	N=9 With IA	N=65 with IA
Pulmonary, probable	17 (30.4)	2 (22.2)	19 (29.2)
Pulmonary, definite	23 (41.1)	4 (44.4)	27 (41.5)
Disseminated	10 (17.9)	3 (33.3)	13 (20.0)
Sinus	4 (7.1)	0 (0.0)	4 (6.2)
Central nervous system	1 (1.8)	0 (0.0)	1 (1.5)
Pulmonary/sinus	1 (1.8)	0 (0.0)	1 (1.5)
Refractory or Intolerant			
	N=56 With IA	N=9 With IA	N=65 with IA
Refractory	46 (82.1)	9 (100.0)	55 (84.6)
Intolerant	10 (17.9)	0 (0.0)	10 (15.4)
Underlying Disease			
Hematologic malignancies [†]	39 (67.2)	7 (63.6)	46 (66.7)
Organ transplant	8 (13.8)	1 (9.1)	9 (13.0)
Solid tumor	2 (3.4)	1 (9.1)	3 (4.3)
Other risk factors/no clear risk factor [‡]	9 (15.5)	2 (18.2)	11 (15.9)
Neutropenic Status (cells/microliter)			
ANC [§] <500	13 (22.4)	3 (27.3)	16 (23.2)
ANC [§] ≥500	45 (77.6)	8 (72.7)	53 (76.8)
[†] Includes bone marrow transplant. [‡] Includes: corticosteroids (4), no risk factor (3), methotrexate use (1), skull trauma (1), mycobacterial infection (1), chronic GVHD (1). [§] ANC = absolute neutrophil count.			

6.3.3 Efficacy Results in the Noncomparative Aspergillus Study (Protocol 019)

Diagnoses of Invasive Aspergillosis

Section 6.3.3 will focus on the 54 patients who met diagnostic criteria for invasive aspergillosis, received at least one dose of caspofungin and had data on which to base an assessment of outcome and are included in the Expert Panel assessment of outcome. As displayed in Table 24, the majority of patients had pulmonary aspergillosis (72.2%). Approximately 19% of patients had disseminated infection (defined as involvement of 2 or more noncontiguous sites or positive blood culture). Other extrapulmonary sites of infection included sinus, central nervous system (CNS), and pulmonary/sinus. All patients with extrapulmonary infections had definite diagnoses, as did 59.0% (23/39) of the patients with pulmonary disease. Twelve of 16 patients with probable pulmonary aspergillosis had culture confirmation of infection by bronchoalveolar lavage or sputum; 3 had repeatedly positive galactomannan ELISA, and 1 patient had a repeated positive polymerase chain reaction for *Aspergillus* (PCR). Most infections documented by culture were caused by *Aspergillus fumigatus*, but *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* were each isolated in small numbers of patients.

The Expert Panel also classified patients by sites of infection that were suggestive of IA but did not meet the strict diagnostic criteria defined in Protocol 019. Three patients (allocation numbers [ANs] 251, 426, and 427) with probable pulmonary aspergillosis were also classified as having possible CNS aspergillosis, based on radiographic imaging studies that demonstrated multiple CNS lesions. One patient (AN 471) enrolled with definite sinus aspergillosis, was classified as also having possible pulmonary aspergillosis, based on chest radiograph findings of bilateral pulmonary infiltrates. None of these 4 patients had culture or pathology data supporting a diagnosis of IA at these additional sites and are therefore identified by the site of infection that met Protocol 019 diagnostic criteria (3 probable pulmonary and 1 definite sinus). This categorization resulted in patients being included in a better prognostic group (i.e., pulmonary instead of disseminated disease) and therefore provides the most conservative estimate of outcome by site of infection.

Table 24

Distribution of Final Diagnoses of *Aspergillus* Infections
 As Determined by the Expert Panel (Protocol 019)

Site of Infection	N=54 [†] n (%)
Definite Pulmonary	23 (42.6)
Probable Pulmonary [‡]	16 (29.6)
Extrapulmonary	15 (27.8)
Disseminated	10
CNS	1
Sinus	3
Pulmonary/sinus	1

[†] Excludes 2 patients considered not assessable for outcome by the Expert Panel (AN 471 with pulmonary/sinus disease and AN 502 with pulmonary disease).
[‡] Includes 3 patients (ANs 251, 426, 427) all with probable pulmonary and 'possible' CNS disease.

Although patients frequently received multiple antifungal drugs prior to entry in the noncomparative Aspergillosis study (Protocol 019), patients are characterized by the treatment regimen to which they were refractory or intolerant.

As shown in Table 25, most patients (81.5%) were refractory to prior antifungal therapies. Antifungal therapy to which patients were refractory included amphotericin B, lipid formulations of amphotericin B, and itraconazole. Approximately 36% (16/44) of patients who were refractory to prior therapy were refractory to multiple agents, including at least one formulation of amphotericin B. Patients in this category were either refractory to agents administered in combination (N=5), agents administered sequentially (N=8), or multiple agents administered both in combination and sequentially (N=3). Seventy percent (70.5%) (31/44) of refractory patients had received >14 days of standard therapy and 56.8% (25/44) had received >21 days of standard therapy prior to entry. Most patients enrolled as refractory had documented progression of IA during initial standard antifungal treatment.

Ten patients were intolerant to initial therapy, including 4 to amphotericin B, 3 to lipid formulations of amphotericin B, 1 to itraconazole, and 2 to multiple agents. Eight of 10 intolerant patients, including the 2 patients who received >14 days of initial therapy, had no improvement noted during the prestudy period.

Table 25

Distribution of Patients by Treatment Reason and Prior Antifungal Treatment
 Expert Panel Assessment (Protocol 019)

Treatment Reason Prior Antifungal Treatment	N=54 [†] n (%)
Refractory [‡] to	44 (81.5)
Amphotericin B	7
Lipid Amphotericin B	7
Itraconazole	13
Voriconazole	1
>1 Antifungal [§]	16
Intolerant to	10 (18.5)
Amphotericin B	4
Lipid Amphotericin B	3
Itraconazole	1
Voriconazole	0
>1 Antifungal [§]	2
Total	54 (100)
[†] Excludes 2 patients considered not assessable for outcome by the Expert Panel (AN 471 and AN 502). [‡] Includes patients who were both refractory and intolerant. [§] Includes 5 patients refractory to combination treatment, 8 patients refractory to sequential treatment, and 3 patients who were refractory to combination and sequential treatment.	

Overall Response (Clinical and Radiographic)

The Expert Panel determined that 22 (40.7%) of 54 patients had a favorable response at the end of IV therapy as assessed by the primary endpoint of clinical and radiographic response. Because patients who received ≤7 days of treatment were unlikely to have evidence of response to study therapy, outcome was also evaluated in patients who received >7 days of caspofungin therapy. Of 45 patients who received >7 days of caspofungin therapy, 22 (48.9%) had a favorable response. All of those who received ≤7 days of therapy either died on treatment or had support withdrawn because of poor overall prognosis. Three patients were assessed as having had a complete response, and 19 patients as having a partial response. Because of the rigorous interpretation of clinical response used by the Expert Panel, it was not unexpected that only a small number of patients met the definition of complete resolution of all radiographic findings at the end of IV therapy. Investigators had determined that 10 of the 22 patients with a favorable response had a complete response.

Sixteen of the 20 patients with a favorable response at the end of IV therapy who continued into follow-up were assessed as having had a favorable response at the 4-week follow-up evaluation. Only one patient (AN 0326) had a documented relapse at 4 weeks in the setting of neutropenia during an allogeneic bone marrow transplant (BMT). Two

patients were lost to follow-up (withdrew from the study) and one patient died during the follow-up period. The continued favorable response in the majority of patients indicates that the improvement seen on caspofungin therapy was durable.

Overall Response by Demographics and Disease Characteristics

Several factors would be expected to influence the response to therapy in patients with IA, and the prevalence of these factors in the overall study population, as well as in those patients with a favorable response, also has been assessed. Data from the 54 patients included in the Expert Panel analysis of outcomes were used for this evaluation. Outcomes classified by factors predicted to influence response to therapy are in Table 26.

Outcome is displayed by whether patients were refractory to or intolerant of other therapies. Most patients were refractory to initial therapy; most had progression of disease on that initial treatment. More than 70% of refractory patients had received >14 days of therapy prior to study entry, and 50% (22/44) of refractory patients had received multiple antifungal drugs (this includes 16 patients who were refractory to more than one antifungal agent and 6 patients who received more than one antifungal agent prior to study entry but met criteria as refractory to only one drug). A favorable response was seen in 34.1% of these refractory patients. The number of patients intolerant to other therapies was small. Moreover, although entry as intolerant did not exclude patients responding to standard therapy, most patients enrolled in Protocol 019 as intolerant, including the 2 who received >14 days of prior antifungal therapy, had no improvement on this standard therapy. The 70% favorable response rate in these patients can therefore be attributed primarily to the effect of caspofungin.

As expected, response rates were lower in subgroups known to be associated with a poor prognosis, such as allogeneic transplants, disseminated disease, neutropenia, and high-dose corticosteroids. However, although response rates were lower, favorable responses were still seen in these subgroups. Nineteen percent of patients with allogeneic transplants, 20% with disseminated disease, 18% with neutropenia, and 32% on high-dose corticosteroids had a favorable response. These response rates are notable because, as described, >80% of the patients in this study were refractory to other antifungal therapy, an added predictor of unfavorable outcome. In addition, the high prevalence of these poor prognostic factors in the population indicates that many patients actually had multiple factors associated with a negative prognosis, a feature not accounted for in Table 26.

Table 26

Patient Outcomes by Demographics and Disease Characteristics
 Protocol 019 Expert Panel Assessment

	N=54 n/m [†]	%	95% CI
Refractory Versus Intolerant			
Refractory [†]	15/44	34.1	20.5, 49.9
Intolerant	7/10	70.0	34.8, 93.3
Gender			
Female	7/21	33.3	14.6, 57.0
Male	15/33	45.5	28.1, 63.6
Underlying Disease			
Hematologic malignancy	10/20	50.0	27.2, 72.8
Allogeneic BMT/P SCT [§]	3/16	18.8	4.1, 45.7
Organ transplant	3/7	42.9	--
Solid tumor	2/2	100.0	--
Other	4/9	44.4	--
Site of Infection			
Pulmonary	18/39	46.2	30.1, 62.8
Disseminated	2/10	20.0	2.5, 55.6
Central nervous system	1/1	100.0	--
Sinus	1/3	33.3	--
Pulmonary/sinus	0/1	0.0	--
Neutropenia			
Neutropenic (ANC [‡] <500)	2/11	18.2	2.3, 51.8
Nonneutropenic	20/43	46.5	31.2, 62.3
Corticosteroids			
<20 mg prednisolone equivalent/day	15/32	46.9	29.1, 65.3
≥20 mg prednisolone equivalent/day	7/22	31.8	13.9, 54.9
[†] Number of patients with favorable response/number of patients in the subgroup. [‡] Includes 16 patients who were both refractory and intolerant. [§] BMT/P SCT = bone marrow transplant/peripheral stem cell transplant. [‡] ANC = absolute neutrophil count.			

There is also a relationship between changes in the degree of immunosuppression and outcome after therapy for IA. The complexity of the patients' underlying diseases makes it difficult to determine the specific contribution to outcome made by each change in immunosuppression; however, an understanding of the basic immune status of patients is helpful in assessing outcome. Patients had clear response to caspofungin without a decrease in immunosuppression.

As displayed in Table 26, 11 of 54 patients were neutropenic at study entry. Six of the 11 patients continued to be neutropenic at the end of IV therapy, and none of these patients had a favorable response. The other 5 patients recovered from neutropenia during the study period, and the 2 favorable responses were in this group. However, these 2 patients (AN 0326, AN 0328) demonstrated evidence of response to therapy prior to recovery of their neutrophil counts. In addition, 1 patient (AN 0330) who is included in the nonneutropenic group became neutropenic (total white blood cell count = 300)

during caspofungin therapy as a result of chemotherapy administered during study therapy. Although this patient was neutropenic at the end of caspofungin therapy, he had a favorable response.

Twenty-two patients were receiving high-dose corticosteroids at study entry. Seven (31.8%) of these patients had a favorable response and 4 of the 7 were still receiving high-dose corticosteroids at the end of therapy. Patients commonly received other immunosuppressive therapy during the trial. Sixteen patients were receiving tacrolimus; 8 were receiving mycophenolate mofetil in addition to tacrolimus and caspofungin. A favorable response was seen in 8 (50%) of these 16 patients, and all were still receiving these agents at the end of caspofungin therapy with a comparable degree of immunosuppression.

Finally, surgical debridement may influence outcome in patients with IA. The Expert Panel commented that surgical debridement or resection could play an important adjunctive role in the treatment of IA and did not necessarily equate with failure of antifungal therapy. Three patients (ANs 0219, 0248, and 0316) were classified as having surgery that likely contributed to overall outcome. In these cases, the Expert Panel determined that caspofungin therapy was an important component of the overall treatment.

Microbiologic Response

Investigators assessed microbiological response in the 47 patients who had culture confirmation of infection. A favorable end-of-treatment assessment of eradication or presumptive eradication was seen in 14 (41.2%) of 34 patients who received >7 days of caspofungin therapy. Favorable microbiological responses were seen in patients with infections caused by *A. fumigatus* (8/33), *A. flavus* (5/9), and *A. niger* (1/4) (1 patient with *A. Terreus* had an unfavorable response). There was no apparent relationship between caspofungin MICs for any of the *Aspergillus* species isolated and microbiologic outcome at discontinuation of IV. In fact, both patients with caspofungin MICs of >64 µg/mL for *A. flavus* had a favorable microbiological outcome. In patients who had persistent positive cultures for *Aspergillus* at the end of caspofungin therapy, relatively little change was noted in MIC (≤2-fold increase) in either medium tested (RPMI or AM3) that correlated with failure.

6.3.4 Efficacy of Caspofungin in 11 Additional Patients in the Noncomparative *Aspergillus* Study (Protocol 019)

As outlined, 11 additional patients have been evaluated by the Expert Panel since the submission of the application. The Expert Panel agreed with investigator assessments regarding final diagnosis; status as refractory or intolerant (all were refractory); and categorization of response as favorable or unfavorable (4 of 9 had a favorable response). Nine of the 11 additional patients met diagnostic criteria as assessed by the Expert Panel. The Expert Panel assessments are described in this section.

Baseline Characteristics

The 11 additional patients were 15 to 71 years of age and primarily Caucasian (90.9%); all were men. Most patients had underlying hematologic malignancies (63.6%), including 2 patients with acute lymphocytic leukemia, and 1 patient each with acute myelogenous leukemia, chronic lymphocytic leukemia, large granular lymphocytic leukemia, non-Hodgkin's lymphoma, and myelodysplasia. Other predisposing conditions were present in 1 patient each and included lung transplant (AN 0191), solid tumor (AN 0102, non-small-cell lung cancer), congenital immunodeficiency with allogeneic BMT (AN 0536, Wiskott-Aldrich Syndrome), and no identified risk factor (AN 0291). Six patients had pulmonary aspergillosis, and 3 had disseminated disease (AN 0318, AN 0386, and AN 0536). The nine patients with IA were all refractory to initial antifungal therapy, including 3 who had received multiple agents prior to study entry. Four patients had received >21 days of prior antifungal therapy. Three patients (AN 0386, AN 0472, and AN 0512) were neutropenic (ANC <500/ μ L) at study entry and 1 (AN 0065) was receiving high-dose corticosteroid therapy (defined as \geq 20 mg prednisolone-equivalents/day).

Overall Response (Clinical and Radiographic)

As assessed by clinical and radiographic response, the Expert Panel determined that 4 (44.4%) of 9 patients who met the criteria for diagnosis of invasive aspergillosis and received at least one dose of caspofungin therapy had a favorable response at the end of therapy. Favorable responses were seen in 3 of 6 patients with pulmonary aspergillosis and 1 of 3 with disseminated disease. All 4 patients with a favorable response were refractory to prior antifungal therapy, including amphotericin B (AN 0102), lipid formulation of amphotericin B (AN 0065 and AN 0318); and more than one antifungal (AN 0291). Two patients (AN 0065 and AN 0318) who had a favorable response became neutropenic prior to completion of caspofungin therapy as a result of chemotherapy administered during a relapse of their underlying hematological malignancies. Four of 7 patients who received >7 days of caspofungin therapy had a favorable response. The 11 additional patients who have recently been evaluated by the Expert Panel are similar to the original 58 with regard to baseline characteristics. The proportion of patients with a favorable response remains consistent with a favorable response in 4/9 (44%).

6.3.5 Summary of Caspofungin Efficacy in the Noncomparative *Aspergillus* Study (Protocol 019)

This section provides an update on the overall study results from the 69 patients enrolled. All tables display the patients in 3 columns; initial 58 patients, additional 11 patients, and the 69 patients combined.

Baseline Characteristics: All Patients Enrolled

As shown in Table 23, the 69 enrolled patients were between 15 and 71 years of age. The mean duration of caspofungin treatment was 33.9 days (range 1 to 162 days). Almost all patients had significant underlying immunosuppression. The most common underlying

disease was hematologic malignancy (66.7%); acute myelogenous leukemia was the malignancy most frequently reported. Thirty-nine percent of patients included in the category of hematologic malignancies had undergone allogeneic bone marrow (BMT) or peripheral stem cell transplants (PSCT). Most other patients were also immunocompromised, and predisposing conditions included solid organ transplants (13.0%), solid tumors (4.3%), and high dose corticosteroid use (5.8%). Approximately 6% had other risk factors for IA, including, in 1 patient each, methotrexate use, skull trauma, chronic graft versus host disease (GVHD; BMT for Wiskott Aldrich Syndrome), and prior pulmonary mycobacterial infection. No clear risk was identified in 3 patients, 2 of the 3 had definite extrapulmonary infections and 1 had definite pulmonary disease. Approximately 23% were neutropenic (absolute neutrophil count [ANC] <500/ μ L), and 36.2% (25/69) had been receiving high-dose corticosteroid therapy (defined as \geq 20 mg prednisolone-equivalents/day) at study entry.

Baseline Characteristics: All Patients Included in the Efficacy Analysis (N=63)

The remaining discussion will focus on the 63 patients (54 + 9) who met diagnostic criteria for IA and are included in the assessment of outcome. As displayed in Table 27, the majority of patients had pulmonary aspergillosis (71.4%). Approximately 21% of patients had disseminated infection (defined as involvement of 2 or more noncontiguous sites or positive blood culture). Other extrapulmonary sites of infection included sinus, central nervous system (CNS), and pulmonary/sinus. All patients with extrapulmonary infections had definite diagnoses, as did 60.0% (27/45) of the patients with pulmonary disease. Thirteen of 19 patients with probable pulmonary aspergillosis had culture confirmation of infection by bronchoalveolar lavage or sputum; 3 had repeatedly positive galactomannan ELISA, and 1 patient had a repeated positive PCR. Most infections documented by culture were caused by *Aspergillus fumigatus*, but *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* were each isolated in small numbers of patients.

Table 27

Distribution of Final Diagnoses of *Aspergillus* Infections
 As Determined by the Expert Panel (Protocol 019)

Site of Infection	N=54 [†] n (%)	Additional Patients N=9 n (%)	N=63 n (%)
Definite Pulmonary	23 (42.6)	4 (44.4)	27 (42.9)
Probable Pulmonary [‡]	16 (29.6)	2 (22.2)	18 (28.6)
Extrapulmonary	15 (27.8)	3 (33.3)	18 (28.6)
Disseminated	10	3	13
CNS	1	0	1
Sinus	3	0	3
Pulmonary/sinus	1	0	1
[†] Excludes 2 patients with IA who had no data on which to base outcome (not assessable by the Expert Panel). [‡] Includes 4 patients (ANs 191, 251, 426, 427) with probable pulmonary and “possible” CNS disease.			

The Expert Panel also classified patients by sites of infection that were suggestive of IA but did not meet the strict diagnostic criteria defined in Protocol 019. Four patients (allocation numbers [ANs] 191, 251, 426, and 427) with probable pulmonary aspergillosis were also classified as having possible CNS aspergillosis, based on radiographic imaging studies that demonstrated multiple CNS lesions. One patient (AN 471), enrolled with definite sinus aspergillosis, was classified as also having possible pulmonary aspergillosis, based on chest radiograph findings of bilateral pulmonary infiltrates. None of these 5 patients had culture or pathology data supporting a diagnosis of IA at these additional sites and are therefore identified by the site of infection that met protocol criteria. This categorization resulted in patients being included in a better prognostic group (i.e., pulmonary instead of disseminated disease) and therefore provides the most conservative estimate of outcome by site of infection.

As shown in Table 28, most patients (84.1%) were refractory to initial antifungal therapies. Initial antifungal therapies included amphotericin B, lipid formulations of amphotericin B, and itraconazole. Approximately 36% (19/53) of patients who were refractory to initial therapy had received multiple agents, including at least one formulation of amphotericin B, prior to study entry. Seventy-two percent (38/53) of refractory patients had received >14 days of standard therapy and 55% (29/53) had received >21 days of standard therapy prior to entry. Most patients enrolled as refractory had documented progression of IA during initial treatment. Ten patients were intolerant

to initial therapy, including 4 to amphotericin B, 3 to lipid formulations of amphotericin B, 1 to itraconazole, and 2 to multiple agents. Eight of 10 intolerant patients, including the 2 patients who received >14 days of initial therapy, had no improvement noted during the prestudy period.

Table 28

Distribution of Patients by Treatment Reason and Prior Antifungal Treatment
 Expert Panel Assessment (Protocol 019)

Treatment Reason Prior Antifungal Treatment	N=54 [†]	Additional Patients N=9	Total N=63
	N (%)	n (%)	n (%)
Refractory [‡]	44 (81.5)	9 (100)	53 (84.1)
Amphotericin B	7	3	10
Lipid amphotericin B	7	3	10
Itraconazole	13	0	13
Voriconazole	1	0	1
>1 Antifungal [§]	16	3	19
Intolerant	10 (18.5)	0 (0.0)	10 (15.9)
Amphotericin B	4	0	4
Lipid amphotericin B	3	0	3
Itraconazole	1	0	1
Voriconazole	0	0	0
>1 Antifungal [‡]	2	0	2
Total	54 (100)	9 (100)	63 (100)
[†] Includes only patients who were assessed for efficacy. [‡] Includes patients who were both refractory and intolerant. [§] Includes combination and sequential treatment.			

Overall Response (Clinical and Radiographic)

The Expert Panel determined that 26 (41.3%) of 63 patients had a favorable response at the end of IV therapy as assessed by the primary endpoint of clinical and radiographic response. Of 52 patients who received >7 days of caspofungin therapy, 26 (50.0%) had a favorable response. All of those who received ≤7 days of therapy either died on treatment or had support withdrawn because of poor overall prognosis. Four patients were assessed as having had a complete response, and 22 patients as having a partial response. Because of the rigorous interpretation of clinical response used by the Expert Panel (requiring complete resolution of all attributable radiographic abnormalities as well as resolution of signs and symptoms), it was not unexpected that only a small number of patients met the definition of complete response at the end of IV therapy.

Overall Response at 4-Week Follow-Up

Eighteen of the 23 patients with a favorable response at the end of IV therapy who continued into follow-up were assessed as having had a favorable response at the 4-week follow-up evaluation. One patient (AN 0326) had a documented relapse. One patient (AN 0065) was considered to have relapse by the investigator because of a new abnormality on chest x-ray. There was no culture confirmation and the patient was treated with itraconazole 200 mg/day. Two patients were lost to follow-up (withdrew from the study) and one patient died during the follow-up period. The continued favorable response in the majority of patients indicates that the improvement seen on caspofungin therapy was durable.

Overall Response by Demographics and Disease Characteristics

Several factors would be expected to influence the response to therapy in patients with IA, and the prevalence of these factors in the overall study population, as well as in those patients with a favorable response, was assessed. Outcomes classified by factors predicted to influence response to therapy are in Table 29.

Outcome is displayed by whether patients were refractory to or intolerant of other therapies. As outlined, most patients (53/63) were refractory to initial therapy; most had progression of disease on that initial treatment. More than 70% of refractory patients had received >14 days of therapy prior to study entry, and 49.1% (26/53) of refractory patients had received multiple antifungal drugs. A favorable response was seen in 35.8% (19/53) of refractory patients. The number of patients intolerant to other therapies was small. Moreover, although entry as intolerant did not exclude patients responding to standard therapy, most patients enrolled in Protocol 019 as intolerant, including the 2 who received >14 days of prior antifungal therapy, had no improvement on this standard therapy. The 70% favorable response rate in these patients can thus be attributed primarily to the effect of caspofungin.

As expected, response rates were lower in subgroups known to be associated with a poor prognosis, such as allogeneic transplants, disseminated disease, neutropenia, and high-dose corticosteroids. However, although response rates were lower, favorable responses were still seen in these subgroups. Seventeen percent of patients with allogeneic transplants, 23% with disseminated disease, 14% with neutropenia, and 35% on high-dose corticosteroids had a favorable response. These response rates are notable because, as described, >80% of the patients in this study were refractory to other antifungal therapy, an added predictor of unfavorable outcome. In addition, the high prevalence of these poor prognostic factors in the population indicates that many patients actually had multiple factors associated with a negative prognosis, a feature not accounted for in Table 29.

Table 29

Patients Outcomes by Demographics and Disease Characteristics
 Protocol 019 Expert Panel Assessment

	N=54 n/m [†] (%)	Additional Patients N=9 N/m [†] (%)	Total N = 63 n/m [†] (%) (95% CI)	
Refractory Versus Intolerant				
Refractory [†]	15/44 (34.1)	4/9 (44.4)	19/53 (35.8)	(23.1, 50.2)
Intolerant	7/10 (70.0)	--	7/10 (70.0)	(34.8, 93.3)
Gender				
Female	7/21 (33.3)	--	7/21 (33.3)	(14.6, 57.0)
Male	15/33 (45.5)	4/9 (44.4)	19/42 (45.2)	(29.8, 61.3)
Underlying Disease				
Hematologic malignancy	10/20 (50.0)	2/4 (50.0)	12/24 (50.0)	(29.1, 70.9)
Allogeneic BMT/PSCT [§]	3/16 (18.8)	0/2 (0.0)	3/18 (16.7)	(3.6, 41.4)
Organ transplant	3/7 (42.9)	0/1 (0.0)	3/8 (37.5)	--
Solid tumor	2/2 (100)	1/1 (100)	3/3 (100)	--
Other	4/9 (44.4)	1/1 (100)	5/10 (50.0)	(18.7, 81.3)
Site of Infection				
Pulmonary	18/39 (46.2)	3/6 (50.0)	21/45 (46.7)	(31.7, 62.1)
Disseminated	2/10 (20.0)	1/3 (33.3)	3/13 (23.1)	(5.0, 53.8)
Central nervous system	1/1 (100)	--	1/1 (100)	--
Sinus	1/3 (33.3)	--	1/3 (33.3)	--
Pulmonary/sinus	0/1 (0.0)	--	0/1 (0/0)	--
Neutropenia				
Neutropenic (ANC [‡] <500)	2/11 (18.2)	0/3 (0.0)	2/14 (14.3)	(1.8, 42.8)
Nonneutropenic	20/43 (46.5)	4/6 (66.7)	24/49 (49.0)	(34.4, 63.7)
Corticosteroids				
<20 mg prednisolone equivalent/day	15/32 (46.9)	3/8 (37.5)	18/40 (45.0)	(29.3, 61.5)
≥20 mg prednisolone equivalent/day	7/22 (31.8)	1/1 (100)	8/23 (34.8)	(16.4, 57.3)
[†] Number of patients with favorable response/number of patients in the subgroup. [‡] Includes patients who were both refractory and intolerant. [§] BMT/PSCT = bone marrow transplant/peripheral stem cell transplant. [‡] ANC = absolute neutrophil count.				

Changes in immunosuppression during therapy also influence outcome. As displayed in Table 29, 14 of 63 patients were neutropenic at study entry. Eight of the 14 patients continued to be neutropenic at the end of IV therapy, and none of these patients had a favorable response. The other 6 patients recovered from neutropenia during the study period, and the 2 favorable responses were in this group. However, these 2 patients (AN 0326, AN 0328) demonstrated evidence of response to therapy prior to recovery of their neutrophil counts. In addition, 3 patients (ANs 0065, 0318, and 0330) who are included in the nonneutropenic group, became neutropenic (total WBC count <300 cells/mm³) during caspofungin therapy as a result of chemotherapy administered

during study therapy. Although these patients were neutropenic at the end of caspofungin therapy, they had a favorable response.

Twenty-three patients were receiving high-dose corticosteroids at study entry. Eight (34.8%) of these patients had a favorable response and 5 of the 8 were still receiving high-dose corticosteroids at the end of therapy. Patients commonly received other immunosuppressive therapy during the trial. Seventeen patients were receiving tacrolimus; 8 were receiving mycophenolate mofetil in addition to tacrolimus and caspofungin. A favorable response was seen in 8 (47%) of these 17 patients, and all were still receiving these agents at the end of caspofungin therapy with a comparable degree of immunosuppression.

Finally, surgical debridement may influence outcome in patients with IA. The Expert Panel commented that surgical debridement or resection could play an important adjunctive role in the treatment of IA and did not necessarily equate with failure of antifungal therapy. Four patients (ANs 0219, 0248, 0291, and 0316) were classified as having surgery that likely contributed to overall outcome. In these cases, the Expert Panel determined that caspofungin therapy was an important component of the overall treatment.

6.3.6 Efficacy of Caspofungin in Patients With *Aspergillus* Infections Treated Under Compassionate Use (Protocol 024/025)

Baseline Characteristics

The criteria for diagnosis and outcome in this study were modeled after Protocol 019. One patient (AN 7151) was a 17-year-old adolescent male with aplastic anemia, who had definite pulmonary aspergillosis refractory to amphotericin B liposome and itraconazole and was treated with caspofungin for 7 days. The second patient (AN 7001) was a 46-year-old woman with no defined risk factor, who had definite disseminated aspergillosis of the lung and spine refractory to amphotericin B liposome and was treated with caspofungin for 89 days. The third patient (AN 7003) was a 57-year-old man with advanced AIDS, who had definite pulmonary aspergillosis refractory to itraconazole and intolerant to amphotericin B lipid complex and was treated in this study with caspofungin for 23 days.

Overall Response (Clinical and Radiographic)

The Expert Panel for Protocol 019 also reviewed the 3 cases from this study and determined that 2 of the 3 patients had a favorable response. The patient with disseminated disease (AN 7001) had a complete response. One (AN 7003) of 2 patients, who had definite pulmonary disease, had a partial response. The other patient (AN 7151) with pulmonary disease, treated only 7 days, was a failure and died from complications related to aplastic anemia shortly after discontinuation of caspofungin therapy.

6.3.7 Efficacy Summary of Caspofungin in the Treatment of IA in Noncomparative or Compassionate Use Studies

As previously discussed, data on the 63 patients in Protocol 019 evaluated by the Expert Panel showed a response rate of 41.3% in patients with well-documented IA and a high prevalence of poor prognostic factors. Favorable responses (complete or partial response) were seen in patients with disseminated disease, hematologic malignancies, allogeneic BMT and neutropenia, as well as in those receiving high-dose corticosteroids. As described, most patients in this study were refractory to substantial initial antifungal therapy, and overall these refractory patients had a favorable response rate of 35.8%. The number of intolerant patients was small, but 7 of 10 had a favorable response. Although improvement on initial therapy was not an exclusion for entry as intolerant, most patients enrolled into Protocol 019 as intolerant had no improvement noted in the prestudy period.

These results are supported by the data from the compassionate use study (Protocol 024/025). The 3 patients in the compassionate use study met the same diagnostic criteria used in Protocol 019, and the Expert Panel determined that 2 of the 3 patients had a favorable response, according to the same definitions of outcome. In these 2 studies, the response rate overall was 42.4% (28/66).

The response rate seen in patients with IA treated with caspofungin, who were primarily refractory to standard therapy, is impressive, given the high prevalence of poor prognostic factors represented in that population.

6.3.8 Historical Data on Invasive Aspergillosis

As described in the preceding sections, all data on caspofungin in the treatment of IA were obtained in noncomparative or compassionate use studies. The Historical Control Study (Protocol 028/029), a retrospective medical chart review, was performed to evaluate patients with well-documented IA treated with standard antifungal therapy from 1995 to 1998, and to provide an approximate comparator group for Protocol 019. The objective of this predefined comparison was to demonstrate that caspofungin was at least as effective as standard therapy. In addition, a literature review of English language publications on IA published from Jan-1995 to Apr-2000 [15] was conducted.

Literature Review

The objective of the literature review was to try to provide a general estimate of outcomes and potential prognostic factors in IA in a time frame contemporary with the enrollment in Protocol 019. However, the applicability was anticipated to be limited because of the strict definitions and requirement for documentation of diagnosis and outcome that were applied in the Caspofungin Noncomparative *Aspergillus* Study (Protocol 019). As expected, several limitations to the literature review were identified and some of the key limitations are outlined below.

The literature review included all publications on IA and was not limited to those describing salvage therapy. Thirty-six of the 250 articles screened were identified as including data on 10 or more adults treated for IA. In most articles, data were presented

in the aggregate, and identification of patient-specific risk factors and outcomes was not possible. These articles included 1527 cases of IA. Case Fatality Rate (CFR) was selected rather than the proportion of patients with a favorable response because information on outcome in many publications was limited to mortality. Only 10 articles, which included 810 patients, included a description of clinical response to therapy and specific antifungal treatment was provided for only 779 of these 810 patients.

In the 33 articles with information on mortality, the overall CFR was 65.6%. Subgroups with a higher-than-average CFR included BMT recipients (88.2%) and patients with CNS or disseminated aspergillosis (91.3%). The ability to examine outcome or prognostic factors in more detail was limited. Diagnostic criteria for IA were often not specified at the patient level, and documentation of outcome varied by report. In many cases, it was not possible to determine the interrelationships among risk factors in the study populations [15].

There are also other limitations to correlating outcome with treatment for IA based on a review of published literature. Although efforts were made to ensure adequate documentation of infection, some studies used different definitions for probable aspergillosis. In these studies [7; 12], probable disease required only an appropriate clinical setting and consistent radiographic findings. There was no requirement for supportive documentation from culture or antigen detection. In other cases, the same definitions of infection were used but eligibility criteria varied. Studies included patients with suspected or possible IA [8; 11]. In either circumstance, it was not possible to determine how outcome was affected by such cases that were not as well documented. Definitions of response to therapy also varied. In some studies [7; 10], patients with stable disease were considered to have a favorable response. Patients who fit into this category were not specifically identified. In addition, it was not possible in a review of published literature to determine the type of documentation that was available to support the assessment of outcome. Interpretation was also complicated by the fact that some studies included both primary and salvage therapy [9] and did not separate diagnoses or outcomes by the therapy received. These limitations, plus the lack of patient-specific data, make it difficult to directly compare outcomes with specific antifungal therapies. The literature review does confirm that the mortality of IA remains high in the 1990's and that the risk factors of BMT and disseminated disease continue to be predictors of poor prognosis in patients with IA [15].

As anticipated, a systematic review of the literature provided general information, but a more appropriate comparison is offered by patient-specific data from a well-designed chart review of patients with underlying disease, diagnoses, and assessments of outcome from a population comparable to those in the Noncomparative *Aspergillus* Study (Protocol 019). Consequently, in the Historical Control Study (Protocol 028/029), every effort was made to identify a population that closely resembled the patients enrolled in Protocol 019. Criteria for diagnosis and outcome were the same in both studies with 1 exception; 2 sputum cultures were required to meet the definition of probable pulmonary aspergillosis in Protocol 019 while only 1 sputum culture was required for Protocol 028/029. Four of 10 sites selected for Protocol 028/029 also participated in

Protocol 019. However, it was not possible to correct for the selection bias that resulted from the enrollment of sicker patients in a salvage study (Protocol 019). The resulting comparison was, therefore, a conservative one.

Limitations of Historical Control Study

Any comparison between results from a prospectively designed clinical trial and data from a historical control group should also recognize the potential limitations of such an approach. There is a potential for bias in the selection of the historical control population. There may also be subtle differences between the selected patient populations, including differences which are not evident in baseline comparisons. Data collected on a historical control group may not be as consistent nor complete as that derived from a clinical trial. Differences in clinical practice based on timeframe or institution may also exist. Several design features of the caspofungin aspergillosis Historical Control Study attempt to address these potential limitations. Criteria from the caspofungin aspergillosis trial were utilized in the Historical Control Study (although the Historical Control Study included all patients meeting pre-specified diagnostic and treatment criteria rather than only those refractory to or intolerant of approved therapy). Potential cases were evaluated for eligibility consecutively and selection of patients in reverse chronologic order was used so that patients enrolled in both studies were treated over a relatively narrow timeframe. In order to minimize differences in clinical management and patient type, a number of the same clinical sites were used to enroll patients into both trials. Patients who would not have survived long enough (at least 7 days) to be enrolled in the prospective trial were similarly excluded from the historical control group. Lastly, logistic regression analyses were prespecified to adjust for potential baseline differences in important prognostic factors between the two patient populations. It is acknowledged that inclusion of these design features cannot overcome some of the inherent potential methodological limitations.

Efficacy of Standard Antifungal Therapy in Patients With IA in the Historical Control Study (Protocol 028/029)

Study Design

Protocol 028/029 was a multicenter retrospective chart review of patients with IA treated from 1995 to 1998. Four sites that collectively enrolled approximately half of the patients in the Noncomparative *Aspergillus* Study (Protocol 019) were also used for the Historical Control Study. In Protocols 028/029, potential cases of IA at each site were initially identified through hospital discharge summaries; consultation records from pulmonary, oncology, or infectious disease units; microbiology laboratory records; and pathology records (including both biopsy and autopsy records). Patient charts were identified for abstraction if the patient met eligibility criteria, including diagnoses of definite IA from any site or probable pulmonary IA, and treatment with at least 7 days of therapeutic doses of standard antifungal therapy to mirror minimum eligibility criteria for the Noncomparative *Aspergillus* Study (Protocol 019). "Standard Antifungal therapy" refers to the use of existing, licensed antifungal agents in any combination. However, in the Historical Control Study (Protocol 028/029), no distinction was made between

primary and salvage therapy. Eligible cases were enrolled starting with 31-Dec-1998 and working backward in time until data collection for the study ended, or until 01-Jan-1995 was reached. The enrollment process was designed to yield, at each site, a consecutive series of cases meeting eligibility criteria comparable to those of Protocol 019. The chart abstraction took place in accordance with a defined protocol with quality control procedures to ensure accuracy of the information abstracted. The 229 eligible patient charts were abstracted by trained abstractors.

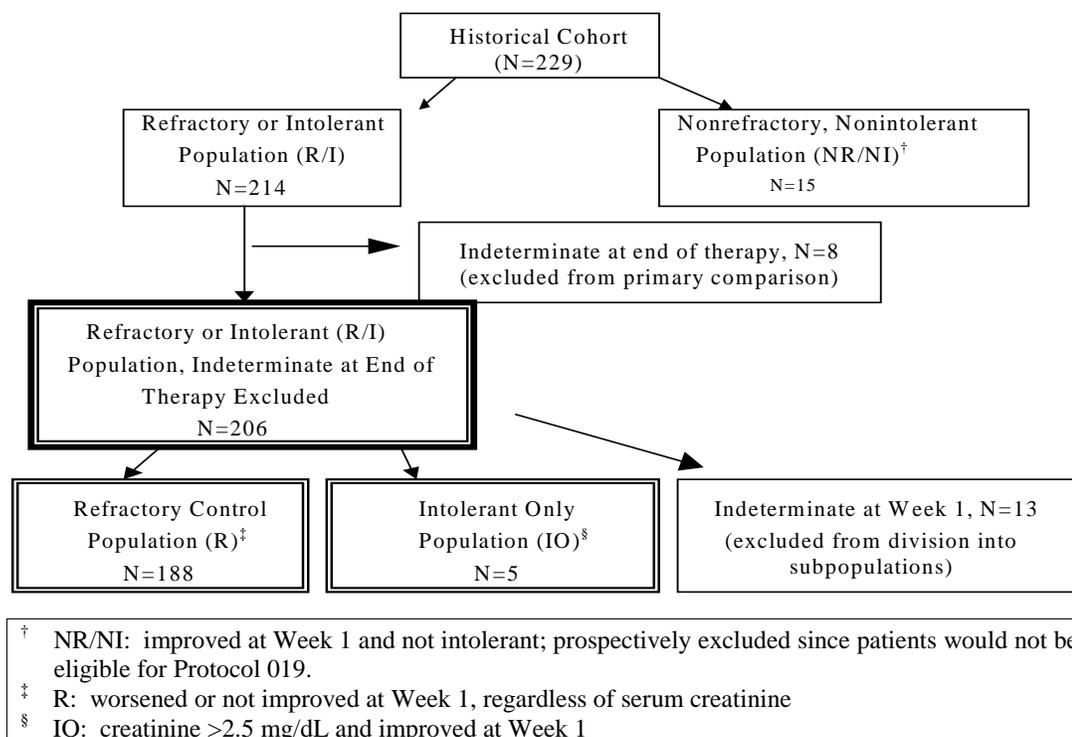
Data regarding the diagnosis of IA, underlying disease, doses and duration of standard antifungal therapy, and data supporting outcome after treatment were abstracted from hospital records and were reviewed by the physician-investigator at each site. Diagnostic criteria for IA and definitions of response were the same as those used in Protocol 019. Diagnosis of IA, weekly clinical status, and clinical response at the end of therapy were assessed by the investigator at each site. To ensure consistency, an Expert review of all abstracted cases, including diagnoses, clinical evaluation at Week 1, and outcome after standard therapy was to be performed. The expert assessments of the patients in the Historical Control study have not been reviewed by the Agency.

Definitions of Patient Population

Duplicating the complex integration of factors involved in deciding to enroll a patient in a salvage study of an investigational agent is not possible in a retrospective study. However, an approximate comparison population was prospectively defined by identifying a group of patients that met minimum eligibility requirements for the prospective study. In the Historical Control Study (Protocol 028/029), patients were assessed at the end of Week 1 of therapy, the first time patients would have been eligible to enroll in Protocol 019. Patients were considered “refractory” if the clinical assessment of their condition was “worsened” or “not improved at the end of Week 1.” Patients were categorized as “intolerant” if their creatinine value was ≥ 2.5 mg/dL at the end of Week 1 of therapy. Based on this assessment, patients were assigned to populations as displayed graphically in Figure 10. The primary population for comparison to Protocol 019 was the refractory/intolerant (R/I) population (N=206), with patients having an indeterminate response at the end of therapy (N=8) excluded.

Figure 10

Partition of Historical Control Patient Populations



Baseline Characteristics

In Protocol 028/029, a majority of the 229 patients had underlying hematologic malignancies (69.4%). Most other patients were also immunocompromised and had solid organ transplants (15.3%) or solid tumors (5.2%). Ten percent had other risk factors or no risk factor identified. Most patients had pulmonary aspergillosis (75.6%). The majority of patients with extrapulmonary disease had disseminated infection (18.3% of the total study population). Approximately 26% were neutropenic at Week 1, and 35% were receiving high-dose corticosteroids at Week 1 (≥ 20 mg prednisolone equivalents/day). The mean duration of standard antifungal therapy was 30.5 days (range 7 to 157 days). The primary antifungal therapy encompassed amphotericin B (34.5%), lipid formulations of amphotericin B (38.4%), and itraconazole (12.7%). Fourteen percent of patients received multiple-drug regimens.

Overall Response

Basing patient assessment on clinical and radiographic response, study-site investigators determined that 35 (17%) of 206 patients in the refractory/intolerant (R/I) population, indeterminate outcomes at the end of therapy excluded, had a favorable response at the end of standard therapy. Efficacy was also examined according to disease and patient characteristics. Response rates were lower in subgroups known to be associated with poor prognosis such as disseminated disease, neutropenia, high-dose corticosteroids, and allogeneic transplants. The proportion of patients with a favorable response in R was 14.4% (27/188) and in IO was 60% (3/5 patients).

Clinically Relevant Predictors of Response

For use as adjustment factors in the quantitative comparison of treatment efficacy between Protocol 019 and Protocol 028/029, a small set of prognostic factors that were clinically relevant predictors of outcomes were identified using stepwise logistic regression in the Historical Control Study. As pre-specified in the data analysis plan, the factors considered as possible predictors of response in the refractory/intolerant (R/I) population were: site of infection, certainty of diagnosis, underlying disease, neutropenia, high-dose corticosteroid use at Week 1, use of immunosuppressive/cytotoxic drugs at Week 1, creatinine value ≥ 2.5 mg/dL at Week 1, age, gender, and race. Disseminated IA and neutropenia at baseline were consistently identified as strong independent predictors of IA outcome (p-values typically < 0.01) in all univariate and multivariate logistic regression models. BMT was the third strongest independent predictors of outcome (p-values 0.07 to 0.11). High-dose corticosteroid use at Week 1 was an additional independent predictor of outcome (p-values sometimes > 0.10). Thus the primary model for the comparison of Protocol 019 and Protocols 028/029 was a model including disseminated IA, neutropenia, and BMT. Additional analyses using other models (e.g., disseminated IA, neutropenia, and high-dose corticosteroid use at baseline; or the 4 predictors together) were also conducted. The prognostic factors identified in the Historical Control Study are consistent with those identified in the literature.

6.3.9 Comparison of Patients in Protocol 019 to Patients in Protocol 028/029

The comparison of caspofungin in Protocol 019 to standard antifungal treatment in the Historical Control group from Protocol 028/029 was based on the initial 58 patients with Expert Panel assessments available at the time of submission of the application. Although the expert panel assessments for the additional 11 patients were not available for comparison, as outlined in Section 6.3.4, the characteristics and outcomes of these 11 patients are similar to those of the first 58 patients.

Baseline Characteristics of the Comparison Populations

As shown in Table 30, the 58 patients treated with caspofungin (Protocol 019) and 229 patients treated with standard therapy (Protocol 028/029) were generally similar with regard to demographics and other baseline characteristics. The majority of patients (~70%) in each study had pulmonary aspergillosis. Approximately 18% had disseminated disease. A majority of patients were immunocompromised, and hematologic malignancies were the most common predisposing condition (>67% in both groups). A smaller proportion of patients in both studies had solid organ transplants or solid tumors. Approximately 10% had other risk factors or no clear risk factor identified. A similar proportion of patients in each study were neutropenic (22.4% in Protocol 019 versus 25.8% in Protocol 028/029). The primary underlying diseases are in Table 31 and are generally similar.

Caspofungin Acetate
 FDA Advisory Committee Meeting Background
 Clinical Efficacy

-106-

Table 30

Baseline Patient Characteristics for Clinical Studies of
Aspergillus Infections (Protocols 019, 028/029)

	Protocol 019	Protocols 028/029
	Caspofungin	Standard Therapy
	N=58	Historical Control Group N=229
	n (%)	n (%)
Gender		
Male	35 (60.3)	122 (53.3)
Female	23 (39.7)	107 (46.7)
Race		
Caucasian	55 (94.8)	192 (83.8)
Hispanic	2 (3.4)	16 (7.0)
Black	1 (1.7)	11 (4.8)
Other	0 (0.0)	10 (4.4)
Age (Years)		
<18	0	0
18 to 25	4	11
26 to 40	13	54
41 to 65	33	139
>65	8	25
Mean	48.4	48.2
Standard deviation	13.3	13.4
Median	51.0	49.0
Range	20 to 71	19 to 78
Site of <i>Aspergillus</i> Infection (Final Diagnosis)		
N=56 With IA		
Pulmonary, probable	17 (30.4)	87 (38.0)
Pulmonary, definite	23 (41.1)	86 (37.6)
Disseminated	10 (17.9)	42 (18.3)
Sinus	4 (7.1)	7 (3.1)
Central nervous system	1 (1.8)	2 (0.9)
Skin	0 (0.0)	5 (2.2)
Pulmonary/sinus	1 (1.8)	0 (0.0)
Refractory or Intolerant		
N=56 With IA		
Refractory	29 (51.8)	--
Intolerant	11 (19.6)	--
Both, refractory and intolerant	16 (28.6)	--
Underlying Disease		
Hematologic malignancies [†]	39 (67.2)	159 (69.4)
Organ transplant	8 (13.8)	35 (15.3)
Solid tumor	2 (3.4)	12 [†] (5.2)
Other risk factors/no clear risk factor	9 (15.5)	23 (10.0)
Neutropenic Status (cells/microliter)		
ANC [‡] <500	13 (22.4)	59 (25.8)
ANC [‡] ≥500	45 (77.6)	170 (74.2)
[†] Includes bone marrow transplant.		
[‡] ANC = absolute neutrophil count.		

Table 31

Distribution of Patients by Primary Background Condition

Primary Background Condition	Protocol 019 N= 58	Protocols 028/029 N=229
	n (%)	n (%)
Hematologic Malignancies	39 (67.2)	159 (69.4)
<i>Acute Leukemia</i>	16 (41.0)	76 (47.8)
Acute myelogenous leukemia	13	60
Acute lymphoblastic leukemia	2	15
Acute biphenotypic leukemia	0	1
Acute undifferentiated leukemia	1	0
<i>Chronic Leukemia</i>	8 (20.5)	35 (22.0)
Chronic myelogenous leukemia	5	28
Chronic lymphocytic leukemia	1	7
Hairy cell leukemia	2	0
<i>Lymphomas</i>	7 (17.9)	24 (15.1)
Non-Hodgkin's lymphoma	4	18
Hodgkin's lymphoma	2	3
Lymphoma, not specified	0	3
T-cell lymphoma	1	0
<i>Myelodysplastic Syndrome</i>	5 (12.8)	11 (6.9)
<i>Plasma Cell Dyscrasia</i>	3 (7.7)	8 (5.0)
Multiple myeloma	3	6
Waldenstrom macroglobulinemia	0	1
POEMS [†] syndrome	0	1
<i>Other</i>	0 (0.0)	5 (3.1)
Aplastic anemia	0	2
Hypereosinophilia syndrome	0	1
Myelofibrosis	0	1
Myeloproliferative disorder	0	1
Bone Marrow/Peripheral Stem Cell Transplantation	20 (34.5)[‡]	94 (41.0)[§]
Allogeneic	15	85
Autologous	5	9
Organ Transplant	8 (13.8)	35 (15.3)
Lung	4	17
Kidney	1	9
Liver	2	5
Heart	1	3
Heart/lung	0	1
Solid Tumor	2 (3.4)	12 (5.2)
Breast cancer	0	4
Adenocarcinoma of the rectum	0	2
Lung cancer	0	2
Adenocarcinoma of the trachea	0	1
Adenocarcinoma of the lung	1	0
Astrocytoma	0	1
Non-small cell lung cancer	1	0
Osteosarcoma	0	1
Prostate cancer	0	1
Other/No Risk	9 (15.5)	23 (10.0)[¶]
[†] POEMS = Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes. [‡] Subset of patients with hematologic malignancies. [§] Subset of patients with hematologic malignancies and breast cancer. Other includes patients with chronic steroid use (4), no risk factor (2), methotrexate (1), mycobacterium of the lung (1), and skull trauma (1). [¶] Other includes patients with chronic steroid use (6), diabetes (3), chronic pulmonary disease (3), and various other chronic conditions (11).		

Patients had clinical and radiographic findings appropriate for the diagnosis of IA at the designated site of infection. Although many patients had multiple diagnostic tests performed, the diagnosis displayed in Table 32 is based on the best available evidence for infection obtained at any time during the study (final diagnosis). The distribution of sites of infection is generally similar in the 2 studies.

Table 32

Distribution of Patients With a Diagnosis of *Aspergillus* Infection

Site of Infection Primary Evidence	Protocol 019 Final Diagnosis N=56 [†]	Protocol 028/029 Final Diagnosis N=214 [‡]
	n (%)	n (%)
Definite Pulmonary	23 (41.1)	80 (37.4)
Probable Pulmonary	17 (30.4)	80 (37.4)
Extrapulmonary	16 (28.6)	54 (25.2)
Disseminated	10	42
CNS	1	2
Sinus	4	6
Skin	0	4
Pulmonary/sinus	1	0

[†] Two patients did not meet diagnostic criteria and are excluded.
[‡] R/I population.

Standard Antifungal Therapy

Patients in both studies received standard antifungal agents for the treatment of IA, either as prior (initial) therapy (Protocol 019) or as part of the usual care for IA (Protocol 028/029). As such, the data are not directly comparable, but do provide an estimate of what was considered standard antifungal therapy in the 2 studies.

Patients in both studies received amphotericin B, lipid formulations of amphotericin B, itraconazole, or multiple agents. However, the distribution of specific drugs differs in the 2 studies. Most commonly, patients in Protocol 019 received multiple-drug regimens as initial therapy (41.1%), each of which included some formulation of amphotericin B. Approximately 38% of patients received a single amphotericin B formulation as initial therapy, and 20% received itraconazole as initial therapy. Patients in Protocol 028/029 most commonly received, as their primary standard antifungal treatment, lipid formulations of amphotericin B (38.8%) and amphotericin B (33.2%). Approximately 15% received multiple drugs, and 13% received itraconazole. According to the classification used in each study, multiple antifungal agents (all regimens included an amphotericin formulation) occurred more frequently in Protocol 019 than in Protocol 028/029, and may reflect the intentional selection of salvage patients in Protocol 019 versus the primary treatment population of Protocol 028/029.

Accounting for Patients in the Analysis

The population in Protocol 019 to be compared with the Historical Control group was defined by the Expert Panel as meeting diagnostic criteria for IA and having data on which to base an assessment of outcome and includes 54 patients. Because Protocol 028/029 was comprised of patients who received primary and not salvage therapy as in Protocol 019, it was not possible to identify completely analogous subpopulations. The partition of patients into populations is displayed in Figure 10. The primary population for comparison in Protocol 028/029 was the R/I population, with indeterminates at the end of therapy excluded, which included 206 patients.

Efficacy Results

As assessed by clinical and radiographic response, the percentage of patients with a favorable response was higher in the caspofungin group from Protocol 019 than the Historical Control group from Protocol 028/029 (40.7 versus 17%, respectively), as shown in Table 33.

Table 33

Proportion of Patients With a Favorable Overall Response at End of Antifungal Therapy

Study Population	n/m [†] (%) (95% CI)
Protocol 019 Expert Panel	22/54 (40.7) (27.6, 55.0)
Protocols 028/029 R/I [‡] , indeterminates excluded	35/206 (17.0) (12.1, 22.8)
[†] n/m = number of patients with favorable response/number of patients in the analysis. [‡] R/I = refractory/intolerant.	

The following sections summarize patient outcomes by potential clinically relevant predictors of outcome, namely, refractory or intolerant, site of infection, underlying disease, neutropenia, and high-dose corticosteroid therapy (≥20 mg prednisolone equivalents/day).

Site of Infection

A favorable response was seen in 18/39 (46.2%) of patients with pulmonary aspergillosis treated with caspofungin in Protocol 019 and 32/154 (20.8%) of patients treated with standard antifungal therapy in the Historical Control group in Protocol 028/029. Similarly, a higher response rate was seen in patients with extrapulmonary aspergillosis treated with caspofungin in Protocol 019 than with standard antifungal therapy in Protocol 028/029 (4/15; 26.7% versus 3/52; 5.8%, respectively). Since the mortality associated with extrapulmonary aspergillosis varies with the site of infection, the distribution of response by specific extrapulmonary infection site is displayed in Table 34. Favorable responses were seen in patients treated with caspofungin who had

disseminated disease (2/10), central nervous system (CNS) infection (1/1), and sinus aspergillosis (1/3). In contrast, none of the 41 patients in Protocol 028/029 with disseminated disease had a favorable response. One patient each with CNS, sinus, and skin disease had a favorable response to standard antifungal therapy in Protocol 028/029. The proportion of patients with CNS or sinus disease who had a favorable response was numerically higher in the caspofungin than the Historical Control group, but the numbers of patients are too small to draw firm conclusions.

Table 34

Proportion of Patients With a Favorable Response by Specific Extrapulmonary Infection Site

Study Population	Extrapulmonary [†]					
	Disseminated n/m [‡]	CNS n/m	Sinus n/m	Pulmonary Sinus n/m	Skin n/m	Total n/m (%)
Protocol 019 Expert Panel	2/10	1/1	1/3	0/1	---	4/15 (26.7)
Protocols 028/029 R/I [§] , indeterminates excluded	0/41	1/2	1/6	---	1/3	3/52 (5.8)

[†] Extrapulmonary disease required definite disease diagnostic criteria.
[‡] n/m = number of patients with favorable response/number of patients in the subgroup.
[§] R/I = refractory/intolerant.

Underlying Disease

Major risk categories of underlying disease are associated with different prognoses with IA. The distribution of patients' response by underlying disease is shown in Table 35. The response rate was consistently higher in patients from Protocol 019 who were treated with caspofungin. Fewer patients with extrapulmonary aspergillosis had a favorable response, regardless of the specific underlying disease.

Table 35

Proportion of Patients With a Favorable Response by Underlying Disease

Study Population	Hematologic Malignancy [†]	Organ Transplant	Solid Tumor [†]	Other	Total
	n/m [§] (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)
Protocol 019 Expert Panel	13/36 (36.1)	3/7 (42.9)	2/2 (100)	4/9 (44.4)	22/54 (40.7)
Protocols 028/029 R/I [‡] , indeterminate excluded	19/144 (13.2)	9/32 (28.1)	2/10 (20.0)	5/20 (25.0)	35/206 (17.0)

[†] Includes patients with bone marrow transplant.
[‡] R/I = refractory/intolerant.
[§] n/m = number of patients with favorable response/number of patients in the subgroup.

Because hematologic malignancies span a range of prognostic groups, it is important to assess the response to therapy within each general risk category, as displayed in Table 36. The small numbers of patients within each group precludes separation of BMT within each category. Acute leukemias were the most common type of hematologic malignancy (~40%), and patients with acute leukemia who were treated with caspofungin in Protocol 019 had a higher response rate than those treated with standard antifungal therapy in Protocol 028/029 (50 versus 13.0%, respectively). A similar pattern was seen with a higher response rate in patients treated with caspofungin in Protocol 019 who had lymphoma, myelodysplastic syndrome, and other malignancies. The response rate for patients with chronic leukemia was similar in the caspofungin (Protocol 019) and standard antifungal therapy (Protocol 028/029) groups (12.5 versus 15.2%, respectively). Of note, 6 of 8 patients with chronic leukemia in Protocol 019 had undergone allogeneic BMTs prior to study entry, increasing their risk of a poor prognosis.

Table 36

Proportion of Patients' With a Favorable Response by Specific Hematologic Malignancy and Underlying Condition

Study Population	Acute Leukemia	Chronic Leukemia	Lymphoma	Myelodysplastic Syndrome	Other	Total
	n/m [†] (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)
Protocol 019 Expert Panel	7/14 (50.0)	1/8 (12.5)	3/7 (42.9)	1/5 (20.0)	1/2 [§] (50.0)	13/36 (36.1)
Protocols 028/029 R/I [†] , indeterminate excluded	9/69 (13.0)	5/33 (15.2)	1/22 (4.5)	1/9 (11.1)	3/11 [‡] (27.3)	19/144 (13.2)

[†] R/I = refractory/intolerant.
[‡] n/m = number of patients with favorable response/number of patients in the subgroup.
[§] Multiple myeloma (2).
[‡] Multiple myeloma (4), aplastic anemia (2), hypereosinophilia syndrome (1), myelofibrosis (1), myeloproliferative disorder (1), POEMS syndrome (1), Waldenstrom macroglobulinemia (1).

Neutropenia and Corticosteroid Use

Other factors that may potentially influence the outcome in patients with IA are neutropenia and use of high-dose corticosteroids. The response rate was lower in patients who were neutropenic and in those receiving high-dose corticosteroids in both studies. However, caspofungin was consistently associated with a higher response than standard antifungal therapy in Protocol 028/029 across the groups. Neutropenia persisting throughout treatment for IA was common (>50%), and no patient with persistent neutropenia had a favorable response in either study. Four of the 7 patients with a favorable response in Protocol 019 were still receiving high-dose corticosteroids at the end of caspofungin therapy, and 3 of the 8 patients with a favorable response in Protocol 028/029 were still receiving high-dose steroids at the end of antifungal therapy.

The proportion of patients with a favorable responses by neutropenic status and by corticosteroid use at study entry is in Table 37.

Table 37

Proportion of Patients With a Favorable Response by Neutropenic Status and by Corticosteroid Use at Baseline

Study Population	Protocol 019 Expert Panel N/m [†] (%) 95% CI	Protocol 028/029 R/I [‡] , Indeterminates Excluded n/m (%) 95% CI
ANC[§]		
Neutropenic	2/11 (18.2) (2.3, 51.8)	4/57 (7.0) (1.9, 17.0)
Nonneutropenic	20/43 (46.5) (31.2, 62.3)	31/149 (20.8) (14.6, 28.2)
Corticosteroid Use		
Prednisolone equivalents: <20 mg/day	15/32 (46.9) (29.1, 65.3)	27/132 (20.5) (13.9, 28.3)
≥20 mg/day	7/22 (31.8) (13.9, 54.9)	8/74 (10.8) (4.8, 20.2)
[†] n/m = number of patients with favorable response/number of patients in the group. [‡] R/I = refractory/intolerant. [§] ANC = absolute neutrophil count.		

Refractory Patients

Because the refractory control (R) subpopulation in Protocol 028/029 included patients who meet only minimum entry requirements for refractory status as defined in the Noncomparative *Aspergillus* Study (Protocol 019) (“worsened” or “not improved” at Week 1), many such patients assigned to the R subpopulation in Protocol 028/029 would probably not have been considered candidates for salvage therapy by their treating physicians. Despite this inherent difference, treatment with caspofungin in Protocol 019 was associated with a higher response rate in the truly refractory patients than was standard antifungal therapy in the R subpopulation in Protocol 028/029 (15/44; 34.1% versus 27/188; 14.4%, respectively).

Intolerant (I) Versus Intolerant Only (IO)

Seven of 10 intolerant patients in Protocol 019 had a favorable response compared with 3 of 5 in the IO subpopulation in Protocol 028/029. However, there is a fundamental difference between the intolerant populations in the 2 studies. To be included in the IO subpopulation in Protocol 028/029, patients were required to have a creatinine ≥2.5 mg/dL and show evidence of clinical improvement at Week 1 of therapy. The narrow scope of this definition is manifested by the fact that only 5 of 206 patients in the

Protocol 028/029 R/I population met these criteria. As described, most intolerant patients in Protocol 019 had not demonstrated evidence of response prior to study entry. The inherent differences in these populations make it difficult to draw firm conclusions.

Comparison of Protocols 019 and 028/029 Using Logistic Regression

A second, more formal predefined quantitative comparison of the results of Protocols 019 and 028/029 was conducted using logistic regression. By way of stepwise logistic regression, the most important predictors of prognosis in Protocol 028/029 were identified as disseminated disease, neutropenia, BMT, and high-dose corticosteroids at Week 1. Because imbalances in these factors in Protocols 019 and 028/029 populations could influence outcome, logistic regression was used to adjust for potential imbalance in identified prognostic factors and outcomes were compared after adjustment. However, as described earlier, it was not possible to correct for the selection bias of enrolling sicker patients in a salvage study such as Protocol 019.

It was prospectively defined that the primary model for the comparison should be a model that contained predictors whose adjusted predictor p-value was <0.10 . When the 4 variables were included in the model, both BMT and high-dose corticosteroids at Week 1 had predictor p-values >0.10 . When BMT or corticosteroids are included with disseminated disease and neutropenia in a 3-variable model, each meets the $p<0.10$ criteria. Therefore, the primary model included 3 variables with BMT, instead of high-dose corticosteroid use at Week 1, because it had a stronger relationship to outcome.

The adjusted odds ratio (OR) and its exact 95% CI for the comparison of Protocol 019 to Protocol 028/029 are displayed in Table 38. The adjusted OR for the primary model (disseminated disease, neutropenia, and BMT) was 3.21 and the lower limit of the CI was 1.48. The analysis demonstrated that caspofungin was at least as effective as standard antifungal therapy in the treatment of patients with IA, thus supporting the overall efficacy of caspofungin. To evaluate the effect of the 4 predictors on outcomes, several models were considered for adjusting the OR. In addition, in Protocol 028/029, neutropenia and hematologic malignancies were highly correlated, so a model was constructed replacing neutropenia with hematologic malignancies. For each of the models considered, the adjustment did not appreciably change the OR or the lower limit of the CI. This supports the result of the descriptive analysis, namely, that the 2 study populations were similar with respect to important prognostic characteristics and that outcome was more favorable in patients receiving caspofungin.

The results for the refractory populations were similar to those of the refractory/intolerant population.

Table 38

Summary of Logistic Regression Analyses for the Comparison of Efficacy Between Protocol 019 and Protocol 028/029

Variables Considered [†]	Odds Ratio [‡] (95% CI)
Expert Panel Refractory or Intolerant, N=54 (Protocol 019) Versus Refractory or Intolerant, N=206 (Protocol 028/029)[§]	
Unadjusted	3.34 (1.64, 6.76)
Diss/Neut/BMT	3.21 (1.48, 7.00)
Diss/Neut/Cort	3.64 (1.68, 7.94)
Diss/Heme /BMT	3.42 (1.62, 7.26)
Diss/Neut/BMT/Cort	3.40 (1.55, 7.53)
Expert Panel Refractory, N=44 (Protocol 019) Versus Refractory Control, N=188 (Protocol 028/029)	
Unadjusted	3.07 (1.35, 6.86)
Diss/Neut/BMT	3.09 (1.27, 7.49)
Diss/Neut/Cort	3.29 (1.37, 7.89)
Diss/Heme/BMT	3.20 (1.35, 7.53)
Diss/Neut/BMT/Cort	3.04 (1.24, 7.40)
[†] Diss = disseminated disease; Neut = neutropenia at baseline; BMT = bone marrow or peripheral stem cell transplantation; Cort = high-dose corticosteroid administration at baseline; Heme = hematologic malignancy. [‡] Odds of favorable outcome in Protocol 019/odds of favorable outcome in Protocol 028/029. [§] Patients were excluded from analysis if data were insufficient to allow an end-of-treatment assessment.	

6.3.10 Summary of Efficacy of Caspofungin in the Treatment of IA

1. Caspofungin 50 mg IV daily, following a 70-mg loading dose on Day 1, is effective in the treatment of well-documented invasive aspergillosis in patients refractory to or intolerant of other therapy, based on the assessments of an Expert Panel.
2. Caspofungin is associated with favorable outcomes in patients with an expected poor prognosis, including those refractory to initial therapy, with disseminated disease, who are neutropenic, or are recipients of allogeneic transplants or high-dose corticosteroids.
3. Caspofungin is effective in the treatment of invasive aspergillosis when compared to a historical control group receiving standard therapy. Using logistic regression, an odds ratio of >3 in favor of caspofungin is seen in the Refractory or Intolerant population and in the Refractory population whether or not adjusting for potential imbalances in prognostic factors and regardless of which factors had adjustment. The lower bound of the 95% CI is >1 in all cases. In this analysis, caspofungin was at least as effective as standard therapy, supporting the overall effectiveness of caspofungin.
4. Documented relapse of invasive aspergillosis is uncommon up to 4 weeks after completion of IV caspofungin therapy.

5. Favorable clinical and microbiological responses are seen in patients with infections due to *A. fumigatus*, *A. flavus*, and *A. niger*. In these patients, there is no apparent correlation between caspofungin minimum inhibitory concentrations at 24 hours in RPMI medium or AM3 medium and outcome.
6. In Phase II studies, caspofungin at 35, 50, and 70 mg IV daily is effective in the treatment of esophageal and oropharyngeal candidiasis.
7. In the Phase II studies of esophageal and oropharyngeal candidiasis, caspofungin at 50 or 70 mg IV daily appears more effective than 35 mg and appears at least as effective as amphotericin B.
8. Most esophageal and oropharyngeal *Candida* infections are caused by *C. albicans*, but there is no apparent difference in clinical or microbiological outcome in patients with mixed infections or infections due to non-*albicans Candida* spp. when compared to those with *C. albicans* alone.

6.4 Efficacy of Caspofungin in Esophageal and Oropharyngeal Candidiasis

As outlined in Section 5.1, Overview of the Development Program, studies in *Candida* infections were conducted concurrently. The results from the completed Phase II studies in Esophageal and Oropharyngeal Candidiasis (Protocols 003, 004, 007) versus amphotericin B are summarized to provide supportive data regarding the efficacy of caspofungin in the treatment of documented fungal infections.

This section is organized as follows: (1) Study Design of the Phase II *Candida* studies; (2) Demographics and other characteristics of the patients enrolled clinical studies; (3) Efficacy of caspofungin in the treatment of *Candida* esophagitis in controlled clinical studies (Protocols 003, 004) with supportive information from the noncomparative pharmacokinetic study in patients with *Candida* esophagitis (Protocol 007); (4) Efficacy of caspofungin in oropharyngeal candidiasis in Protocol 004; (5) Microbiology of infection and microbiological outcomes; (6) Subgroup and treatment by factor analysis, and (7) Summary of clinical efficacy results in patients with esophageal or oropharyngeal candidiasis.

6.4.1 Clinical Efficacy Studies of Caspofungin in Oropharyngeal and Esophageal Candidiasis (Protocols 003, 004, and 007)

Study Design

In each of the Phase II *Candida* studies, patients were required to have symptoms of and microbiological documentation for oropharyngeal or esophageal candidiasis. Severity of disease was graded according to a 3-point scale for patients with oropharyngeal candidiasis and a 4-point scale for patients with *Candida* esophagitis, based on an oropharyngeal exam or endoscopy (Grade 0 [no lesions] to Grade 3 or 4 [extensive disease]). Primary efficacy analyses were based on the modified intention to treat (MITT) approach (i.e., inclusion of all patients who met the definition of disease and received at least 1 dose of study therapy).

6.4.2 Demographics and Other Characteristics of the Patients Enrolled in the Phase II *Candida* Studies (Protocols 003, 004, and 007)

In general, the baseline demographics and other characteristic of patients with *Candida* infections (Protocols 003, 004, and 007) are similar as outlined in Table 39. The studies were conducted in adults at least 18 years of age with documented oropharyngeal or esophageal candidiasis. The majority of patients in each study were male (>75%) with a mean age of approximately 36 years. The patients were diverse and in the comparative studies (Protocols 003, 004) were primarily Hispanic (35.2% to 64.8%). In the noncomparative study (Protocol 007), patients were primarily black (71.4%). The majority (>79%) had advanced HIV infection with low baseline CD4 cell counts (median 13 to 69 cells/mm³) at study entry. Severity of esophagitis as assessed by endoscopy grade at study entry was generally similar (~40% with Grade 3 or 4 esophagitis).

Secondary Diagnoses

The most common secondary diagnosis in *Candida* studies included: HIV infection, diarrhea, anemia, nutritional abnormality, weight loss, *Pneumocystis carinii* pneumonia, pulmonary tuberculosis, dermatomycosis, and herpes zoster infection .

Prior Therapies

The majority of patients (≥80%) in *Candida* studies received prior therapies. The most common prior therapies included: fluconazole, isoniazid, lamivudine, sulfamethoxazole and/or trimethoprim, stavudine, zidovudine, midazolam, ranitidine, and multivitamins .

Concomitant Therapies

The most common concomitant therapies in *Candida* studies included: isoniazid, lamivudine, stavudine, sulfamethoxazole and/or trimethoprim, zidovudine, acetaminophen, dipyron, and multivitamins.

6.4.3 Efficacy of Caspofungin in the Phase II *Candida* Esophagitis Studies (Protocols 003, 004, 007)

Controlled Studies of *Candida* Esophagitis (Protocols 003, 004)

Modified Intent-to-Treat (MITT) Analysis

The MITT analysis included all patients who met diagnostic criteria for *Candida* esophagitis, received at least one dose of caspofungin. The proportion of patients in the MITT analysis with a favorable overall combined response of symptomatic and endoscopic improvement, and its 95% CI, are summarized by treatment group and study in Table 40. The effect of caspofungin on the proportion of patients with a favorable response is consistent across studies. In both studies, 35, 50, and 70 mg of caspofungin were effective according to the MITT analysis, and a high percentage of patients in each group had a favorable response. The proportion of patients with a favorable response was numerically higher at 50 and 70 mg than at 35 mg caspofungin, and in these Phase II Studies, all doses appeared at least as effective as amphotericin B.

Table 39

Baseline Patient Characteristics of Phase II Oropharyngeal and Esophageal Candidiasis Studies by Protocol

	Active-Comparator Controlled Studies				Noncomparative	All Studies Combined	
	Protocol 003		Protocol 004		Protocol 007		
	Caspofungin (N=74)	Amphotericin B (N=54)	Caspofungin (N=105)	Amphotericin B (N=35)	Caspofungin (N=14)	Caspofungin (N=193)	Amphotericin B (N=89)
	n (%)	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)
Candida Infection							
Esophagitis	74 (100.0)	54 (100.0)	65 (61.9)	23 (65.7)	14 (100.0)	153 (79.3)	77 (86.5)
Oropharyngitis	0 (0.0)	0 (0.0)	40 (38.1)	12 (34.3)	0 (0/0)	40 (20.7)	12 (13.5)
Gender							
Male	60 (81.1)	41 (75.9)	82 (78.1)	28 (80.0)	11 (78.6)	153 (79.3)	69 (77.5)
Female	14 (18.9)	13 (24.1)	23 (21.9)	7 (20.0)	3 (21.4)	40 (20.7)	20 (22.5)
Race							
Caucasian	11 (14.9)	7 (13.0)	23 (21.9)	3 (8.6)	4 (28.6)	38 (19.7)	10 (11.2)
Black	1 (01.4)	2 (03.7)	12 (11.4)	3 (8.6)	10 (71.4)	23 (11.9)	5 (5.6)
Hispanic	46 (62.2)	35 (64.8)	37 (35.2)	16 (45.7)	0 (0.0)	83 (43.0)	51 (57.3)
Other	16 (21.6)	10 (18.5)	33 (31.4)	13 (37.1)	0 (0.0)	49 (25.4)	23 (25.8)
Age							
18 to 25	12	10	16	3	0	28	13
26 to 40	44	27	58	21	7	109	48
41 to 65	18	16	31	10	0	56	26
>65	0	1	0	1	0	0	2
Mean	36.2	36.7	35.2	36.1	41.0	36.0	36.4
SD [†]	10.0	11.2	9.8	10.7	7.8	9.8	10.9
Median	35.0	35.0	34.0	34.0	39.5	35.0	34.0
Range	21 to 65	22 to 66	18 to 63	21 to 68	30 to 54	18 to 65	21 to 68

Table 39 (Cont.)

Baseline Patient Characteristics of Phase II Oropharyngeal and Esophageal Candidiasis Studies by Protocol

	Active-Comparator Controlled Studies				Noncomparative	All Studies Combined	
	Protocol 003		Protocol 004		Protocol 007	Caspofungin (N=193)	Amphotericin B (N=89)
	Caspofungin (N=74)	Amphotericin B (N=54)	Caspofungin (N=105)	Amphotericin B (N=35)	Caspofungin (N=14)		
	n (%)	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)
HIV Positive							
Yes	59 (79.7)	44 (81.5)	102 (97.1)	35 (100.0)	14 (100.0)	175 (90.7)	79 (88.8)
No	15 (20.3)	10 (18.5)	3 (02.9)	0 (0.0)	0 (0.0)	18 (9.3)	10 (11.2)
Baseline Endoscopy Grade							
Grade 0.5	11 (14.9)	5 (9.3)	5 (4.8)	3 (8.6)	1 (7.1)	17 (8.8)	8 (9.0)
Grade 1	18 (24.3)	15 (27.8)	6 (5.7)	1 (2.9)	1 (7.1)	25 (12.8)	16 (18.0)
Grade 2	12 (16.2)	9 (16.7)	15 (14.3)	3 (8.6)	2 (14.3)	29 (15.0)	12 (13/5)
Grade 3	24 (32.4)	18 (33.3)	30 (28.6)	12 (34.3)	8 (57.1)	62 (32.1)	30 (33.7)
Grade 4	8 (10.8)	7 (13.0)	8 (7.6)	4 (11.4)	2 (14.3)	18 (9.3)	11 (12.4)
Missing	1 (1.4)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)
Baseline Oropharyngeal Exam Grade							
Grade 1	NA	NA	14	4	NA [†]	14	4
Grade 2	NA	NA	18	4	NA	18	4
Grade 3	NA	NA	8	4	NA	8	4

Table 39 (Cont.)

Baseline Patient Characteristics of Phase II Oropharyngeal and Esophageal Candidiasis Studies by Protocol

	Active-Comparator Controlled Studies				Noncomparative	All Studies Combined	
	Protocol 003		Protocol 004		Protocol 007		
	Caspofungin (N=74)	Amphotericin B (N=54)	Caspofungin (N=105)	Amphotericin B (N=35)	Caspofungin (N=14)	Caspofungin (N=193)	Amphotericin B (N=89)
	n (%)	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)
CD4 Counts (/mm³)							
N	59	43	99	34	12	170	77
Mean	88.3	78.6	76.6	59.4	19.7	76.6	70.1
SD	96.0	57.8	139.6	65.9	24.1	121.5	61.8
Median	55.0	69.0	30.0	29.0	13.0	36.5	58.0
Range	2 to 430	3 to 227	0 to 879	0 to 260	0 to 80	0 to 879	0 to 260
[†] NA = Not applicable. [‡] SD = Standard deviation.							

Table 40

Proportion (%) of Esophageal Patients With a Favorable Overall Response
 in the Modified Intent-to-Treat Analysis by Protocol

Treatment Group	Protocol	Patients With Favorable Overall Response n/m [†] (%)	95% CI
Caspofungin acetate 35 mg	004	14/21 (66.7)	(43.0,85.4)
Caspofungin acetate 50 mg	003	34/46 (73.9)	(58.9, 85.7)
	004	18/20 (90.0)	(68.3, 98.9)
Caspofungin acetate 70 mg	003	25/28 (89.3)	(71.8, 97.7)
	004	17/22 (77.3)	(54.6, 92.2)
Amphotericin B 0.5 mg/kg	003	34/54 (63.0)	(48.7, 75.7)
	004	14/23 (60.9)	(38.5, 80.3)

[†] n/m = number of patients with favorable assessment/patients with data at time point.

Evaluable Patients Analysis

The proportion (%) of esophageal patients with a favorable overall combined response by the Evaluable Patients analysis by protocol is displayed in Table 41. The pattern of response is similar to that seen in the MITT analysis, with each caspofungin group having a high percentage of patients with a favorable response. Furthermore, consistent effects across studies are observed regardless of the analytical approach used.

Table 41

Proportion (%) of Esophageal Patients With a Favorable Overall Response
 in the Evaluable-Patients Analysis by Protocol

Treatment Group	Protocol	Patients With Favorable Overall Response n/m [†] (%)	95% CI
Caspofungin acetate 35 mg	004	13/15 (86.7)	(59.5, 98.3)
Caspofungin acetate 50 mg	003	33/43 (76.7)	(61.4, 88.2)
	004	18/19 (94.7)	(74.0, 99.9)
Caspofungin acetate 70 mg	003	24/27 (88.9)	(70.8, 97.6)
	004	17/20 (85.0)	(62.1, 96.8)
Amphotericin B 0.5 mg/kg	003	34/50 (68.0)	(53.3, 80.5)
	004	14/20 (70.0)	(45.7, 88.1)

[†] n/m = Number of patients with favorable assessment/patients with data at time point.

Noncomparative Pharmacokinetic Study in Patients With Candida Esophagitis

A total of 14 HIV-infected patients were enrolled in the noncomparative pharmacokinetic study of patients with *Candida* esophagitis (Protocol 007). This protocol included patients with advanced HIV disease. The median CD4 cell count was 13 cells/mm³, with a range from 0 to 80 cells/mm³. Both the 50- and 70-mg doses of caspofungin were effective as assessed by the proportion of patients with a favorable symptom and endoscopic response. The proportion of patients with a favorable response was lower in each group (66.7%) than was seen in the comparative studies, but may have been due to the small sample size in Protocol 007 or the fact that the patients had very advanced HIV infection.

6.4.4 Efficacy of Caspofungin in Oropharyngeal Candidiasis

All doses of caspofungin were effective in patients with oropharyngeal candidiasis in the Oropharyngeal and Esophageal Candidiasis Study (Protocol 004) as assessed by symptoms and oropharyngeal lesions and a high percentage of patients had a favorable response in each group (85 to 93%). The pattern of response was consistent with the response seen in patients with *Candida* esophagitis, but the proportion of patients with favorable responses was higher in patients with oropharyngeal candidiasis. Caspofungin, at all doses, had a numerically higher response rate (85 to 95%) than amphotericin B (66.7%). Results were consistent in the Evaluable Patients analysis (92 to 100% caspofungin versus 80% amphotericin B).

Relapse of Symptomatic Esophageal or Oropharyngeal Candidiasis

Patients in Protocol 004 who had a favorable response at the end of therapy were assessed for relapse at 14 and 28 days posttherapy. As expected in patients with advanced HIV disease, relapse occurred in all groups and was more common at 28 days than 14 days. For patients with *Candida* esophagitis, relapse in the caspofungin groups was numerically lower than in the amphotericin B group (28 day: 14.3 to 23.5% for caspofungin 35- and 70-mg group, respectively, versus 35.7% for amphotericin B). Relapse in patients with oropharyngeal disease was more common in caspofungin-treated patients at 70 mg (60%) than in patients treated with amphotericin B (37.5%) or in those treated with the 35- or 50-mg doses of caspofungin (36.4 and 30.8%, respectively). The number of patients in each group is small (n=8 to 13) and the results must therefore be viewed cautiously.

6.4.5 Microbiology

Candida isolates were obtained from 258 of the 282 patients enrolled in Protocols 003, 004, and 007. Most infections (N=212) were due to *C. albicans* alone. Three patients had infections due to non-*albicans Candida* spp. (*C. krusei*, *C. guilliermondii*, *C. tropicalis*). The remainder were mixed infections with *C. albicans* and non-*albicans Candida* spp. (N=41) or mixed infections with non-*albicans Candida* spp. (N=2).

Because there is no standardized in vitro susceptibility testing method for glucan synthesis inhibitors, MICs were determined in 2 different media (RPMI and AM3) using

the NCCLS Protocol M27-A. For each of the *Candida* species tested, the MICs differed by medium. MICs of caspofungin ranged higher in RPMI than in AM3 for *C. albicans*, *C. guilliermondii*, *C. parapsilosis*, and *C. tropicalis*. By NCCLS criteria, the MIC₉₀ of caspofungin for *C. albicans* was 1 µg/mL in RPMI and 0.125 µg/mL in AM3. The MIC₉₀ of caspofungin for *C. guilliermondii*, *C. krusei*, and *C. glabrata* were >8 (trailing), 2, and 2 µg/mL, respectively in RPMI (and >2, 1, and 0.25 µg/mL, respectively, in AM3). The number of isolates of other *Candida* species was small (<10 each).

Microbiology in the Comparative Studies of *Candida* Esophagitis (Protocols 003, 004)

In the Phase II comparative studies (Protocols 003 and 004), 198 patients with *Candida* esophagitis had isolates made available to the Merck Clinical Microbiology Laboratory for identification and susceptibility testing. The majority (>75%) had infections caused by *C. albicans* alone. In each study, the percentage of evaluable patients with a favorable microbiological response was higher in caspofungin groups than the amphotericin B group (~79 to 89% versus 66%, respectively) and was generally similar to the overall clinical response (~84 to 89% versus 68%, respectively) seen in each treatment group.

Response was also assessed by baseline pathogen. A favorable overall clinical response was seen in >75% of patients with *C. albicans* treated with caspofungin and in 70 to 72% of patients treated with amphotericin B. The percentage of patients with a favorable microbiological response was consistent across studies. Although the number of infections caused by *Candida* spp. other than *C. albicans* was small, no apparent difference was noted in the frequency of favorable clinical or microbiological response by species isolated at entry. In addition, for patients treated with 50 or 70 mg caspofungin, no apparent association was noted between MIC at baseline and outcome. Patients with *Candida* isolates with MICs >8 for caspofungin in RPMI medium had favorable clinical and microbiological responses. The MICs in AM3 for these *Candida* species ranged lower (0.06 to >2 µg/mL).

The distribution of pathogens in patients who failed caspofungin therapy is consistent with the distribution of infections in the study population overall, and the majority had no pathogen isolated at the end of therapy. In the cases of microbiological persistence, the MICs in RPMI and AM3 media were generally unchanged (≤2-fold increase) after therapy with caspofungin.

Microbiology in the Open, Noncomparative Study in *Candida* Esophagitis (Protocol 007)

Eleven infections in the noncomparative study in *Candida* esophagitis were due to *C. albicans* and 1 was a mixed infection with *C. albicans* and *C. glabrata*. A favorable microbiological response was seen in 5 (56%) of the 9 evaluable patients with *C. albicans*, and a favorable clinical response was seen in 6 (66.7%) of these 9 patients. The patient with a mixed infection of *C. albicans* and *C. glabrata* had an unfavorable clinical and microbiological response.

Microbiology in Patients With Oropharyngeal Disease

The distribution of pathogens in patients with oropharyngeal candidiasis and microbiological outcomes were similar to that seen in patients with esophageal candidiasis.

6.4.6 Subgroup and Treatment by Factor Analysis

The consistency of the treatment effects of caspofungin on the primary endpoint was evaluated among various subgroups of patients classified according to demographic parameters and disease characteristics by pooled data from Phase II comparative studies (Protocols 003 and 004). Very few patients >65 years of age enrolled in Phase II studies. There was no apparent difference in outcome, as assessed by clinical plus endoscopic response, based on gender, race, or severity of esophagitis at baseline.

6.4.7 Summary of Clinical Efficacy Results in Patients With Oropharyngeal and Esophageal Candidiasis

The Phase II studies demonstrate that caspofungin at doses of 35, 50, and 70 mg administered once daily is effective in the treatment of esophageal and oropharyngeal candidiasis. The studies included a majority of patients with advanced HIV disease with CD4 cell counts <50 cells/mm³.

In the 2 comparative studies, all doses of caspofungin tested were effective and a high percentage of patients with *Candida* esophagitis experienced favorable responses. Caspofungin at 50 or 70 mg daily had a numerically higher response than at the 35-mg daily dose and all doses were similar to amphotericin B. Furthermore, there was no apparent difference in response rate between 50 and 70 mg caspofungin. Caspofungin was also shown to be effective in the treatment of *Candida* esophagitis in the noncomparative pharmacokinetic *Candida* esophagitis study (Protocol 007). Patients in Protocol 004 with oropharyngeal candidiasis had a similar pattern of response to those with *Candida* esophagitis in Protocols 003 and 004. A consistent pattern of clinical response was seen regardless of site of infection, study, or analytical method.

As expected, the majority of infections were due to *C. albicans*. The percentage of patients with a favorable microbiological response was similar to the percentage with a favorable clinical response and did not appear to depend on the specific pathogen(s) isolated or the MIC at baseline. In the cases with microbiological persistence, there was little change in MIC (≤ 2 -fold increase) for caspofungin in either RPMI or AM3 media after treatment.

Overall, the results of the clinical and microbiological responses seen in the Phase II studies support the hypothesis that caspofungin is effective in the treatment of esophageal and oropharyngeal candidiasis.

6.5 Concentration-Effect Relationship for Treatment Outcome

As described in Section 5.6.4, sparse pharmacokinetic sampling was conducted in all of the efficacy studies of caspofungin. Two population pharmacokinetic/pharmacodynamic analyses were completed to support the initial application: a combined analysis of data from the Phase II localized candidiasis studies (Protocols 003, 004, and 007) and an analysis of data from the Noncomparative *Aspergillus* Study (Protocol 019). In these population pharmacokinetic analyses, the potential for $AUC_{0-24\text{ hr}}$, $C_{1\text{ hr}}$, and $C_{24\text{ hr}}$ to predict overall treatment outcome (favorable/unfavorable) at the end of IV therapy in evaluable patients was explored. In the localized candidiasis analysis, $C_{24\text{ hr}}$ was found to be a statistically significant factor in predicting treatment outcome, while $AUC_{0-24\text{ hr}}$ was found to be a marginally significant factor in predicting treatment outcome. The odds ratio estimated for $C_{24\text{ hr}}$ indicates that the chance of a positive treatment outcome increased 3.48 times for every 2.72-fold increase of $C_{24\text{ hr}}$. Though significant or marginally significant, the predictive potential of $C_{24\text{ hr}}$ and $AUC_{0-24\text{ hr}}$ exhibited a high degree of variability such that these parameters did not carry reliable prediction of treatment outcome. Because $C_{24\text{ hr}}$ and $AUC_{0-24\text{ hr}}$ in patients are themselves somewhat correlated ($r^2=0.84$), it is not possible to distinguish whether one parameter or the other or some combination of both is the best predictor of treatment outcome. In the population pharmacokinetic analysis of patients with invasive aspergillosis, neither $C_{1\text{ hr}}$ nor $C_{24\text{ hr}}$ was found to predict treatment outcome. A similar distribution of individual pharmacokinetic values was seen for aspergillosis patients with favorable and unfavorable treatment outcomes.

The different results from the 2 population studies may be due to the smaller range of pharmacokinetic parameter values obtained in the aspergillosis study, where 1 fixed dose (50 mg daily with a 70-mg loading dose on Day 1) was used, rather than the range of doses (35, 50, and 70 mg daily) evaluated in the local candidiasis studies. In addition, the nature of the fungal infections and the high prevalence of infections refractory to standard therapy suggest that the factors influencing the probability of successful treatment in the aspergillosis patient population are more complicated than those determining successful treatment of patients with esophageal and oropharyngeal infections receiving mostly first-line therapy. These added complications likely reduce the relative contribution of pharmacokinetics towards determining patient outcome in salvage therapy in patients with invasive aspergillosis.

7. Clinical Safety

7.1 Introduction

As previously noted, the data in this document are designed to support the use of caspofungin in the treatment of invasive aspergillosis. The safety data supporting the use of caspofungin are derived from clinical pharmacology (Phase I) studies and several clinical studies (Phase II/III) in patients with *Aspergillus* or *Candida* infections. Although the focus of this application is on the treatment of IA, studies in patients with *Candida* infections provide an important supportive safety database for caspofungin, because these patients had less severe diseases than the patients with *Aspergillus* infections and fewer confounding acute background illnesses. In addition, *Candida* infections permitted evaluation in blinded, controlled studies providing a much larger safety database with an active comparator and an assessment of a higher dose of caspofungin (70 mg/day for up to 14 days). Therefore, the *Candida* safety database will be described prior to the IA safety database.

This summary of safety describes the overall safety profile of caspofungin. All adverse experiences have been reviewed, but because of the high background incidence of AEs in the patient populations enrolled in caspofungin clinical trials, the focus of the discussion will be on adverse experiences considered drug related by investigators. The total study population encompasses both healthy subjects who participated in the clinical pharmacology (Phase I) studies and patients with *Candida* or *Aspergillus* infections in the clinical studies. In the clinical pharmacology studies, a total of 274 subjects received caspofungin for 1 to 21 days; 126 of these subjects received caspofungin at doses of ≥ 50 mg alone or with other drugs for >7 days. In clinical studies a total of 338 patients received caspofungin for 1 to 162 days; 217 of these patients received 50 or 70 mg caspofungin for >7 days. Clinical studies include controlled studies, employing fluconazole or amphotericin B as a comparator, in patients with esophageal and/or oropharyngeal candidiasis (Protocols 003, 004, and 020); an open-label, noncomparative clinical study in patients with esophageal candidiasis (Protocol 007); an open-label noncomparative study in patients with invasive aspergillosis who were refractory to or intolerant of other therapies (Protocol 019); and a compassionate-use study (Protocol 024/025) for the treatment of *Aspergillus* and *Candida* infections in patients who are refractory to or intolerant of amphotericin B formulations. Patients enrolled in caspofungin clinical trials were diverse; nearly half were women and a significant percentage were Hispanic or Mestizo. Patients had a number of underlying diseases including malignancies, organ and bone marrow transplants, HIV infection, and diabetes mellitus. Patients generally also received a number of concomitant medications.

Reports of all clinical pharmacology studies, with the exception of Protocol 030, have been completed with data from case report forms (CRFs), and their results have been described in individual clinical study reports (CSRs). For Protocol 030, the multiple dose hepatic insufficiency study, no final CRF data were available in the initial application, but serious adverse experiences required to be reported within 24 hours of onset of the event to the Merck Worldwide Adverse Experience System (WAES) database by the

cutoff date of 31-Mar-2000 are summarized. All data from completed clinical studies (Protocols 003, 004, 020, and 007) and the ongoing clinical study (Protocol 019) that had been entered in CRFs by the visit cutoff dates for each study are also reported in individual CSRs and summarized in this section. For the 11 additional patients with *Aspergillus* infections in Protocol 019, who completed therapy after the data cutoff date, an overview of final safety is included in this document. For the ongoing Noncomparative *Aspergillus* Study (Protocol 019), serious adverse experiences from sources other than CRFs, i.e., the WAES database, are reported from the CRF cutoff date of 07-Feb-2000 through 19-Apr-2000. For the ongoing compassionate use study, safety data are limited to serious adverse experiences, select nonserious adverse experiences, and all drug-related adverse experiences leading to discontinuation of therapy; were reported only in the WAES database, and had a cutoff date of 31-Mar-2000. It should be noted that safety data from the ongoing clinical studies in Invasive Candidiasis (Protocol 014) and Empirical Therapy (Protocol 026) are limited to serious adverse experiences reported to the WAES database by the cutoff date of 31-Mar-2000. Because these studies remain blinded, serious adverse experiences are included without designation of treatment group.

Organization and Grouping of Studies

This safety section is grouped into 2 main parts to allow for an overall assessment of caspofungin in (1) clinical pharmacology (Phase I) and (2) clinical studies (Phase II/III). The clinical pharmacology studies included single- and multiple-dose studies in healthy subjects, pharmacokinetics in special populations, and drug-drug interaction studies. Data are grouped by dose of caspofungin (<50, 50, or >50 mg) alone or caspofungin with concomitant medications (if a second drug was administered as part of a drug interaction study).

In the clinical studies, the safety profile of caspofungin is defined by tabulating the adverse experiences by caspofungin dose (35, 50, and 70 mg). The controlled clinical studies in *Candida* infections (Protocols 003, 004, and 020) are presented first and include data on the comparator agents, amphotericin B, and fluconazole. These controlled studies allow an assessment of background incidences of adverse experiences. This discussion is followed by an examination of data from a noncomparative clinical study of *Candida* infections (Protocol 007). Data from the noncomparative study in *Aspergillus* infections (Protocol 019) are presented separately, because this study provides important safety information on caspofungin when administered to a severely immunocompromised group of patients with aspergillosis, who require a longer duration of therapy with caspofungin than those in other clinical studies. The data from the compassionate use study (Protocol 024/025) provide further evidence that caspofungin is generally well tolerated in patients with *Aspergillus* infections. Two additional blinded clinical studies are ongoing: Protocol 014 comparing caspofungin to amphotericin B for the treatment of invasive candidiasis and Protocol 026 comparing caspofungin to AmBisome for empirical therapy in patients with persistent fever and neutropenia. Serious adverse experiences are included from these studies in a blinded fashion since these studies are ongoing.

7.2 Overall Extent of Exposure of the Study Population

In the clinical pharmacology studies, safety data are based on adverse experiences for all 274 subjects. The 47 subjects who received 50 mg caspofungin alone were given 2 to 16 days of therapy. One hundred sixteen subjects received >50 mg caspofungin alone. A majority of subjects (72 of 116) who received >50 mg caspofungin alone received a single 70-mg dose. As a result, safety is evaluated separately in the 26 individuals who received >7 days of caspofungin 70 mg. The other 111 subjects in clinical pharmacology studies received either caspofungin <50 mg alone (N=28) or caspofungin with other drugs (N=83).

Table 42 summarizes the overall extent of exposure to caspofungin in all the clinical pharmacology (Phase I) studies.

Table 42

Duration of Caspofungin Treatment by Daily Dose for Phase I Studies

Treatment Group	Days of Treatment				Total Subject-Days on Caspofungin Acetate	Range of Treatment Duration on Caspofungin Acetate (Days)	Mean Treatment Duration on Caspofungin Acetate (Days)
	1	2 to 7	8 to 14	>15			
Caspofungin Alone							
Total subjects on caspofungin <50 mg (N=28)	2	14	12	0	212	1 to 14	7.6
Total subjects on caspofungin 50 mg (N=47) [†]	0	4	38	5	579	2 to 16	12.3
Total subjects on caspofungin >50 mg (N=116) [‡]	72	18	16	10	507	1 to 21	4.4
Caspofungin and Other Drugs							
Total subjects on caspofungin <50 mg (N=8)	0	8	0	0	24	3	3.0
Total subjects on caspofungin 50 mg (N=34) [§]	0	1	21	12	438	2 to 16	12.9
Total subjects on caspofungin >50 mg (N=41)	3	14	24	0	335	1 to 11	8.2
[†] Nineteen subjects received a loading dose of caspofungin 70 mg on Day 1, followed by caspofungin acetate 50 mg daily for remainder of treatment period; 28 subjects received 50 mg daily. [‡] Eleven subjects received single doses of caspofungin <50 mg in addition to single doses of caspofungin >50 mg. [§] Eight subjects received a loading dose of caspofungin 70 mg on Day 1, followed by caspofungin 50 mg daily for remainder of treatment period; 26 subjects received 50 mg daily without the loading dose.							

Caspofungin Acetate
 FDA Advisory Committee Meeting Background
 Clinical Safety

-128-

The safety data of caspofungin were based on adverse experiences for all patients from clinical studies involving both *Candida* (Protocols 003, 004, 007, and 020) and *Aspergillus* (Protocols 019, and 024/025) infections, and include 277 patients (263 patients from Protocols 003, 004, and 020; 14 patients from Protocol 007) with *Candida* infections, and 61 patients (58 patients from Protocol 019 and 3 patients from Protocol 024/025) with *Aspergillus* infections. Of note, the 11 additional patients with IA enrolled in Protocol 019 are not included in Table 43 because these patients were not combined in the original application. The safety data for these patients are summarized separately.

Table 43 summarizes the overall extent of exposure to caspofungin in all clinical studies of *Candida* and *Aspergillus* infections. In these studies, a total of 338 patients were exposed to caspofungin, and caspofungin 50 mg was the most commonly administered dose for a mean duration of therapy of 16 days (range, 1 to 162 days) (Table 43). The extent of exposure to caspofungin in clinical studies of *Aspergillus* infections is also displayed separately. The total duration of exposure to caspofungin 50 mg in patients with *Aspergillus* infections was longer with a mean duration of therapy of 31.5 days (range, 1 to 162 days).

Table 43

Duration of Caspofungin Therapy by Dose for All Caspofungin Clinical Studies

Treatment Group	Days of Therapy						Total Patient-Days on Caspofungin	Range of Duration on Caspofungin (Days)	Mean Duration on Caspofungin (Days)
	1 to 7	8 to 14	15 to 28	29 to 60	61 to 90	≥91			
Total patients on caspofungin 35 mg (N=34)	13	21	0	0	0	0	291	1 to 14	8.6
Total patients on caspofungin 50 mg (N=233)	72	116	21	17	5	2	3731	1 to 162	16.0
Total patients on caspofungin 70 mg (N=71)	15	54	1	1	0	0	828	4 to 56	11.7
<i>Aspergillus</i> patients on caspofungin 50 mg [†] (N=61)	13	10	14	17	5	2	1921	1 to 162	31.5

Note: The table displays the number of patients receiving each daily dose. A patient may be counted multiple times if, during the course of the study, the patient's daily dosage changed.
[†] Patients received a loading dose of caspofungin 70 mg on Day 1 and then received caspofungin 50 mg for the remainder of the treatment period.

7.3 Overview of Safety Results

This safety section presents data demonstrating that caspofungin at therapeutic doses of 50 and 70 mg is generally safe and well tolerated in 274 subjects in clinical pharmacology studies and in 338 patients in clinical research studies of *Candida* and *Aspergillus* infections.

In clinical pharmacology studies, a total of 274 subjects received caspofungin for up to 21 days, including 126 subjects receiving caspofungin at doses of ≥ 50 mg alone or with other drugs for >7 days. The adverse experience profile of caspofungin in these subjects is generally favorable:

- Caspofungin is generally well tolerated in single and multiple doses. The most common clinical adverse experiences in subjects who received caspofungin alone were pruritus at the IV site, infused-vein complications (such as erythema, induration, and pain), and headache. Most of these clinical adverse experiences were transient, mild or moderate in intensity and did not result in discontinuation of therapy. The most common clinical adverse experiences in subjects receiving caspofungin with other drugs are generally similar to those observed in subjects receiving caspofungin alone, with the exception of coadministration with itraconazole. Multiple doses of caspofungin administered with itraconazole are generally well tolerated, but there may be a higher incidence of rash on combination therapy (4/11 patients) than on caspofungin alone (0/28 patients). The rash rate did not appear significantly different than when itraconazole was administered alone (0/8 patients). The most common laboratory adverse experiences following administration of caspofungin with and without other drugs are increases in alanine transaminase (ALT) and/or aspartate transaminase (AST). These increases were generally mild, none exceeding 4-fold the upper limit of normal (ULN); and they returned to baseline following completion or discontinuation of dosing. Concomitant administration of caspofungin with cyclosporin A may be associated with increases in ALT and/or AST. The safety profile of caspofungin is generally similar between subjects receiving multiple caspofungin doses of 50 mg and those receiving doses of >50 mg, including 10 patients who received 70 mg for 21 days.

A total of 338 patients with *Candida* or *Aspergillus* infections were treated with caspofungin. Of these, 277 patients with *Candida* infections (Protocols 003, 004, 007, and 020) and 61 patients with *Aspergillus* infections (Protocols 019 and 024/025) were treated for up to 26 and 162 days, respectively. The adverse experience profile of caspofungin in these patients is generally favorable.

- In controlled clinical studies of *Candida* infections (Protocols 003, 004, and 020), caspofungin was generally well tolerated at all 3 doses of 35, 50, and 70 mg. There were no dose-related toxicities. The most common drug-related clinical adverse experiences in patients receiving 50 mg caspofungin were fever (12.2%) and phlebitis/thrombophlebitis and/or infused-vein complication (18.3%). The most common drug-related laboratory adverse experiences in patients receiving 50 mg

casposfungin were increased ALT (10.5%), increased AST (13.0%), decreased hemoglobin (12.3%), and decreased hematocrit (11.0%). Few of these drug-related adverse experiences lead to discontinuation of therapy. The overall incidence of clinical and laboratory adverse experiences is generally comparable to that observed with fluconazole and was better than that observed with amphotericin B. There were no serious drug-related clinical or laboratory adverse experiences and very few discontinuations due to drug-related clinical or laboratory adverse experiences.

- In a noncomparative clinical study for *Aspergillus* infections, the adverse experience profile is generally similar to that observed in the controlled clinical studies for *Candida* infections. The safety profile of casposfungin did not appear to change with extended therapy. In the *Aspergillus* study, there were no laboratory adverse experiences of increased ALT and/or AST attributed to concomitant administration of tacrolimus. There were no clinically significant clinical adverse experiences of rash with concomitant administration of casposfungin and itraconazole.

7.4 Clinical Pharmacology (Phase I) Studies

Clinical Adverse Experiences

The clinical adverse experience profile for the clinical pharmacology (Phase I) studies is in Table 44.

Table 44

Clinical Adverse Experience Summary by Treatment Group for Phase I Studies

Number (%) of subjects:	Caspofungin Alone <50 mg (N=28)	Caspofungin Alone 50 mg (N=47)	Caspofungin Alone >50 mg (N=116)	Caspofungin <50 mg and Other Drugs (N=8)	Caspofungin 50 mg and Other Drugs (N=34)	Caspofungin >50 mg and Other Drugs (N=41)	Other Drugs and Placebo (N=38)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With one or more adverse experiences	19 (67.9)	19 (40.4)	47 (40.5)	0 (0.0)	22 (64.7)	20 (48.8)	23 (60.5)
With no adverse experience	9 (32.1)	28 (59.6)	69 (59.5)	8 (100.0)	12 (35.3)	21 (51.2)	15 (39.5)
With drug-related adverse experiences [†]	10 (35.7)	9 (19.1)	23 (19.8)	0 (0.0)	13 (38.2)	13 (31.7)	14 (36.8)
With serious adverse experiences	1 (3.6)	1 (2.1)	3 (2.6)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
With serious drug-related adverse experiences [†]	0 (0.0)	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)	0 (0.0)
Discontinued due to an adverse experience	3 (10.7)	3 (6.4)	1 (0.9)	0 (0.0)	1 (2.9)	3 (7.3)	2 (5.3)
Discontinued due to a drug-related adverse experience [†]	1 (3.6)	0 (0.0)	1 (0.9)	0 (0.0)	1 (2.9)	2 (4.8)	0 (0.0)
Discontinued due to a serious adverse experience	1 (3.6)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to a serious drug-related adverse experience [†]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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

Of the subjects who received caspofungin alone at daily doses of 50 mg or >50 mg, approximately 40% had one or more clinical adverse experiences. The incidence of serious clinical adverse experiences was low in all treatment groups, 0 to 3.6%, and none was considered to be drug related by the investigator. The rate of discontinuation due to a clinical adverse experience ranged from 0 to 10.7% of subjects across treatment groups.

The specific drug-related clinical adverse experiences that occurred most commonly ($\geq 10\%$ in any treatment category) in the caspofungin alone groups were pruritus at the injection site, headache, and infused-vein complication (erythema, induration, and/or pain at the site of infusion). Overall, clinical adverse experiences were generally transient and mainly mild-to-moderate in intensity.

Among patients treated with caspofungin >50 mg with or without other drugs, the drug-related clinical adverse experiences that occurred most commonly ($\geq 10\%$) were pruritus at the injection site and infused-vein complication. In the subgroup of subjects who received multiple 70-mg doses of caspofungin (N=27), 67% had one or more clinical adverse experiences. The drug-related clinical adverse experiences that occurred most commonly ($\geq 10\%$) in these subjects were pruritus at the injection site, headache, and infused-vein complication. The adverse experiences seen in subjects who received >50 mg caspofungin were similar to those seen in subjects in both the caspofungin alone <50 mg and 50-mg groups.

Serious Adverse Experiences

There were only 6 subjects in Clinical Pharmacology studies who had serious clinical adverse experiences (trauma; fever/tremor/cellulitis; pulmonary edema; abdominal pain/cholelithiasis/pancreatitis; dyspnea/ascites; deep-vein thrombosis), and none was judged to be related to study drug by the investigator. There were no deaths in caspofungin clinical pharmacology studies (based on CRF information).

Discontinuations Due to Clinical Adverse Experiences

Clinical adverse experiences resulting in discontinuation occurred in 13 subjects in the clinical pharmacology studies and were considered to be drug-related by the investigator in 5 subjects. The clinical adverse experience that resulted in the highest incidence of discontinuation was rash, which occurred in subjects who received caspofungin with other drugs (i.e., itraconazole) or other drugs alone (i.e., itraconazole or cyclosporin A). The 5 drug-related adverse experiences that resulted in discontinuation were: dizziness (1), chest pain (1), and rash (3).

Laboratory Adverse Experiences

The number of subjects in Clinical Pharmacology studies with laboratory adverse experiences is summarized in Table 45.

Table 45

Laboratory Adverse Experience Summary by Treatment Group for Phase I Studies

Number of patients with at least one laboratory test postbaseline: Number (%) of subjects:	Caspofungin <50 mg (N=28)		Caspofungin Alone 50 mg (N=47)		Caspofungin Alone >50 mg (N=116)		Caspofungin <50 mg and Other Drugs (N=8)		Caspofungin 50 mg and Other Drugs (N=34)		Caspofungin >50 mg and Other Drugs (N=41)		Other Drugs and Placebo (N=38)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
with one or more adverse experiences	0		2 (4.3)		8 (6.9)		0 (0.0)		1 (2.9)		9 (22.0)		0 (0.0)	
with no adverse experience	28	100.0	45	(95.7)	108	(93.1)	8	(100.0)	33	(97.1)	32	(78.0)	37	(100.0)
with drug-related adverse experiences [†]	0	(0.0)	1	(2.1)	5	(4.3)	0	(0.0)	0	(0.0)	8	(19.5)	0	(0.0)
with serious adverse experiences	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse experiences [†]	0	(0.0)	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)	0	(0.0)
Discontinued due to an adverse experience	0	(0.0)	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to a drug-related adverse experience [†]	0	(0.0)	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse experience [†]	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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

Most drug-related laboratory adverse experiences in the Clinical Pharmacology studies were increases in ALT or AST. Laboratory adverse experiences occurred with highest incidence in subjects receiving caspofungin at a dose >50 mg alone (6.9%) or with other drugs (22%). In the subgroup (N=27) who received multiple 70-mg doses, only 1 subject had a laboratory adverse experience (increased AST). In the caspofungin >50 mg with other drugs treatment group, most subjects who had an elevated ALT and AST received caspofungin 70 mg daily with cyclosporin A (N=4) or tacrolimus (N=3). The increases in transaminases returned to near baseline or within the normal range within 23 days after discontinuation of therapy.

Serious Laboratory Adverse Experiences in Clinical Pharmacology Studies

There were no deaths in caspofungin Clinical Pharmacology studies. One subject in the Clinical Pharmacology studies (AN 0030; Protocol 009, Hepatic Insufficiency Study) who received a single 70-mg dose of caspofungin had a serious laboratory adverse experience (increased amylase) that was not considered drug related, since this laboratory adverse experience was coincident with the serious clinical adverse experience of pancreatitis.

Discontinuations Due to Laboratory Adverse Experiences in Clinical Pharmacology Studies

One subject (AN 0932, Protocol 021 [itraconazole interaction study]) who received caspofungin had 2 laboratory adverse experiences (increased ALT and AST to <2 times baseline) considered to be drug related by the investigator; the subject was discontinued. Values returned to prestudy baseline by Day 12.

Selected Safety Measurements in Clinical Pharmacology (Phase I) Studies

Tolerability at the Site of Infusion

Of the 274 subjects in Clinical Pharmacology studies who received caspofungin, 229 (84%) subjects had no adverse experience localized to the site of caspofungin infusion. Forty-five (16%) subjects who received caspofungin had at least one adverse experience at the site of infusion (pruritus or infused-vein complication). All were considered mild or moderate and only one (hemorrhage at IV site [AN 0147, Protocol 023]), which was considered to be not drug related, led to study discontinuation.

Elevations in Serum Transaminases

A summary of ALT or AST laboratory adverse experiences in the Clinical Pharmacology studies is in Table 46. In the caspofungin alone treatment groups, the incidence of increased transaminase values appears similarly low in the 50-mg and >50-mg alone groups. In these subjects, elevations were <4-fold ULN and returned to normal during follow-up. Increases in transaminases occurred most commonly (22%) in subjects receiving caspofungin at a dose >50 mg with other drugs; most of these subjects received concomitant cyclosporin A (N=4) or tacrolimus (N=3).

Table 46

Number (%) of Subjects With Alanine or Aspartate Aminotransferase
 Laboratory Adverse Experiences in Phase I Studies

	Caspofungin Acetate Dose									Other Drugs and Placebo		
	<50 mg			50 mg			>50 mg					
	(N=28)			(N=47)			(N=116)			(N=38)		
	n/m	%	DR [†]	n/m	%	DR [†]	n/m	%	DR [†]	n/m	%	DR [†]
Caspofungin Alone	0/28	(0.0)	0/28	2/47	(4.3)	1/47	3/115	(6.1)	3/115	0/37	(0.0)	0/37
Caspofungin and Other Drugs	N=8			N=34			N=41					
	0/8	(0.0)	0/8	0/34	(0.0)	0/34	9/41	(22.0)	8/41			

[†] DR = drug related. Number of subjects reporting laboratory adverse experiences, considered by the investigator to be possibly, probably, or definitely drug related/number of subjects with laboratory test.
[‡] Eight subjects received a loading dose of caspofungin acetate 70 mg on Day 1, and then received caspofungin acetate 50 mg daily for remainder of treatment period; 26 subjects received 50 mg daily.
[§] Nineteen subjects received a loading dose of caspofungin acetate 70 mg on Day 1, and then received caspofungin acetate 50 mg daily for remainder of treatment period; 28 subjects received 50 mg daily.
 N = Total number of subjects per treatment group.
 N/m = Number of subjects with clinically significant laboratory abnormality/number of subjects with laboratory test.

Elevations in Serum Creatinine

One subject (AN 0384) with advanced renal insufficiency in the Renal Insufficiency Study (Protocol 011) had an increased serum creatinine from 2.64 mg/dL at baseline to 3.10 and 3.03 mg/dL reported as an adverse experience on Days 10 and 29, respectively, following a single 70-mg IV dose of caspofungin on Day 1, which was considered to be not drug related.

Clinically Significant Laboratory Abnormalities (CSLAs)

The assessment of relative laboratory safety of all treatment groups in caspofungin clinical trials was accomplished by predefining CSLAs for specified tests. To be included in the CSLA table, a subject had to demonstrate a worsening from baseline for a particular laboratory test, and his/her worst laboratory value had to meet the predefined criteria for a CSLA, regardless of the clinical setting, the magnitude of change from baseline, or whether the investigator classified the result as a laboratory adverse experience.

CSLAs were uncommon in the caspofungin Clinical Pharmacology studies. The laboratory parameters that showed CSLAs included decreased neutrophils or platelets, and increased creatinine, AST, ALT, and total bilirubin. Four subjects had increases in serum creatinine above ULN in the caspofungin >50 mg alone group and all were in the renal insufficiency study (Protocol 011). Increases were <2-fold the prestudy baseline value and only 1 was reported as a laboratory adverse experience. Transaminase elevations of 2.5 x baseline occurred in 4.3 to 25% of subjects across the treatment groups. The highest incidence rates were in the group of subjects who received

caspofungin <50 mg with other drugs (2 out of 8 subjects) and those who received caspofungin >50 mg with other drugs (8 out of 41 subjects). These elevations above baseline only exceeded 2.5 times ULN for 0 to 3.6% of subjects across the treatment groups. A few subjects had elevations in total bilirubin of >2.5 x baseline. These increases in total bilirubin were generally not accompanied by increases in direct bilirubin, ALT or AST.

Serious Adverse Experiences Reported for the Ongoing Clinical Pharmacology Study (Protocol 030)

One subject (AN 0016) in the ongoing multiple-dose hepatic insufficiency study (Protocol 030) had a serious adverse experience of mild bronchitis that resulted in hospitalization 11 days after completion of caspofungin therapy and was considered to be not drug related.

Drug-Drug Interactions in Clinical Pharmacology Studies

Several clinical pharmacology drug interaction studies were conducted as outlined in Section 5.7. These were parallel panel studies in which subjects received caspofungin alone, the drug of interest alone, or the 2 regimens in combination. In the itraconazole interaction study (Protocol 021), caspofungin administered alone or with multiple doses of itraconazole was generally well tolerated, but there appeared to be a higher incidence of rash on combination treatment than on caspofungin alone. Four of 11 subjects who received itraconazole and caspofungin together developed a rash with pruritus of mild or moderate intensity, most frequently early in therapy, which was judged to be drug related. It is unclear, given the small data set in this study, whether the true incidence of dermatologic adverse experiences is higher on caspofungin plus itraconazole than on itraconazole alone.

In the amphotericin B interaction study (Protocol 016), coadministration of a single dose of amphotericin B with caspofungin daily was generally well tolerated. Forty of the 43 adverse experiences reported in this study occurred when the drugs were administered concomitantly. The most common drug-related adverse experiences were chills, fever, and local IV site reactions. Fever and chills were observed only in subjects who received amphotericin B with or without caspofungin. Adverse experiences were mild, none was serious, and none required discontinuation.

In the interaction studies with the immunosuppressants cyclosporin A (Protocols 013 and 017), tacrolimus (Protocol 017), and mycophenolate (Protocol 023), administration of these drugs to healthy subjects was limited to single doses or 2 doses administered 12 hours apart. In Protocol 013, subjects received a single dose of cyclosporin A (or placebo) on the tenth day of caspofungin 70 mg daily (or placebo). All treatments were well tolerated. Two of 8 subjects in the cyclosporin A/caspofungin group had laboratory adverse experiences of increased ALT or AST while receiving caspofungin alone or after both drugs. All transaminase values were <2-fold ULN and the elevations resolved off drug. In Protocol 017-00, 2 doses of cyclosporin 12 hours apart were given on the tenth day of caspofungin. In 3 of the first 4 subjects who received both drugs, ALT values

increased to 2- to 3-fold ULN. Increases in AST paralleled increases in ALT, but were of lesser magnitude. All changes resolved off drug. In Protocol 017-02, a 35-mg dose of caspofungin was coadministered with cyclosporin A (or placebo) on Day 1, followed by caspofungin alone. ALT values subsequently increased above ULN in 2 of the 8 subjects. No values exceeded twice the ULN. Again, AST values increased in parallel but to a lesser magnitude. Changes in ALT and AST resolved off drug. These minimal elevations in ALT and AST occurred in a pattern similar to that seen in Protocol 017 (Immunosuppressant Interaction Study). Consequently, subjects were discontinued from test drug on Day 4. Further coadministration of cyclosporin A and caspofungin has not been undertaken in healthy subjects.

In Protocol 017-00, 2 doses of tacrolimus 12 hours apart were given on the tenth day of caspofungin 70 mg daily. ALT values increased to just above the ULN in 2 of 12 subjects and to 2-fold ULN in a third subject. All values returned rapidly to within the normal range following completion of therapy. In Protocol 017-03, subjects received the same regimen of tacrolimus on Days 1 and 10 of caspofungin therapy. Increases to <2-fold ULN were seen in several subjects receiving caspofungin 50 mg daily either with tacrolimus or its placebo, but were not judged to be adverse experiences. Elevations in ALT in subjects receiving concomitant caspofungin and tacrolimus were slight to modest. Thus, enrollment of patients receiving continuous treatment with tacrolimus in caspofungin clinical studies has been undertaken with stringent transaminase entry criteria and careful monitoring of ALT and AST.

Coadministration of caspofungin and mycophenolate was generally well tolerated. Two of 18 subjects reported adverse experiences that were considered to be possibly drug related (mild diarrhea and mild headache). There were no serious adverse experiences. No subject was discontinued due to a clinical adverse experience; no laboratory adverse experiences were reported.

Drug-Disease Interactions in Clinical Pharmacology (Phase I) Studies

In subjects with renal or hepatic insufficiency, single doses of caspofungin were generally well tolerated, with no serious adverse experiences judged to be drug related, and no discontinuations due to adverse experiences. One subject (AN 0387) in the renal insufficiency study had a serious adverse experience of pulmonary edema 54 days after receiving caspofungin that was considered to be not drug related. Two subjects (AN 0030 and 0036) in the hepatic insufficiency study had serious adverse experiences (pancreatitis/cholelithiasis/abdominal pain/increased amylase; ascites) that were not deemed to be drug related.

7.5 Clinical Safety in Patients with *Candida* Infections

The baseline characteristics of all patients enrolled in the Phase II and III clinical studies for *Candida* infections (Protocols 003, 004, 020, and 007) are summarized in Table 47. The demographics of the study populations were fairly consistent across the 5 treatment groups. The majority of patients in controlled trials of *Candida* infections were men ($\geq 64.7\%$) with a mean age of 36.4. These patients were ethnically diverse with at least

Caspofungin Acetate
 FDA Advisory Committee Meeting Background
 Clinical Safety

-137-

50% in each group being Hispanic and/or Mestizo. Most (>87%) had advanced HIV infection with low CD4 cell counts (median 27 to 58 cells/mm³) at study entry.

Table 47

Baseline Patient Characteristics by Disease and Therapy Group for All Completed Clinical Studies of *Candida* Infections (Protocols 003, 004, 007, and 020)

	Studies for <i>Candida</i> Infections (Protocols 003, 004, 020, and 007)				
	Caspofungin Acetate 35 mg (N=34)	Caspofungin Acetate 50 mg (N=172)	Caspofungin Acetate 70 mg (N=71)	Amphotericin B 0.5 mg/kg (N=89)	Fluconazole 200 mg (N=93)
	n (%)	n (%)	n (%)	n (%)	n (%)
Gender					
Male	22 (64.7)	127 (73.8)	58 (81.7)	69 (77.5)	72 (77.4)
Female	12 (35.3)	45 (26.2)	13 (18.3)	20 (22.5)	21 (22.6)
Age (Years)					
<18	0	0	0	0	0
18 to 25	5	25	8	13	13
26 to 40	15	99	47	48	55
41 to 65	14	48	16	26	20
>65	0	0	0	2	5
Mean	37.0	36.6	35.4	36.4	35.7
SD	10.0	10.3	9.7	10.9	12.1
Median	36.5	36.0	34.0	34.0	32.0
Range	18 to 58	19 to 65	20 to 65	21 to 68	18 to 73
Race					
Asian	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Black	4 (11.8)	15 (8.7)	8 (11.3)	5 (5.6)	7 (7.5)
Caucasian	11 (32.4)	26 (15.1)	13 (18.3)	10 (11.2)	13 (14.0)
Hispanic	8 (23.5)	85 (49.4)	30 (42.3)	51 (57.3)	46 (49.5)
Hispanic/White	0 (0.0)	3 (1.7)	0 (0.0)	1 (1.1)	3 (3.2)
Mestizo	11 (32.4)	40 (23.3)	18 (25.4)	22 (24.7)	22 (23.7)
Mulatto	0 (0.0)	3 (1.7)	1 (1.4)	0 (0.0)	2 (2.2)
Primary Underlying Disease					
HIV-positive	32 (94.1)	153 (89.0)	63 (88.7)	79 (88.8)	81 (87.1)
CD4 Count (cells/mm³) for HIV-Positive Patients					
N	31	147	61	77	76
Mean	109.2	73.4	63.7	70.1	62.9
SD	198.1	111.9	95.7	61.8	119.0
Median	48.0	35.0	27.0	58.0	31.0
Range	2 to 879	0 to 830	0 to 561	0 to 260	0 to 952

Clinical Adverse Experiences in Controlled Clinical Studies for *Candida* Infections (Protocols 003, 004, 020)

A summary of clinical adverse experiences in controlled clinical studies for *Candida* infections for Protocols 003, 004, and 020 by treatment group is in Table 48. As expected in this patient population with advanced HIV infection, the overall incidence of clinical adverse experiences was high and generally similar for all 5 treatment groups.

Clinical adverse experiences considered by the investigator to be drug related occurred in 241 (54.2%) of the 445 enrolled patients in all treatment groups with a notably higher incidence in the amphotericin B group (94.4%). The incidence of drug-related clinical adverse experiences was generally similar among the 3 caspofungin groups, ranging from 45.1 to 55.4%.

There were no serious drug-related clinical adverse experiences reported in the 3 caspofungin groups. The incidence of serious drug-related clinical adverse experience was 4.5% in the amphotericin B group, and 1.1% in the fluconazole group.

As expected in this patient population, deaths were reported in all 5 treatment groups, but none of these deaths was classified by investigators as drug related. Very few patients (6/445 patients, or 1.3%) discontinued therapy due to a drug-related clinical adverse experience in any treatment group.

Table 48

Clinical Adverse Experience Summary by Treatment Group for Controlled Clinical Studies in *Candida* Infections (Protocols 003, 004, and 020)

Number (%) of patients:	Caspofungin 35 mg (N=34)		Caspofungin 50 mg (N=164)		Caspofungin 70 mg (N=65)		Amphotericin B 0.5 mg/kg (N=89)		Fluconazole 200 mg (N=93)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
with one or more adverse experiences	33	(97.1)	145	(88.4)	57	(87.7)	87	(97.8)	82	(88.2)
with no adverse experience	1	(2.9)	19	(11.6)	8	(12.3)	2	(2.2)	11	(11.8)
with drug-related adverse experiences [†]	17	(50.0)	74	(45.1)	36	(55.4)	84	(94.4)	30	(32.3)
with serious adverse experiences	8	(23.5)	31	(18.9)	10	(15.4)	20	(22.5)	22	(23.7)
with serious drug-related adverse experiences [†]	0	(0.0)	0	(0.0)	0	(0.0)	4	(4.5)	1	(1.1)
who died	3	(8.8)	9	(5.5)	3	(4.6)	7	(7.9)	6	(6.5)
discontinued therapy due to an adverse experience	4	(11.8)	2	(1.2)	1	(1.5)	7	(7.9)	3	(3.2)
discontinued therapy due to a drug-related adverse experience [†]	2	(5.9)	0	(0.0)	1	(1.5)	3	(3.4)	0	(0.0)
discontinued therapy due to a serious adverse experience	2	(5.9)	0	(0.0)	0	(0.0)	5	(5.6)	2	(2.2)
discontinued therapy due to a serious drug-related adverse experience [†]	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.2)	0	(0.0)

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

As expected in this patient population with advanced HIV infection, clinical adverse experiences were common as shown in Table 49. The most common clinical adverse experiences (≥15%) in at least 1 of the 3 caspofungin groups, irrespective of causality, were fever, chest pain, phlebitis/thrombophlebitis and/or infused vein complication, diarrhea, headache, and rash. None of the clinical adverse experiences of chest pain was considered to be drug related.

The incidence of drug related fever was 20.6% in the caspofungin 35-mg group, 12.2% in the caspofungin 50-mg group, and 26.2% in the caspofungin 70-mg group. Most of these fevers were considered mild, occurred on a single day or intermittently, resolved on

therapy; and none resulted in discontinuation of therapy. Some patients had preexisting fever. The incidence of drug-related fever in the 3 caspofungin groups was numerically higher than that observed in the fluconazole group (1.1%), but lower than that observed in the amphotericin B group (69.7%). A more accurate comparison of the incidence of fever was in Protocol 020 where the caspofungin 50-mg group was directly compared to fluconazole. In this study, the incidence of fever was similar between the 2 treatment groups, with 22.6% (3.6% drug related) reported in patients receiving caspofungin and 23.7% (1.1% drug related) reported in patients receiving fluconazole. In Protocol 020, the drug-related fevers reported in the caspofungin groups were mild, occurred on a single day, and did not result in discontinuation of therapy (2/3) or occurred intermittently (1/3) and was temporally related to cryptococcal infection. Underlying opportunistic infections and concomitant medications may contribute to the development of fever in these patients and may explain why the incidence of drug-related fever was higher in these clinical studies compared to that in clinical pharmacology studies with healthy subjects.

Because the constellation of clinical findings associated with phlebitis may also be reported as individual adverse experiences (and classified as infused-vein complication), a better assessment is provided by evaluating the number (%) of patients who experienced phlebitis/thrombophlebitis and/or an infused-vein complication, instead of considering these findings as individual adverse experiences. In the caspofungin 35-, 50-, and 70-mg groups, 11.8, 18.3, and 15.4%, respectively, reported phlebitis/thrombophlebitis and/or an infused-vein complication considered to be drug related. This was comparable to that observed in the fluconazole group (17.2% drug related), but lower than that observed in the amphotericin group (22.5% drug related). Most of these adverse experiences were not serious and did not result in discontinuation of therapy. To minimize confounding factors due to the administration of several medications, local tolerability of study drug at the site of infusion was also evaluated by means of a prospectively defined formal tolerability assessment. By this assessment, >90% of patients who received caspofungin through a peripheral line had a rating of "well tolerated" or "moderately well tolerated."

Diarrhea and headache were also reported commonly ($\geq 15\%$ of patients) in patients receiving caspofungin, and incidences were similar to those in patients receiving comparator agents (amphotericin B and/or fluconazole). Although rash was reported in 14.7% of patients in the caspofungin 35-mg group, the incidence was 3.0% (0.6% drug related) and 7.7% (4.6% drug related), respectively, in the caspofungin 50- and 70-mg groups. Most of these rashes were mild-to-moderate in intensity and resolved without interruption of therapy; only 2 patients discontinued therapy due to rash; 1 patient was in the 35 mg caspofungin group and the second was in the 70 mg caspofungin group. Both rashes resolved after discontinuation of therapy.

Table 49

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence $\geq 5.0\%$ in One or More Treatment Groups) by Body System in Controlled Clinical Studies for *Candida* Infections (Protocols 003, 004, and 020) Total and Drug Related[†]

	Caspofungin Acetate 35 mg (N=34)			Caspofungin Acetate 50 mg (N=164)			Caspofungin Acetate 70 mg (N=65)			Amphotericin B 0.5 mg/kg (N= 89)			Fluconazole 200 mg (N=93)		
	n	(%)	DR [†]	n	(%)	DR [†]	n	(%)	DR [†]	n	(%)	DR [†]	n	(%)	DR [†]
Patients with one or more clinical adverse experiences	33	(97.1)	17	145	(88.4)	74	57	(87.7)	36	87	(97.8)	84	82	(88.2)	30
Patients with no clinical adverse experience	1	(2.9)	-	19	(11.6)	-	8	(12.3)	-	2	(2.2)	-	11	(11.8)	-
Body as a Whole/Site Unspecified	23	(67.6)	9	86	(52.4)	27	38	(58.5)	22	83	(93.3)	78	40	(43.0)	3
Asthenia/fatigue	0	(0.0)	0	4	(2.4)	0	0	(0.0)	0	10	(11.2)	6	2	(2.2)	0
Chills	2	(5.9)	1	6	(3.7)	2	2	(3.1)	1	68	(76.4)	67	3	(3.2)	0
Death	3	(8.8)	0	9	(5.5)	0	3	(4.6)	0	7	(7.9)	0	6	(6.5)	0
Edema/swelling	1	(2.9)	1	1	(0.6)	0	1	(1.5)	0	7	(7.9)	5	2	(2.2)	0
Fever	13	(38.2)	7	54	(32.9)	20	25	(38.5)	17	66	(74.2)	62	22	(23.7)	1
Malaise	0	(0.0)	0	2	(1.2)	0	0	(0.0)	0	5	(5.6)	5	0	(0.0)	0
Pain	0	(0.0)	0	1	(0.6)	1	4	(6.2)	3	7	(7.9)	5	2	(2.2)	0
Pain, abdominal	3	(8.8)	0	18	(11.0)	5	7	(10.8)	0	16	(18.0)	8	13	(14.0)	2
Pain, chest	6	(17.6)	0	9	(5.5)	0	5	(7.7)	0	6	(6.7)	1	3	(3.2)	0
Toxoplasmosis	2	(5.9)	0	4	(2.4)	0	1	(1.5)	0	1	(1.1)	0	0	(0.0)	0
Cardiovascular System	8	(23.5)	5	49	(29.9)	31	19	(29.2)	12	33	(37.1)	25	31	(33.3)	16
Infused-vein complication	1	(2.9)	1	14	(8.5)	12	3	(4.6)	1	0	(0.0)	0	14	(15.1)	8
Phlebitis/thrombophlebitis	3	(8.8)	3	29	(17.7)	21	11	(16.9)	9	24	(27.0)	20	10	(10.8)	8
Phlebitis/thrombophlebitis and/ or infused-vein complication	4	(11.8)	4	39	(23.8)	30	14	(21.5)	10	24	(27.0)	20	22	(23.7)	16
Tachycardia	3	(8.8)	1	5	(3.0)	1	1	(1.5)	0	8	(9.0)	4	5	(5.4)	0

Table 49 (Cont.)

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence $\geq 5.0\%$ in One or More Treatment Groups)
 by Body System in Controlled Clinical Studies for *Candida* Infections (Protocols 003, 004, and 020)
 Total and Drug Related[†]

	Caspofungin Acetate 35 mg (N=34)			Caspofungin Acetate 50 mg (N=164)			Caspofungin Acetate 70 mg (N=65)			Amphotericin B 0.5 mg/kg (N= 89)			Fluconazole 200 mg (N=93)		
	n	(%)	DR [†]	n	(%)	DR [†]	n	(%)	DR [†]	n	(%)	DR [†]	n	(%)	DR [†]
Digestive System	20	(58.8)	5	78	(47.6)	15	29	(44.6)	6	49	(55.1)	32	52	(55.9)	12
Candidiasis, oral	3	(8.8)	0	10	(6.1)	0	6	(9.2)	0	2	(2.2)	1	3	(3.2)	0
Diarrhea	8	(23.5)	1	36	(22.0)	4	12	(18.5)	2	21	(23.6)	10	18	(19.4)	2
Nausea	4	(11.8)	3	16	(9.8)	7	6	(9.2)	2	24	(27.0)	19	14	(15.1)	6
Odynophagia	1	(2.9)	0	10	(6.1)	0	1	(1.5)	0	1	(1.1)	0	0	(0.0)	0
Vomiting	1	(2.9)	0	9	(5.5)	2	4	(6.2)	2	19	(21.3)	12	7	(7.5)	3
Hemic & Lymphatic System	1	(2.9)	0	9	(5.5)	3	5	(7.7)	0	11	(12.4)	8	6	(6.5)	2
Anemia	0	(0.0)	0	5	(3.0)	3	1	(1.5)	0	10	(11.2)	8	2	(2.2)	0
Metabolic/Nutritional/Immune	2	(5.9)	0	16	(9.8)	3	7	(10.8)	3	19	(21.3)	15	10	(10.8)	1
Dehydration	1	(2.9)	0	7	(4.3)	0	2	(3.1)	0	0	(0.0)	0	5	(5.4)	0
Hypokalemia	0	(0.0)	0	2	(1.2)	1	2	(3.1)	2	6	(6.7)	6	2	(2.2)	0
Musculoskeletal System	4	(11.8)	1	10	(6.1)	3	4	(6.2)	3	12	(13.5)	9	8	(8.6)	3
Pain, arm		(5.9)	0	2	(1.2)	1	0	(0.0)	0	1	(1.1)	1	0	(0.0)	0
Pain, musculoskeletal	0	(0.0)	0	2	(1.2)	1	0	(0.0)	0	5	(5.6)	4	1	(1.1)	0
Nervous System & Psychiatric	12	(35.3)	4	42	(25.6)	16	20	(30.8)	7	37	(41.6)	26	23	(24.7)	2
Anxiety	0	(0.0)	0	1	(0.6)	1	0	(0.0)	0	1	(1.1)	1	5	(5.4)	0
Dizziness	2	(5.9)	0	4	(2.4)	0	2	(3.1)	1	1	(1.1)	1	3	(3.2)	2
Headache	9	(26.5)	4	26	(15.9)	14	11	(16.9)	5	22	(24.7)	17	8	(8.6)	1
Insomnia	1	(2.9)	0	5	(3.0)	1	4	(6.2)	0	3	(3.4)	2	1	(1.1)	0

Table 49 (Cont.)
 Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥5.0% in One or More Treatment Groups)
 by Body System in Controlled Clinical Studies for *Candida* Infections (Protocols 003, 004, and 020)
 Total and Drug Related[†]

	Caspofungin Acetate 35 mg (N=34)			Caspofungin Acetate 50 mg (N=164)			Caspofungin Acetate 70 mg (N=65)			Amphotericin B 0.5 mg/kg (N= 89)			Fluconazole 200 mg (N=93)		
	n	(%)	DR [†]	n	(%)	DR [†]	n	(%)	DR [†]	n	(%)	DR [†]	n	(%)	DR [†]
Seizure disorder	2	(5.9)	0	2	(1.2)	0	1	(1.5)	0	1	(1.1)	0	4	(4.3)	0
Tremor	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	7	(7.9)	7	0	(0.0)	0
Respiratory System	15	(44.1)	0	45	(27.4)	3	21	(32.3)	2	27	(30.3)	7	27	(29.0)	0
Bronchitis	4	(11.8)	0	7	(4.3)	0	2	(3.1)	0	0	(0.0)	0	1	(1.1)	0
Cough	4	(11.8)	0	11	(6.7)	0	3	(4.6)	0	10	(11.2)	0	3	(3.2)	0
Infection, respiratory, upper	1	(2.9)	0	1	(0.6)	0	2	(3.1)	0	5	(5.6)	0	1	(1.1)	0
Pharyngitis	2	(5.9)	0	6	(3.7)	1	5	(7.7)	1	2	(2.2)	0	4	(4.3)	0
Pneumonia	1	(2.9)	0	4	(2.4)	0	4	(6.2)	0	2	(2.2)	0	2	(2.2)	0
Pneumonia, pneumocystis	1	(2.9)	0	4	(2.4)	0	1	(1.5)	0	4	(4.5)	0	5	(5.4)	0
Sinusitis	3	(8.8)	0	4	(2.4)	0	1	(1.5)	0	1	(1.1)	0	2	(2.2)	0
Tachypnea	1	(2.9)	0	3	(1.8)	1	0	(0.0)	0	7	(7.9)	4	1	(1.1)	0
Skin & Skin Appendage	8	(23.5)	3	33	(20.1)	8	18	(27.7)	7	23	(25.8)	15	20	(21.5)	1
Erythema	1	(2.9)	0	6	(3.7)	2	8	(12.3)	1	9	(10.1)	7	0	(0.0)	0
Induration	0	(0.0)	0	1	(0.6)	0	3	(4.6)	2	7	(7.9)	6	0	(0.0)	0
Pruritus	3	(8.8)	1	4	(2.4)	3	4	(6.2)	1	1	(1.1)	0	1	(1.1)	0
Rash	5	(14.7)	3	5	(3.0)	1	5	(7.7)	3	5	(5.6)	3	0	(0.0)	0
Special Senses	5	(14.7)	1	7	(4.3)	2	6	(9.2)	0	8	(9.0)	0	5	(5.4)	0
Urogenital System	2	(5.9)	0	9	(5.5)	2	3	(4.6)	0	6	(6.7)	1	8	(8.6)	0

[†] DR= Drug related. Number of patients reporting clinical adverse experiences, considered by the investigator to be possibly, probably, or definitely drug related. Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. All body systems are listed in which at least one patient had an adverse experience.

Serious Clinical Adverse Experiences, Including Deaths, in Controlled Clinical Studies for *Candida* Infections (Protocols 003, 004, and 020)

Of the 445 enrolled patients, 91 patients (20.4%) reported at least one serious clinical adverse experience; the incidence was generally similar among the 5 treatment groups. The majority of these serious clinical adverse experiences (86/91 patients or 94.5%) were considered to be not drug related, but were related to the patients' underlying illnesses.

Twenty-eight deaths were reported across treatment groups: 3 patients (8.8%) in the caspofungin 35-mg group, 9 (5.5%) in the caspofungin 50-mg group, 3 (4.6%) in the caspofungin 70-mg group, 7 (7.9%) in the amphotericin B group, and 6 (6.5%) in the fluconazole group. The causes of death were consistent with complications of underlying disease, and the deaths were not unexpected in a population of moderately to severely immunocompromised patients. None of the patients who died had serious adverse experience(s), including death, classified as drug related. Sixty-three patients (14.2%) had greater than or equal to one serious nonfatal adverse experience; 92.1% (58/63) of these serious adverse experiences were considered to be not drug related, and reflect the patients' underlying diseases. Five patients reported serious drug-related clinical adverse experiences: none in any of the 3 caspofungin groups, 4 (4.5%; low cardiac output, vein thrombosis, anaphylaxis/toxic epidermal necrolysis, and hypokalemia) in the amphotericin B group, and 1 (1.1%; cellulitis) in the fluconazole group. In all 5 treatment groups, the majority of the nonfatal serious adverse experiences and deaths occurred off study drug.

Discontinuations Due to Clinical Adverse Experiences in Controlled Clinical Studies of *Candida* Infections (Protocols 003, 004, and 020)

Seventeen (3.8%) patients discontinued therapy due to a clinical adverse experience: 4 (11.8%) in the caspofungin 35-mg group, 2 (1.2%) in the caspofungin 50-mg group, 1 (1.5%) in the caspofungin 70-mg group, 7 (7.9%) in the amphotericin B group, and 3 (3.2%) in the fluconazole group. Of these patients, 2 (5.9%) in the caspofungin 35-mg group (AN 1049, infused vein complications; AN 2302, rash), none in the caspofungin 50-mg group, 1 (1.5%) in the caspofungin 70-mg group (AN 0683, rash), 3 (3.4%) in the amphotericin B group (AN 0133, erythema multiforme; AN 0687, anaphylaxis; and AN 1316, hypokalemia), and none in the fluconazole group discontinued therapy due to a drug-related clinical adverse experience.

Laboratory Adverse Experiences in Controlled Clinical Studies for *Candida* Infections (Protocols 003, 004, and 020)

As expected in this patient population with advanced HIV infection, laboratory adverse experiences were common and are summarized in Table 50. The incidence of all laboratory adverse experiences was generally similar (55.4 to 57.6%) among the 3 caspofungin and the fluconazole groups. The incidence was higher in the amphotericin B group (88.8%). Similarly, drug-related laboratory adverse experiences occurred more commonly in the amphotericin B group (83.1%) compared to the remaining 4 treatment groups (33.8 to 48.5%).

Caspofungin Acetate
 FDA Advisory Committee Meeting Background
 Clinical Safety

-144-

No serious laboratory adverse experiences were reported in the 3 caspofungin groups. One patient (1.1%) in the amphotericin B group was reported as having a serious laboratory adverse experience (AN 2400; decreased hemoglobin) that was also considered to be drug related, and 2 patients (AN 5644, increased fasting blood glucose; and AN 5510, decreased neutrophils) on fluconazole had serious laboratory adverse experiences that were not considered drug related. One patient (AN 5510) in the fluconazole group discontinued therapy due to a serious laboratory adverse experience that was not classified as drug related. No patients in any of the treatment groups discontinued therapy due to a serious drug-related laboratory adverse experience.

No deaths due to laboratory adverse experiences were reported in the caspofungin or the amphotericin B groups. One death (AN 5644) was reported in a patient who had a serious laboratory adverse experience in the fluconazole group. The death was due to a clinical adverse experience that was not considered to be drug related.

The incidence of discontinuation of therapy due to a laboratory adverse experience was generally similar (1.5 to 2.4%) among the 3 caspofungin and the fluconazole groups. However, it was noted to be higher in the amphotericin B group (12.4%), and all laboratory adverse experiences leading to discontinuation of amphotericin B therapy were considered to be drug related.

Table 50

Laboratory Adverse Experience Summary by Caspofungin Dose for Controlled Clinical Studies in *Candida* Infections (Protocols 003, 004, and 020)

Number of patients with at least one laboratory test postbaseline Number (%) of patients:	Caspofungin Acetate 35 mg		Caspofungin Acetate 50 mg		Caspofungin Acetate 70 mg		Amphotericin B 0.5 mg/kg		Fluconazole 200 mg	
	(N=33)		(N=164)		(N=65)		(N=89)		(N=92)	
	n	(%)	N	(%)	n	(%)	n	(%)	n	(%)
with one or more adverse experiences	19	(57.6)	94	(57.3)	36	(55.4)	79	(88.8)	54	(58.7)
with no adverse experience	14	(42.4)	70	(42.7)	29	(44.6)	10	(11.2)	38	(41.3)
with drug-related adverse experiences [†]	16	(48.5)	67	(40.9)	22	(33.8)	74	(83.1)	32	(34.8)
with serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	2	(2.2)
with serious drug-related adverse experiences [†]	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
discontinued therapy due to an adverse experience	0	(0.0)	4	(2.4)	1	(1.5)	11	(12.4)	2	(2.2)
discontinued therapy due to a drug-related adverse experience [†]	0	(0.0)	2	(1.2)	1	(1.5)	11	(12.4)	1	(1.1)
discontinued therapy due to a serious adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
discontinued therapy due to a serious drug-related adverse experience [†]	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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

In Protocols 003, 004, and 020, the most common laboratory adverse experiences and drug-related laboratory adverse experiences in caspofungin groups were increased ALT,

increased AST, increased alkaline phosphatase, decreased hemoglobin, and decreased hematocrit. There was no dose-effect relationship. The incidence of increased ALT considered to be drug related was comparable among the caspofungin 50- and 70-mg groups, and the fluconazole group with incidences of 10.5, 10.8, and 12.0%, respectively. These incidences were lower than those observed in the caspofungin 35 mg (8/33 patients—24.2%) and amphotericin B groups (20/88 patients—22.7%) (Table 51).

Similar trends were observed with respect to increased AST and increased alkaline phosphatase, since increases in ALT, AST, and alkaline phosphatase were observed in the same patients in many of the cases. Most of the increases in ALT, AST, and alkaline phosphatase were <5-fold ULN, transient, and did not limit therapy. Many of these laboratory abnormalities occurred off-treatment during the follow-up period. While increases in these liver function tests did occur, the interpretation of these laboratory values was confounded by concurrent diseases, concomitant medications, and elevated baseline values.

The incidences of drug-related decreased hemoglobin and drug-related decreased hematocrit were generally similar among the 3 caspofungin and the fluconazole groups, but lower than those observed in the amphotericin B group. Decreased serum albumin, increased serum creatinine, and decreased serum potassium were generally reported more commonly in the amphotericin B group than in the 3 caspofungin or the fluconazole groups.

Table 51
 Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence $\geq 5.0\%$ in One or More Treatment Groups) by
 Laboratory Test Category in Controlled Clinical Studies for *Candida* Infections (Protocols 003, 004, and 020)
 Total and Drug Related[†]

	Caspofungin Acetate 35 mg (N=34)		Caspofungin Acetate 50 mg (N=164)		Caspofungin Acetate 70 mg (N=65)		Amphotericin B 0.5 mg/kg (N=89)		Fluconazole 200 mg (N=93)	
	n/m (%)	DR [†]	n/m (%)	DR [†]	n/m (%)	DR [†]	n/m (%)	DR [†]	n/m (%)	DR [†]
Patients with one or more laboratory adverse experiences	19/33 (57.6)	16/33	94/164 (57.3)	67/164	36/65 (55.4)	22/65	79/89 (88.8)	74/89	54/92 (58.7)	32/92
Patients with no laboratory adverse experience	14/33 (42.4)	-	70/164 (42.7)	-	29/65 (44.6)	-	10/89 (11.2)	-	38/92 (41.3)	-
Blood Chemistry	19/33 (57.6)	14/33	68/163 (41.7)	48/163	25/65 (38.5)	18/65	69/89 (77.5)	66/89	40/92 (43.5)	26/92
Alanine aminotransferase (ALT) increased	12/33 (36.4)	8/33	30/162 (18.5)	17/162	8/65 (12.3)	7/65	23/88 (26.1)	20/88	16/92 (17.4)	11/92
Arterial pH decreased	0/0 (0.0)	0/0	0/0 (0.0)	0/0	0/0 (0.0)	0/0	0/0 (0.0)	0/0	1/2 (50.0)	0/2
Aspartate aminotransferase (AST) increased	13/33 (39.4)	9/33	31/162 (19.1)	21/162	9/65 (13.8)	7/65	24/88 (27.3)	20/88	18/92 (19.6)	12/92
Blood culture positive	0/0 (0.0)	0/0	0/0 (0.0)	0/0	0/0 (0.0)	0/0	0/0 (0.0)	0/0	1/8 (12.5)	0/8
Blood urea increased	0/32 (0.0)	0/32	0/153 (0.0)	0/153	0/64 (0.0)	0/64	12/87 (13.8)	9/87	2/81 (2.5)	1/81
Direct serum bilirubin increased	1/29 (3.4)	1/29	4/159 (2.5)	1/159	0/59 (0.0)	0/59	3/81 (3.7)	2/81	5/90 (5.6)	3/90
Nonfasting blood glucose increased	0/0 (0.0)	0/0	0/9 (0.0)	0/9	0/0 (0.0)	0/0	0/0 (0.0)	0/0	1/13 (7.7)	0/13
Serum albumin decreased	0/33 (0.0)	0/33	21/163 (12.9)	14/163	5/65 (7.7)	3/65	17/87 (19.5)	13/87	8/92 (8.7)	5/92
Serum alkaline phosphatase increased	9/33 (27.3)	8/33	24/163 (14.7)	17/163	10/65 (15.4)	5/65	22/88 (25.0)	17/88	16/92 (17.4)	11/92
Serum amylase increased	0/0 (0.0)	0/0	0/0 (0.0)	0/0	0/0 (0.0)	0/0	0/0 (0.0)	0/0	1/2 (50.0)	0/2
Serum bicarbonate decreased	5/23 (21.7)	0/23	1/107 (0.9)	1/107	2/45 (4.4)	0/45	8/61 (13.1)	4/61	4/60 (6.7)	0/60
Serum calcium decreased	0/33 (0.0)	0/33	6/163 (3.7)	3/163	3/65 (4.6)	0/65	3/88 (3.4)	1/88	5/92 (5.4)	3/92
Serum creatinine phosphokinase (CPK) increased	0/0 (0.0)	0/0	0/0 (0.0)	0/0	0/0 (0.0)	0/0	0/0 (0.0)	0/0	1/1 (100.0)	1/1
Serum creatinine increased	1/33 (3.0)	0/33	1/163 (0.6)	0/163	2/65 (3.1)	1/65	27/89 (30.3)	25/89	3/92 (3.3)	2/92
Serum magnesium decreased	1/1 (100.0)	1/1	1/1 (100.0)	0/1	0/0 (0.0)	0/0	2/2 (100.0)	2/2	0/0 (0.0)	0/0
Serum potassium decreased	3/33 (9.1)	1/33	10/163 (6.1)	6/163	7/65 (10.8)	7/65	29/89 (32.6)	28/89	8/92 (8.7)	4/92
Serum sodium decreased	3/33 (9.1)	1/33	6/163 (3.7)	3/163	2/65 (3.1)	1/65	3/89 (3.4)	1/89	9/92 (9.8)	3/92
Total serum bilirubin increased	0/33 (0.0)	0/33	3/163 (1.8)	0/163	0/65 (0.0)	0/65	8/88 (9.1)	4/88	5/92 (5.4)	3/92
Total serum protein decreased	0/33 (0.0)	0/33	9/163 (5.5)	5/163	2/65 (3.1)	0/65	8/87 (9.2)	3/87	5/92 (5.4)	3/92

Table 51 (Cont.)

Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence ≥5.0% in One or More Treatment Groups) by Laboratory Test Category in Controlled Clinical Studies for *Candida* Infections (Protocols 003, 004, and 020) Total and Drug Related[†]

	Caspofungin Acetate 35 mg (N=34)			Caspofungin Acetate 50 mg (N=164)			Caspofungin Acetate 70 mg (N=65)			Amphotericin B 0.5 mg/kg (N=89)			Fluconazole 200 mg (N=93)		
	n/m	(%)	DR [†]	n/m	(%)	DR [†]	n/m	(%)	DR [†]	n/m	(%)	DR [†]	n/m	(%)	DR [†]
Hematology	8/33	(24.2)	6/33	51/164	(31.1)	36/164	16/65	(24.6)	7/65	48/89	(53.9)	37/89	27/92	(29.3)	12/92
Hematocrit decreased	3/33	(9.1)	3/33	26/163	(16.0)	18/163	7/65	(10.8)	1/65	36/89	(40.4)	29/89	15/92	(16.3)	5/92
Hemoglobin decreased	4/33	(12.1)	4/33	29/163	(17.8)	20/163	8/64	(12.5)	2/64	41/89	(46.1)	33/89	15/92	(16.3)	5/92
Neutrophils decreased	1/33	(3.0)	0/33	6/163	(3.7)	3/163	3/64	(4.7)	2/64	3/88	(3.4)	1/88	6/92	(6.5)	3/92
Platelet count decreased	0/33	(0.0)	0/33	8/163	(4.9)	5/163	3/65	(4.6)	1/65	6/89	(6.7)	3/89	5/92	(5.4)	2/92
White blood cell (WBC) count decreased	5/33	(15.2)	4/33	14/163	(8.6)	10/163	7/65	(10.8)	3/65	10/89	(11.2)	7/89	18/92	(19.6)	8/92
Urinalysis	1/32	(3.1)	0/32	9/163	(5.5)	3/163	10/64	(15.6)	3/64	27/88	(30.7)	19/88	13/91	(14.3)	7/91
Calcium oxalate crystals present	1/9	(11.1)	0/9	0/95	(0.0)	0/95	0/26	(0.0)	0/26	0/50	(0.0)	0/50	0/78	(0.0)	0/78
Trichomonas present	0/0	(0.0)	0/0	0/1	(0.0)	0/1	2/2	(100.0)	0/2	0/1	(0.0)	0/1	0/0	(0.0)	0/0
Urine blood increased	0/9	(0.0)	0/9	0/95	(0.0)	0/95	2/26	(7.7)	0/26	3/50	(6.0)	2/50	0/78	(0.0)	0/78
Urine casts increased	0/9	(0.0)	0/9	0/95	(0.0)	0/95	1/26	(3.8)	0/26	5/50	(10.0)	4/50	1/78	(1.3)	0/78
Urine culture positive	0/0	(0.0)	0/0	0/2	(0.0)	0/2	0/0	(0.0)	0/0	0/0	(0.0)	0/0	1/3	(33.3)	0/3
Urine nitrate positive	0/0	(0.0)	0/0	0/1	(0.0)	0/1	0/0	(0.0)	0/0	1/1	(100.0)	0/1	0/0	(0.0)	0/0
Urine protein increased	0/32	(0.0)	0/32	3/163	(1.8)	2/163	4/64	(6.3)	0/64	5/88	(5.7)	4/88	5/91	(5.5)	3/91
Urine pus	0/0	(0.0)	0/0	0/0	(0.0)	0/0	0/0	(0.0)	0/0	1/1	(100.0)	0/1	0/0	(0.0)	0/0
Urine red blood cell count (RBC) increased	0/9	(0.0)	0/9	1/95	(1.1)	1/95	3/26	(11.5)	1/26	8/50	(16.0)	6/50	6/78	(7.7)	4/78
Urine white blood cell count (WBC) increased	0/9	(0.0)	0/9	3/95	(3.2)	0/95	5/26	(19.2)	2/26	17/50	(34.0)	12/50	5/78	(6.4)	0/78
Miscellaneous	0/1	(0.0)	0/1	2/3	(66.7)	0/3	0/0	(0.0)	0/0	0/0	(0.0)	0/0	4/8	(50.0)	0/8
Parasites, intestinal	0/0	(0.0)	0/0	1/1	(100.0)	0/1	0/0	(0.0)	0/0	0/0	(0.0)	0/0	0/1	(0.0)	0/1
Stool, culture positive	0/1	(0.0)	0/1	1/2	(50.0)	0/2	0/0	(0.0)	0/0	0/0	(0.0)	0/0	4/6	(66.7)	0/6

[†] DR = Drug related. Number of patients reporting laboratory adverse experiences, considered by the investigator to be possibly, probably, or definitely drug related/number of patients with laboratory test (DR).

n/m = Number of patients reporting laboratory adverse experiences/number of patients with laboratory test.

Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

All categories are listed in which at least one patient had an adverse experience.

Serious Laboratory Adverse Experiences in Controlled Clinical Studies for *Candida* Infections (Protocols 003, 004, and 020)

In Protocols 003, 004, and 020, there were very few serious laboratory adverse experiences. There were no serious laboratory adverse experiences reported in the 3 caspofungin groups. One patient (AN 2400) (1.1%) in the amphotericin B group was reported as having a serious laboratory adverse experience (decreased hemoglobin) that was considered to be drug related; and 2 patients in the fluconazole group had serious laboratory adverse experiences (decreased neutrophils, AN 5510; increased fasting blood sugar, AN 5644), neither of which was considered to be drug related. One patient (AN 5644) in the fluconazole group died.

Discontinuations Due to Laboratory Adverse Experiences in Controlled Clinical Studies for *Candida* Infections (Protocols 003, 004, and 020)

Of the 445 patients who enrolled in *Candida* studies, only 18 (4.0%) discontinued therapy due to a laboratory adverse experience: 4 patients (2.4%) in the caspofungin 50-mg group, 1 (1.5%) in the caspofungin 70-mg group, 11 (12.4%) in the amphotericin B group, and 2 (2.2%) in the fluconazole group. In the amphotericin B group, all laboratory adverse experiences leading to discontinuation were considered to be drug related and the majority of these patients (8/11 patients or 72.7%) had increased serum creatinine. The drug-related laboratory adverse experiences that led to discontinuation of therapy in the caspofungin groups included increased ALT/increased AST/increased alkaline phosphatase (AN 0159), decreased platelet count (AN 0109), and increased serum creatinine (AN 0682). In each of the 3 patients, the laboratory abnormalities were present at baseline and could be explained by their underlying diseases. The drug-related laboratory adverse experience that led to discontinuation of therapy in the fluconazole group was increased AST (AN 5525).

Adverse Experiences Reported in the Noncomparative Clinical Study for *Candida* Esophagitis (Protocol 007)

As expected in patients with advanced HIV infection (mean CD4 cell count of 19.7 cells/mm³), clinical and laboratory adverse experiences were common in the 14 patients in this noncomparative *Candida* esophagitis study treated with either caspofungin 50 or 70 mg. Drug-related clinical adverse experiences occurred in 3 patients (37.5%) in the caspofungin 50-mg group and 5 patients (83.3%) in the caspofungin 70-mg group. There were no discontinuations due to a drug-related clinical adverse experience. The most frequently reported drug-related clinical experiences were infused-vein complications and fever, occurring in both the 50- and 70-mg groups. These adverse experiences occurred on a single day, were generally mild to moderate, and did not lead to discontinuation of therapy. One patient in each group experienced serious clinical adverse experiences during the study, but none was considered drug related. One of these patients (AN 1643) died due to complications of his underlying HIV infection during the retreatment phase of the study (aspiration pneumonia, AIDS, respiratory

failure). The other patient (AN 1677) experienced hepatitis and pancreatitis off drug that was considered not drug related.

The most commonly reported laboratory adverse experiences were increased ALT, increased AST, decreased platelet counts, and decreased white blood cell (WBC) count. These adverse experiences were generally mild and resolved during follow-up. No patient experienced a serious laboratory adverse experience or discontinued due to a laboratory adverse experience.

In summary, caspofungin at doses of 50 and 70 mg was generally well tolerated. The adverse experience profile in this noncomparative study is consistent with that observed for patients treated with caspofungin in the controlled clinical studies (Protocols 003, 004, and 020) of *Candida* patients.

7.6 Clinical Safety in Patients with *Aspergillus* Infections

Noncomparative Clinical Study of Invasive Aspergillosis (Protocol 019)

Of the 58 patients with invasive aspergillosis enrolled in Protocol 019, 27 (47%) received caspofungin for ≥ 28 days, including 21 patients treated for 28 to 60 days, 4 treated for 61 to 90 days, and 2 treated for >90 days. These patients had complicated medical histories including severe underlying diseases with several concomitant illnesses and concomitant therapies. Most were severely immunocompromised and had cancer and bone marrow, stem cell, or organ transplantations.

Clinical Adverse Experiences in Protocol 019

As expected in this patient population, the overall incidence of clinical adverse experiences was high (93.1%), as is shown in Table 52. However, the incidence of drug-related clinical adverse experiences was only 13.8%.

Similarly, although the incidence of serious clinical adverse experiences was high (75.9%), there were few serious drug-related clinical adverse experiences (1.7%) and few serious drug-related clinical adverse experiences causing therapy discontinuation (1.7%). Deaths during therapy or follow-up were reported in 53.4% of the patients, but none was considered to be drug related.

Table 52
 Clinical Adverse Experience Summary by Caspofungin Dose in
 a Noncomparative *Aspergillus* Study (Protocol 019)

Number (%) of patients:	Caspofungin Acetate 50 mg [†] (N=58)	
	n	(%)
with one or more adverse experiences	54	(93.1)
with no adverse experience	4	(6.9)
with drug-related adverse experiences [‡]	8	(13.8)
with serious adverse experiences	44	(75.9)
with serious drug-related adverse experiences [‡]	1	(1.7)
who died	31	(53.4)
discontinued therapy due to an adverse experience	23	(39.7)
discontinued therapy due to a drug-related adverse experience [‡]	1	(1.7)
discontinued therapy due to a serious adverse experience	23	(39.7)
discontinued therapy due to a serious drug-related adverse experience [‡]	1	(1.7)

[†] Patients received a loading dose of caspofungin acetate 70 mg on Day 1 and then received caspofungin acetate 50 mg for remainder of treatment period.
[‡] Considered by the investigator to be possibly, probably, or definitely drug related.

As expected in seriously ill patients, clinical adverse experiences were common in this study, as is shown in Table 53. The most common clinical adverse experiences included death (53.4%), edema/swelling (20.7%), fever (20.7%), hypotension (20.7%), rash (19.0%), nausea (15.5%), and headache (15.5%). The most common drug-related clinical adverse experiences each occurred at 3.4% (2 patients) were fever, infused-vein complications, nausea, and vomiting.

Caspofungin Acetate
 FDA Advisory Committee Meeting Background
 Clinical Safety

-151-

Table 53

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence $\geq 5.0\%$)
 in a Noncomparative *Aspergillus* Study (Protocol 019) Total and Drug Related[†]

	Caspofungin Acetate 50 mg [‡] (N=58)		
	n	(%)	DR [†]
Patients with one or more clinical adverse experiences	54	(93.1)	8
Patients with no clinical adverse experience	4	(6.9)	-
Body as a Whole/Site Unspecified	46	(79.3)	4
Aspergillosis	7	(12.1)	0
Asthenia/fatigue	3	(5.2)	0
Bacteremia	3	(5.2)	0
Death	31	(53.4)	0
Distention, abdominal	3	(5.2)	0
Edema/swelling	12	(20.7)	0
Pain, abdominal	5	(8.6)	0
Fever	12	(20.7)	2
Cardiovascular System	27	(46.6)	2
Arrhythmia	4	(6.9)	0
Bradycardia	3	(5.2)	0
Heart failure	3	(5.2)	0
Hypertension	3	(5.2)	0
Hypotension	12	(20.7)	0
Infused-vein complication	4	(6.9)	2
Tachycardia	5	(8.6)	0
Digestive System	30	(51.7)	4
Anorexia	3	(5.2)	0
Constipation	4	(6.9)	0
Diarrhea	8	(13.8)	1
Dyspepsia	3	(5.2)	0
Hepatomegaly	3	(5.2)	0
Jaundice	4	(6.9)	0
Nausea	9	(15.5)	2
Vomiting	8	(13.8)	2
Endocrine System	1	(1.7)	0
Hemic and Lymphatic System	18	(31.0)	0
Anemia	5	(8.6)	0
Leukemia, acute myelogenous	3	(5.2)	0
Metabolic/Nutritional/Immune	13	(22.4)	1
Acidosis	3	(5.2)	1
Graft versus host disease	6	(10.3)	0
Musculoskeletal System	13	(22.4)	0
Pain, back	5	(8.6)	0
Pain, shoulder	5	(8.6)	0

Table 53 (Cont.)

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence $\geq 5.0\%$)
 in a Noncomparative *Aspergillus* Study (Protocol 019) Total and Drug Related[†]

	Caspofungin Acetate 50 mg [‡] (N=58)		
	n	(%)	DR [†]
Nervous System and Psychiatric	21	(36.2)	1
Agitation	4	(6.9)	0
Headache	9	(15.5)	1
Respiratory System	42	(72.4)	1
Aspergillosis, pulmonary	3	(5.2)	0
Chest sound abnormality	4	(6.9)	0
Congestion, nasal	3	(5.2)	0
Dyspnea	6	(10.3)	1
Hemoptysis	3	(5.2)	0
Hemorrhage, pulmonary	3	(5.2)	0
Pneumonia	3	(5.2)	0
Pneumothorax	3	(5.2)	0
Rales/rhonchi	3	(5.2)	0
Respiratory distress	5	(8.6)	0
Respiratory distress syndrome	3	(5.2)	0
Respiratory failure	8	(13.8)	0
Respiratory insufficiency	4	(6.9)	0
Skin and Skin Appendage	25	(43.1)	2
Contusion	3	(5.2)	0
Erythema	5	(8.6)	0
Rash	11	(19.0)	1
Special Senses	8	(13.8)	0
Urogenital System	12	(20.7)	1
Renal insufficiency	4	(6.9)	0
[†] Considered by the investigator to be possibly, probably, or definitely drug related (DR). [‡] Patients received a loading dose of caspofungin acetate 70 mg on Day 1 and then received caspofungin acetate 50 mg for remainder of treatment period. Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. All body systems are listed in which at least 1 patient had an adverse experience.			

Serious Clinical Adverse Experiences

Of the 58 enrolled patients, 44 patients (75.9%) reported at least one serious clinical adverse experience. The majority of these serious clinical adverse experiences (43/44 patients or 97.7%) were not considered to be drug related, but were related to the patients' underlying illnesses. Deaths on therapy, during follow-up, or poststudy, were

reported in 31 patients (53.4%), a percentage not unexpected in a population with both severe immunosuppression and *Aspergillus* infections. None of the deaths was classified as drug related by the investigator.

Thirteen of 58 patients (22.4%) reported at least one serious nonfatal clinical adverse experience. Only 1 of these (AN 0186) was considered drug related; the other 12 were due to the patients' underlying diseases. All but 1 of these adverse experiences were considered to be not drug related and reflected the patients' severe underlying illnesses. The 1 patient (AN 0186) with the serious drug-related adverse experience was a 38-year-old man who underwent an allogeneic BMT for refractory multiple myeloma and developed definite pulmonary aspergillosis. On Day 24 of caspofungin therapy, the patient developed bilateral lower lobe infiltrates, was treated with methylprednisolone, ganciclovir, and trimethoprim-sulfamethoxazole; caspofungin was discontinued. No specific etiology of the pulmonary infiltrates was identified on bronchoscopy, and the investigator considered the pulmonary infiltrates to be possibly due to caspofungin.

Twenty-three patients (39.7%) discontinued therapy due to a clinical adverse experience; all met the criteria for serious, and only 1 (pulmonary infiltrates, described above) was considered to be drug related.

Laboratory Adverse Experiences in Protocol 019

Although laboratory adverse experiences were common (63.2%) in the severely immunocompromised patients in Protocol 019, only 15.8% of patients had drug-related laboratory adverse experiences, as summarized in Table 54. There was only one serious laboratory adverse experiences (AN 0056) (1.8%) that was considered to be drug related (increased serum calcium). One patient (AN 0216) (1.8%) discontinued therapy due to laboratory adverse experiences (elevations in blood urea nitrogen [BUN] and serum creatinine) which were not considered to be drug related. There were no deaths due to a laboratory adverse experience.

Table 54

Laboratory Adverse Experience Summary
 in a Noncomparative *Aspergillus* Study (Protocol 019)

Number of patients with at least one laboratory test postbaseline Number (%) of patients:	Caspofungin Acetate 50 mg [†]	
	(N=57)	
	n	(%)
with one or more adverse experiences	36	(63.2)
with no adverse experience	22	(38.6)
with drug-related adverse experiences [‡]	9	(15.8)
with serious adverse experiences	1	(1.8)
with serious drug-related adverse experiences [‡]	1	(1.8)
who died	0	(0.0)
discontinued therapy due to an adverse experience	1	(1.8)
discontinued therapy due to a drug-related adverse experience [‡]	0	(0.0)
discontinued therapy due to a serious adverse experience	0	(0.0)
discontinued therapy due to a serious drug-related adverse experience [‡]	0	(0.0)

[†] Patients received a loading dose of caspofungin acetate 70 mg on Day 1 and then received caspofungin acetate 50 mg for remainder of treatment period.
[‡] Considered by the investigator to be possibly, probably, or definitely drug related.

Of the scheduled laboratory tests collected per protocol, the most common laboratory adverse experiences among the total patient population were increased serum alkaline phosphatase (21.1%) and increased AST (14.8%), as shown in Table 55. Elevations in liver enzymes were typically associated with the patients' underlying disease. Drug-related laboratory adverse experiences were uncommon; the only drug-related laboratory adverse experiences reported in more than 1 patient was an increase in urine protein (3/51 patients or 5.9%), and increased tacrolimus levels (2/17 patients or 11.8%). Elevations in tacrolimus levels are difficult to interpret in patients receiving a number of concomitant medications that often undergo dose changes. Increased eosinophils were also reported as a drug-related laboratory adverse experience in 2 patients (ANs 0059 and 0251).

Serious Laboratory Adverse Experiences

The single serious laboratory adverse experience (1.8%), considered by the investigator to be drug related, was increased serum calcium in a patient (AN 0056) who underwent an allogeneic BMT for Hodgkin's disease and developed disseminated aspergillosis involving the lung and spine.

Adverse Experiences in Patients Treated ≥28 Days in a Noncomparative Clinical Study of *Aspergillus* Infections (Protocol 019)

As described in Section 7.2 (Overall Extent of Exposure of the Study Population), Protocol 019 included a number of patients (27/58 patients or 47%) who were treated for

≥28 days. The general pattern of clinical and laboratory adverse experiences in patients receiving ≥28 days of therapy is similar to that seen in patients treated for <28 days and is consistent with the severity of underlying disease. Overall, no new drug-related adverse experiences emerged after 28 days of therapy, and caspofungin was well tolerated in patients receiving up to 162 days of treatment.

Systemic Infusion-Related Reactions in a Noncomparative *Aspergillus* Study (Protocol 019)

In Protocol 019, systemic infusion-related reactions were reported in 10 patients (17.2%), with the most frequently reported symptoms being nausea (8.6%) and fever (5.2%). The majority of these systemic infusion-related reactions (8/10 patients or 80.0%) were mild, isolated experiences, and did not result in discontinuation or interruption of therapy.

Adverse Experiences Reported in the 11 Additional Patients in the Noncomparative *Aspergillus* Study (Protocol 019)

Six of the 11 additional patients received caspofungin for ≥28 days; 1 for 29 to 60 days, 3 for 61 to 90 days; and 2 for 109 and 114 days. In these 11 patients, caspofungin was generally well tolerated and the safety profile of caspofungin was similar to that observed in the 58 patients reported above. There were only 2 patients with drug-related adverse experiences, there were no serious drug-related adverse experiences, and no patients discontinued therapy due to a drug-related adverse experience. Among these 11 patients, there was a pediatric patient (AN 0536, age 15) treated with 1 mg/kg/day caspofungin who tolerated caspofungin well with no drug-related clinical or laboratory adverse experience reported during 71 days of therapy; and a patient (AN 0511) who received caspofungin concomitantly with cyclosporin A for 9 days.

Caspofungin Acetate
 FDA Advisory Committee Meeting Background
 Clinical Safety

-156-

Table 55

Number (%) of Patients With Specific Laboratory Adverse Experiences
 (Incidence $\geq 5.0\%$) by Laboratory Test Category in a Noncomparative
Aspergillus Study (Protocol 019) Total and Drug Related[†]

	Caspofungin Acetate 50 mg [‡] (N=58)		
	n/m	(%)	DR [†]
Patients with one or more laboratory adverse experiences	36/57	(63.2)	9/57
Patients with no laboratory adverse experience	21/57	(36.8)	
Blood Chemistry	32/57	(56.1)	6/57
Alanine aminotransferase (ALT) increased	8/57	(14.0)	0/57
Anion gap increased	1/1	(100.0)	0/1
Arterial partial pressure of oxygen (P _{O2}) decreased	1/1	(100.0)	0/1
Aspartate aminotransferase (AST) increased	8/54	(14.8)	0/54
Blood urea increased	7/53	(13.2)	0/53
Direct serum bilirubin increased	5/37	(13.5)	0/37
Serum alkaline phosphatase increased	12/57	(21.1)	1/57
Serum amylase increased	1/1	(100.0)	0/1
Serum creatinine increased	7/57	(12.3)	0/57
Serum lactate dehydrogenase (LDH) increased	2/2	(100.0)	1/2
Serum lipase increased	1/1	(100.0)	0/1
Serum magnesium decreased	1/2	(50.0)	0/2
Serum phosphate increased	4/51	(7.8)	0/51
Serum potassium decreased	7/57	(12.3)	1/57
Serum potassium increased	5/57	(8.8)	0/57
Tacrolimus level increased	2/17	(11.8)	2/17
Total serum bilirubin increased	7/57	(12.3)	0/57
Hematology	15/57	(26.3)	4/57
Hematocrit decreased	3/57	(5.3)	0/57
Platelet count decreased	5/57	(8.8)	1/57
Prothrombin time increased	3/50	(6.0)	1/50
Partial thromboplastin time (PTT) increased	4/52	(7.7)	1/52
WBC count decreased	3/57	(5.3)	1/57
Urinalysis	11/52	(21.2)	3/52
Urine blood increased	2/37	(5.4)	0/37
Urine glucose increased	3/51	(5.9)	0/51
Urine protein increased	7/51	(13.7)	3/51
Urine red blood cells (RBCs) increased	5/37	(13.5)	1/37
Urine white blood cells (WBCs) increased	2/37	(5.4)	0/37
[†] DR = Drug related. Number of patients reporting laboratory adverse experiences, considered by the investigator to be possibly, probably, or definitely drug related/number of patients with laboratory test. [‡] Patients received a loading dose of caspofungin acetate 70 mg on Day 1 and then received caspofungin acetate 50 mg for remainder of treatment period. n/m = Number of patients reporting laboratory adverse experiences/number of patients with laboratory test. Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. All categories are listed in which at least 1 patient had an adverse experience.			

This patient's liver function tests, which were closely monitored during therapy, did not show elevations from baseline.

Adverse Experiences in Compassionate Use (Protocol 024/025)

Only limited, essential safety data including serious adverse experiences, select nonserious adverse experiences, and drug-related adverse experiences leading to discontinuation of therapy were collected for the compassionate use study (Protocol 024/025) and these were reported directly to the Merck Worldwide Adverse Experience System (WAES) database. The WAES database serves as a repository for the reporting of “serious” adverse experiences and adverse experiences of special interest from clinical studies, including expanded access programs, reports from the medical literature, and all adverse experiences from marketed use that are reported to Merck & Co., Inc. This spontaneous reporting system is a voluntary system of adverse experience reporting for the purpose of generating early warning signals. Adverse experience reports are included in the WAES database regardless of the reporter’s assessment of causal relationship to the drug. All 3 patients included in this Summary had *Aspergillus* infections. By the cutoff date, 1 of the 3 enrolled patients reported serious clinical adverse experiences. This patient (AN 07151) experienced multiple organ failure and cardiac arrest which led to death. None of these adverse experiences was considered to be drug related, all occurred while the patient was off study drug, and all were consistent with his underlying disease. No serious laboratory adverse experiences were reported by any of the 3 enrolled patients. No patients in this study discontinued study therapy due to a drug-related clinical or laboratory adverse experience.

Additional Safety Measurements in Phase II/III Clinical Studies

Tolerability at the Site of Infusion of Caspofungin

Tolerability at the site of infusion was closely monitored in clinical studies. Information on overall tolerability in patients who received study drug was available in 496 (324 via a peripheral line; 172 via a central line) of the 517 patients enrolled in the caspofungin clinical studies. In the controlled clinical studies for *Candida* infections (Protocols 003, 004, and 020), 97.1% of all patients in the 3 caspofungin groups had a rating of “well tolerated” or “moderately well tolerated.” This was comparable to the incidence of “well tolerated” or “moderately well tolerated” ratings in the fluconazole group (95.6%) and higher than that reported in the amphotericin B group (89.4%). Only 3 of 173 patients (1.7%) who received caspofungin via a peripheral line had a rating of “poorly tolerated.” Most of the complaints reported by these 3 patients were minor (mild erythema, mild thrombophlebitis, and mild pain) and did not result in discontinuation of therapy or a change from peripheral to central line.

In the noncomparative studies, Protocol 007 and 019, caspofungin was generally well tolerated in patients who received study drug via a peripheral or central line.

Elevations in Serum Transaminases Reported as Laboratory Adverse Experiences

In preclinical studies in the monkey, but not in the rat, mild elevations in serum ALT and AST (approximately 1.5 to 3 times control) were noted at doses of 5 mg/kg/day (approximately 3.5-fold the AUC time curve for humans administered a 70-mg dose).

These elevations tended to decrease over time despite continued dosing of caspofungin. Based on these results, liver enzymes were monitored closely during all clinical studies.

The number (%) of patients with increased ALT or AST laboratory adverse experiences in the completed clinical studies is shown in Table 56. Evaluation of elevated ALT and/or AST is difficult in patients with severe underlying diseases and several concomitant medications. Comparative clinical studies provide a better assessment of elevated ALT and/or AST than the noncomparative clinical studies, because they have a control group to help account for background incidence. In the controlled clinical studies for *Candida* infections (Protocols 003, 004, and 020), the incidence of reported laboratory adverse experiences of increased ALT and/or AST that were considered to be drug related were 9/33 patients (27.3%) in the caspofungin 35-mg group, 22/162 (13.6%) in the 50-mg group, and 8/65 (12.3%) in the 70-mg group. These data show that, within the 3 caspofungin groups, there was no apparent dose-effect relationship. The incidence of drug-related increased ALT and/or AST in the caspofungin 50- and 70-mg groups was comparable to that reported in the fluconazole group (14.1%; 13/92 patients). There were fewer drug-related increases in ALT and/or AST in the 50- and 70-mg groups compared to those in the amphotericin B group (23.9%; 21/88 patients). Most of the increases in ALT and AST were <5-fold ULN, transient, and did not limit therapy. Many occurred off treatment during the follow-up period. While increases in ALT and AST did occur, the interpretation of these laboratory values was confounded by concurrent diseases, concomitant medications, and elevated baseline values.

In the noncomparative *Aspergillus* study (Protocol 019), increased ALT and/or AST occurred in 16.7% of patients, as might be expected in this severely ill population. None of these adverse experiences was considered to be drug related and none resulted in discontinuation of therapy. The low incidence of elevated ALT and AST is notable because 47.0% of patients received more than 28 days of caspofungin therapy (and 1 patient up to 162 days).

Table 56

Number (%) of Patients With Increased Alanine or Aspartate Aminotransferase
 Laboratory Adverse Experiences in Caspofungin Clinical Studies

	Caspofungin Acetate 35 mg		Caspofungin Acetate 50 mg		Caspofungin Acetate 70 mg		Amphotericin B 0.5 mg/kg		Fluconazole 200 mg	
	n/m (%)	DR [†]	n/m (%)	DR [†]	n/m (%)	DR [†]	n/m (%)	DR [†]	n/m (%)	DR [†]
Controlled <i>Candida</i> Studies (Protocols 003, 004, and 020)	13/33 (39.4)	9/33	35/162 (21.6)	22/162	10/65 (15.4)	8/65	25/88 (28.4)	21/88	20/92 (21.7)	13/92
Noncomparative <i>Candida</i> Study (Protocol 007)	N/A		2/8 (25.0)	0/8	3/6 (50.0)	3/6	N/A		N/A	
Noncomparative <i>Aspergillus</i> Study (Protocol 019) [‡]	N/A		9/54 (16.7)	0/54	N/A		N/A		N/A	

[†] DR = Drug related. Considered by the investigator to be possibly, probably, or definitely drug related.
[‡] Patients received a loading dose of caspofungin acetate 70 mg on Day 1 and then received caspofungin acetate 50 mg for remainder of treatment period.
 n/m = Number of patients reporting laboratory adverse experiences/number of patients with laboratory test.
 N/A = Not applicable.

Elevations in Serum Creatinine Reported as Laboratory Adverse Experiences

Serum creatinine elevations were closely monitored in all clinical studies because of the known association of increased creatinine with amphotericin B, the comparator in the Phase II *Candida* studies. In the controlled Phase II/III clinical studies of *Candida* infections (Protocols 003, 004, and 020), the overall incidence of increased serum creatinine was consistently low in all 3 caspofungin groups, with a range of 0.6% (1/163 patients) to 3.1% (2/65 patients); only 1 patient reported to have a drug-related increased serum creatinine. The drug-related elevation in serum creatinine was in a patient (AN 0682) with diabetes mellitus and hypertension whose creatinine increased to 2.2 mg/dL from a baseline of 1.6 mg/dL and returned to baseline during follow-up. The incidence of increased serum creatinine in the 3 caspofungin groups were comparable to the overall (3/92 patients or 3.3%;) and the drug-related (2/92 patients or 2.2%) frequencies of increased creatinine reported in the fluconazole group, and considerably lower than those reported overall (30.3%) and drug related (28.1%) in the amphotericin B group.

Data from the noncomparative clinical studies in *Candida* (Protocol 007) and *Aspergillus* infections (Protocol 019) were consistent with those observed in the controlled studies, with no patients reporting drug-related increased serum creatinine in either study.

Clinically Significant Laboratory Abnormalities (CSLAs)

The assessment of relative laboratory safety of all treatment groups in caspofungin clinical trials was accomplished by predefining CSLAs for specified tests. To be included in the CSLA table, a patient had to demonstrate a worsening from baseline for a

particular laboratory test, and his/her worst laboratory value had to meet the predefined criteria for a CSLA, regardless of the clinical setting, the magnitude of change from baseline, or whether the investigator classified the result as a laboratory adverse experience.

Given the background diseases, the concurrent illnesses, and the concomitant therapies these patients received, the controlled studies provided better insight into the CSLAs than the noncomparative studies since they permitted a comparison with the CSLAs for the comparator agent. In the controlled studies for *Candida* infections (Protocols 003, 004, and 020), the most common CSLAs in patients receiving caspofungin 50 mg were: decreased absolute neutrophil count <1000 (16/162 or 9.9%); decreased hemoglobin <8 g/dL (19/163 or 11.7%); increased AST >2.5 times the baseline value (18/162 or 11.1%); and increased ALT >2.5 times the baseline value (24/160 or 15%). This pattern is similar in the caspofungin 35-, 50-, and 70-mg groups, as well as in the amphotericin B and fluconazole groups. In fact, careful evaluation of these laboratory abnormalities in the individual studies showed that, in some patients, the laboratory abnormalities occurred off caspofungin therapy during the follow-up period, and several of these abnormalities occurred in the setting of concurrent medical conditions, concomitant therapies, and elevated baseline laboratory values.

The CSLA profiles in the noncomparative studies, Protocol 007 and Protocol 019, are similar to those observed in the controlled studies.

7.7 Serious Adverse Experiences From Sources Other Than Case Report Forms

Serious Adverse Experiences Reported After Case Report Form Cutoff Dates for Studies of *Candida* and *Aspergillus* Infections

A total of 26 serious adverse experiences were reported in 13 patients in Protocols 004, 019, and 024/025 after the data cutoff for each study, but none was considered to be drug related by the investigator. These serious adverse experiences were not unexpected in immunocompromised patients and were generally similar to those previously reported in clinical studies for *Candida* and *Aspergillus* infections. Patient AN 0472 in the noncomparative Aspergillosis Study, who had one of the serious, nondrug-related adverse experiences listed as “anaphylaxis,” had an anaphylactic reaction to a stem cell infusion and not to caspofungin.

Serious Adverse Experiences Reported for Ongoing Blinded, Controlled Clinical Studies

There are 2 ongoing blinded, controlled clinical studies: Protocol 014 comparing caspofungin with amphotericin B (1:1 randomization) for the treatment of invasive candidiasis and Protocol 026 comparing caspofungin with AmBisome (1:1 randomization) for the empirical therapy of patients with persistent fever and neutropenia. No final CRF data were available at the time of preparation of this document; however, serious adverse experiences reported to the WAES database by the cutoff date of 31-Mar-2000 for both of these studies are summarized. The studies and the individual serious adverse experiences remain blinded, and the only information available

is whether the serious adverse experience would be considered drug related. The only exception is for Protocol 014 patient AN 4779, whose serious adverse experiences were reported as hypertension, seizure, and tachycardia, related to study drug. The patient was unblinded for medical reasons and he was in the amphotericin B treatment group.

A total of 86 patients, 84 in Protocol 014 and 2 in Protocol 026, reported 221 serious adverse experiences. The majority of the adverse experiences were considered to be not drug related. Only 20 serious adverse experiences were considered to be drug related. The most frequently reported drug-related serious adverse experience was renal failure (6 reports of "acute renal failure" and 1 report of "renal failure"). Other serious drug-related adverse experiences included: hypertension (2), tachycardia (1), venous thrombosis (1), duodenal disorder (1), erosive gastritis (1), gastritis (1), neutropenia (1), cholestasis (1), hepatic function abnormality (1), acidosis (1), seizure (1), respiratory condition (1), and respiratory insufficiency (1). Since the studies remain blinded, whether these adverse experiences were related to caspofungin or to an amphotericin formulation is unknown. All serious adverse experiences are being reviewed by an external Data Safety Monitoring Board (DSMB) on an ongoing basis.

7.8 Drug-Drug Interactions in Clinical Studies

The evaluation of drug-drug interactions resulting in adverse experiences was assessed by formal drug-drug interaction studies in the Clinical Pharmacology studies which, as described in Section 5.7, showed that there were no clinically significant adverse experiences noted in subjects receiving caspofungin with amphotericin B or mycophenolate. However, mild elevations of serum transaminases were noted in some subjects receiving caspofungin and cyclosporin A and very mild elevations (none exceeding 2-fold the ULN) were noted in some subjects receiving caspofungin and tacrolimus. Finally, it was unclear from the itraconazole interaction study (Protocol 021) whether the true incidence of rash is higher on caspofungin plus itraconazole than on itraconazole alone.

The *Aspergillus* study (Protocol 019) provided an opportunity to evaluate the potential for adverse experiences with the coadministration of caspofungin and tacrolimus or itraconazole. In Protocol 019, there were no adverse experiences of increased ALT and/or AST attributable to concomitant administration of caspofungin and tacrolimus in 17 patients who received both drugs for 1 to 162 days. Neither were there any clinically significant adverse experiences of rash with concomitant or sequential administration of caspofungin and itraconazole. Additionally, there was a patient (AN 511) receiving caspofungin and cyclosporin A concomitantly who experienced no elevations in hepatic transaminases at any time during 9 days of study therapy with daily monitoring of liver function tests.

In addition to the above-mentioned drugs, patients generally received multiple other concomitant medications because of their severe underlying medical conditions. Due to the large number of concomitant medications in this patient population, it is not possible to investigate the effect of each specific concomitant therapy on caspofungin. However, there were no reports of clinical adverse experiences relating to "drug interaction."

7.9 Drug-Demographic Interactions in Clinical Studies

CRF data tabulations of adverse experiences in all clinical studies were performed to determine whether the safety profile of caspofungin dosed at 50 mg was consistent across subgroups of age, gender, race, and weight. Because of the small number (9/230 or 3.9%) of patients aged ≥ 65 years, no conclusions can be made regarding the effect of age on the safety profile of caspofungin. Based on the tabulations of clinical, laboratory, serious clinical, and serious laboratory adverse experiences, caspofungin was generally well tolerated in patients with *Aspergillus* and *Candida* infections, regardless of age, gender, or race. In addition, caspofungin was generally well tolerated irrespective of patient weight (<60 kg versus ≥ 60 kg).

7.10 Drug-Disease Interactions in Clinical Studies

Adverse Experience Profile in Patients With and Without Renal Insufficiency

Of the 230 patients receiving caspofungin 50 mg, there were 218 patients (94.8%) with baseline creatinine clearance ≥ 30 mL/minute. All patients with creatinine clearance <30 mL/minute or on dialysis at baseline were from the clinical study of *Aspergillus* infection (Protocol 019). Given the small number of patients with renal insufficiency, no firm conclusions can be reached about the effect of renal function on the safety profile of caspofungin, although tabulations of clinical, laboratory, serious clinical, and serious laboratory adverse experiences showed that caspofungin was generally well tolerated in patients with and without renal insufficiency.

7.11 Potential Risks Based on Structure/Chemical Properties

Based on the structure and chemical properties of caspofungin, the potential risks include adverse experiences as a result of histamine release and adverse experiences related to the covalent binding of caspofungin's degradates to plasma proteins. High doses of caspofungin did produce signs of histamine release in the rat and monkey during bolus infusion. No signs of histamine release occurred in the 5-, 14-, or 27-week studies in monkeys where caspofungin was administered using a 20-minute infusion. Histamine-release reactions were not noted, despite careful monitoring, in clinical pharmacology studies or in patients with *Aspergillus* or *Candida* infections in clinical studies. Respiratory adverse experiences such as pneumonitis, wheezing, and asthma were reported in caspofungin treated patients, but were rarely considered drug-related. In the controlled *Candida* studies, most patients had advanced HIV infection and these clinical events were typically associated with other concurrent conditions such as bacterial pneumonia or COPD. In the noncomparative *aspergillus* study, respiratory adverse experiences were also common but >70% of patients had pulmonary aspergillosis and findings were most often associated with worsening IA or concurrent pulmonary processes such as bacterial pneumonia. In patients in whom these adverse experiences were reported no pattern of findings suggested that respiratory adverse experiences were related to histamine release.

From Protocol 010, a study evaluating the metabolism of caspofungin, there is evidence of low levels of irreversible binding of caspofungin's degradates to plasma proteins (3 to

7 pmol/mg protein). Caspofungin degrades chemically to L-747969, a major component of extractable radioactivity in plasma at later time points. During degradation, in vitro studies suggest that 2 potentially reactive intermediates are formed. Irreversible binding of caspofungin degradates to plasma proteins was also seen in preclinical studies in monkeys (at 5 mg/kg, the extent of binding in plasma was 3- to 5-fold greater than in humans). These findings may raise the concern of potential adverse effects associated with the presence of long-lived caspofungin degradates.

To address this concern, the preclinical toxicology studies in monkeys were carefully reviewed and no safety-related issues were identified in the 5-, 14- and 27-week studies in monkeys receiving doses that produced exposures approximating those of humans and in a 5-week safety study in monkeys with exposures 6 to 7 times the maximum human exposure. Therefore, in preclinical safety studies, the presence of long-lived degradates was not associated with adverse effects.

Safety monitoring in clinical studies included monitoring of all safety parameters, including but not limited to systemic reactions and hematologic, hepatic, and renal abnormalities. Review of clinical and laboratory adverse experiences has suggested no link to any effects of this low level of covalent binding. Long-term treatment (up to 162 days) with caspofungin was generally well tolerated. There were no unusual adverse experiences noted in the 2 patients who received caspofungin retreatment. Adverse experiences suggestive of potential allergic reactions were unusual in clinical studies with caspofungin. Twenty-six patients (7.8%) reported a rash; of these, only 8 were considered to be drug related and none had associated systemic symptoms. As anticipated, patients with advanced HIV infection, malignancies, and transplants often received many medications and frequently had underlying diseases associated with skin findings (i.e., graft-versus-host disease).

Eosinophilia was rarely reported (10 patients total) in clinical trials, and there was no pattern of other findings to suggest a systemic allergic reaction. Most patients with eosinophilia had advanced AIDS with concurrent opportunistic/parasitic infections requiring several concomitant medications. This makes it difficult to determine whether eosinophilia was associated with caspofungin or another concomitant therapy. In clinical pharmacology studies involving healthy subjects, eosinophilia was not reported.

7.12 Concentration-Effect Relationship for Adverse Experiences

The potential for $AUC_{0-24 \text{ hr}}$, $C_{1 \text{ hr}}$, and $C_{24 \text{ hr}}$ following multiple doses to predict the occurrence/absence of select clinical adverse experiences or predefined Clinically Significant Laboratory Abnormalities was investigated in the population pharmacokinetic analyses. For both patients with localized candidiasis and with invasive aspergillosis, the results suggest that, with the possible exception of nausea, the occurrence of adverse experiences or laboratory abnormalities examined in these analyses is not increased by higher caspofungin plasma concentrations over the range of pharmacokinetic parameters observed. Trends in the data from the small number of patients who experienced nausea suggest that exposure and peak drug concentrations may be factors contributing to the occurrence of nausea. Even if a larger dataset were to identify a statistically significant

correlation between nausea and caspofungin pharmacokinetics, the relatively low incidence of this adverse event and the absence of life-threatening consequences suggest that this should not be considered a dose-limiting toxicity.

7.13 Overdose and Abuse

There have been no reports of drug abuse or intentional or accidental overdose with caspofungin in clinical studies or from the WAES as of 19-Apr-2000. The highest single dose of caspofungin administered was 100 mg, and the highest multiple dose of caspofungin administered was 70 mg/day for 21 days. There is no clinical information with regard to potential adverse experiences associated with caspofungin overdosage. Because caspofungin is available only as an IV formulation, overdose or abuse would not be expected to occur.

7.14 Safety Conclusions

1. Caspofungin 50 mg is generally well tolerated in healthy subjects and patients with invasive *Aspergillus* and *Candida* infections who received several concomitant medications. There are few serious drug-related adverse experiences or discontinuations in therapy due to drug-related adverse experiences.
2. The most common drug-related clinical adverse experiences in patients receiving caspofungin 50 mg are fever and phlebitis/thrombophlebitis and/or infused vein complications. Most of these adverse experiences are mild and do not lead to discontinuation of therapy. The evaluation of fever is confounded by the patients' underlying advanced AIDS diseases and its presence at baseline in some patients.
3. The most common drug-related laboratory adverse experiences in patients receiving caspofungin 50 mg are increased ALT, increased AST, decreased hemoglobin, and decreased hematocrit. Most of the increases in ALT and AST are <5-fold the ULN, transient, and do not limit therapy. The evaluation of these adverse experiences is also confounded by the patients' underlying diseases and their presence at baseline in some patients.
4. There is no evidence of dose-related toxicities (range: 35 to 70 mg).
5. The safety profile of caspofungin does not appear to change with extended therapy (up to 162 days).
6. Coadministration of cyclosporin A with caspofungin is not recommended based on mild increases in ALT/AST in Phase I studies. Implications for multiple-dose safety require further studies.

8. Recommended Caspofungin Dosing Information for Patients With Invasive Aspergillosis

As described in Section 6.2, the selection of the dose of a new chemical entity for the treatment of IA is complex. Typical dose-ranging studies are not feasible for this rare disease associated with a high mortality. In addition, because mortality is high early in treatment, it is important to ensure that effective drug levels are achieved rapidly. The selection of the caspofungin dose for the treatment of IA was based on the integration of data from in vitro and in vivo preclinical studies in IA, human pharmacokinetics, and safety and efficacy data from less serious fungal infections such as esophageal candidiasis.

For the treatment of invasive aspergillosis in patients refractory to or intolerant of other therapies, the recommended caspofungin dosing regimen is 50 mg daily IV, following a 70 mg loading dose on Day 1. No dosage adjustment is necessary on the basis of race, gender, age, renal impairment, mild hepatic insufficiency, or concomitant medications. Concomitant use of caspofungin and cyclosporin A is not recommended based on mild (≤ 3 fold ULN) elevations in ALT seen in healthy subjects in a Phase I drug interaction study.

Data Supporting the Recommended Caspofungin Dosing Regimen

Data from the ongoing *Aspergillus* study (Protocol 019) demonstrate that the recommended caspofungin dosing regimen produced compelling results in the treatment of IA in patients when the expected prognosis was poor. Favorable responses were seen in patients refractory to other therapies, those with underlying hematologic malignancies or disseminated disease, and patients receiving corticosteroids. These efficacy results were supported by comparison to a historical control group (Protocol 028/029), in which favorable outcomes were more common in patients treated with caspofungin than those treated with standard antifungal therapy.

The selection of the 50-mg caspofungin dose is supported by its favorable safety and tolerability profile, as established in 467 individuals receiving caspofungin at doses of 50 mg or greater, in 343 individuals for durations >7 days, and in 27 patients for durations ≥ 28 days. Safety data from the Phase II/III randomized, blinded, comparative trials in *Candida* infections showed that caspofungin 50 mg daily was generally well tolerated. In the Phase III *Candida* esophagitis study (Protocol 020), caspofungin had a safety profile that was similar to fluconazole, as assessed by drug-related adverse experiences and drug-related adverse experiences leading to discontinuation of therapy. In the Phase II studies (Protocols 003, 004), caspofungin was generally better tolerated than amphotericin B. Data from the noncomparative *Aspergillus* study (Protocol 019) showed that caspofungin was generally well tolerated in patients receiving long-term therapy (≥ 28 days).

Concomitant Therapy

Drug interaction studies examined the effect of caspofungin on the pharmacokinetics of other drugs and the effect of other drugs on caspofungin pharmacokinetics. Results from the Phase I studies with itraconazole, cyclosporin A, and tacrolimus supported the in vitro studies that showed that caspofungin would not be expected to inhibit the metabolism of other drugs by cytochrome P-450 (CYP) enzymes and that CYP3A4 inhibitors would not affect caspofungin pharmacokinetics. However, in the Phase I study of cyclosporin A and caspofungin, some subjects experienced mild, transient elevations in ALT to 3-fold ULN. Based on these enzyme elevations, concomitant administration of cyclosporin A with caspofungin cannot be recommended. Additional data on multiple dosing in patients is needed to determine if the 2 drugs can be safely administered together.

Summary

A caspofungin dosing regimen of 50 mg IV daily, after a 70-mg loading dose on Day 1, is recommended for patients with IA. This is based on favorable caspofungin pharmacokinetics, the demonstration of a substantial antifungal effect, and the favorable adverse experience profile seen with this regimen.

Additional data have provided an increased understanding of the safety, tolerability, and pharmacokinetics of caspofungin. Further evaluation of the population pharmacokinetics from patients with *Candida* esophagitis showed that, in contrast to healthy subjects, most patients appeared to reach steady state within 2 weeks of daily dosing of caspofungin at 50 or 70 mg. Population pharmacokinetic analyses from the IA study (Protocol 019) showed no continued accumulation of caspofungin with long-term therapy (>28 days). $C_{24\text{ hr}}$ data in patients with IA were consistent with what was seen in patients with *Candida* infections; levels ranged higher and were more variable, and some patients had low $C_{24\text{ hr}}$. The safety data presented in this document show no evidence of dose-related toxicity across the doses of caspofungin evaluated (35 to 70 mg) in multiple-dose regimens. Additional safety and pharmacokinetic data suggest that it may be reasonable to consider increasing the dose of caspofungin from 50 to 70 mg daily in patients with IA who are not responding to but are tolerating therapy. While there are no efficacy data at this time to support a better outcome in patients treated with 70 mg daily, the available safety data provide support that caspofungin 70 mg is well tolerated in individuals treated for up to 21 days. The lack of a dose response for toxicities over the 35- to 70-mg dose range and the absence of a correlation of higher plasma concentrations with dose-limiting toxicities over the dose range studied both suggest that the risk associated with increasing the dose from 50 to 70 mg daily is minimal.

8.1 Conclusions

1. The recommended dosing regimen for the treatment of IA in patients refractory to or intolerant of other therapies is 50 mg daily IV, following a 70 mg loading dose on Day 1.
2. Caspofungin in the Noncomparative *Aspergillus* Study showed compelling efficacy (41% favorable response) in patients with IA who were refractory to or intolerant of other therapies.
3. No dose adjustments are necessary in the elderly or on the basis of gender or race.
4. No dosage adjustment is recommended for patients with mild to moderate renal insufficiency. Caspofungin is not cleared by hemodialysis, so there is no need for a supplementary dose after dialysis.
5. No dosage adjustment is recommended for patients with mild hepatic insufficiency. A dose reduction is recommended for moderate hepatic insufficiency to 35 mg caspofungin daily, following a 70 mg loading dose on Day 1, based on results of a single dose study which indicate that the effect of moderate hepatic insufficiency is somewhat more pronounced than in patients with mild dysfunction.
6. No dosage adjustments are necessary when caspofungin is coadministered with itraconazole, amphotericin B, mycophenolate mofetil, or tacrolimus. Standard monitoring of tacrolimus blood concentrations should be used to determine whether patients receiving concurrent caspofungin require dosage adjustments of tacrolimus.
7. Coadministration of cyclosporin A cannot be recommended until additional data regarding multiple dose administration in patients are available, due to the mild transient elevations in ALT and AST that were seen in some subjects in Phase I studies (as described in Section 7.4).

9. Summary of Benefits and Risks

Invasive aspergillosis (IA) is a fungal infection with a grave prognosis. First-line treatment for this condition is currently limited to a single polyene agent, amphotericin B deoxycholate (FUNGIZONE™) [6]. Although amphotericin B has proven efficacy against *Aspergillus*, numerous clinical and laboratory adverse experiences are associated with its administration. Nephrotoxicity and systemic infusion-related reactions (fever, rigors, and tachypnea) can be disabling and frequently limit therapy. Lipid formulations of amphotericin (ABELCET™, AmBisome™, and Amphotec™) and itraconazole have shown efficacy as salvage agents for the treatment of IA in patients who are refractory to or intolerant of amphotericin B. Even with an improved safety profile, nephrotoxicity and systemic infusion-related reactions associated with lipid formulations of amphotericin approach 20% [2; 3; 4; 14]. Although such reactions are rare with itraconazole dextrin injection, multiple drug-drug interactions mediated through the cytochrome P-450 enzyme system impact the use of this azole agent [5]. Even with the introduction of these newer therapies, IA remains a serious medical entity with few treatment alternatives. In a recent review of over 1200 cases, only ~34% of patients treated for IA had a favorable response to therapy, and the crude mortality was 87% [12]. There is a tremendous need for the development of new antifungal agents to treat this serious disease.

Caspofungin has a unique mechanism of action. It inhibits the synthesis of β -1,3-D glucan, an essential component of the cell wall of many pathogenic fungi. The unique mechanism of action of glucan synthesis inhibitors should result in a lack of cross-resistance with available polyene and azole antifungals. The clinical benefit of caspofungin acetate as salvage treatment for IA has been demonstrated by the results of the noncomparative *Aspergillus* study (Protocol 019). As of 31-March-2000, 69 patients with documented cases of IA either refractory to or intolerant of current antifungal therapy have completed therapy in this open-label, noncomparative study. A favorable response (defined as a complete or partial response) has been documented in 41% of the patients in the trial. The diagnosis and response to therapy with caspofungin for the patients enrolled in Protocol 019, as well as 3 additional patients with IA from the compassionate-use study, have been confirmed by an independent Expert Panel. The Panel's decisions were based on case report form data and a review of radiographic, culture, and pathology reports. Radiographic films were reviewed during a face-to-face meeting of the Expert Panel.

Favorable responses to caspofungin acetate therapy have been seen across a wide clinical spectrum and have included patients with factors typically associated with a poor prognosis. Clinical response has been documented in patients with pulmonary (definite and probable) and extrapulmonary IA, including cases of disseminated disease. Favorable responses have been confirmed in infections with a variety of *Aspergillus* species, including *A. fumigatus*, *A. flavus*, and *A. niger*. Favorable responses in patients refractory to initial therapy included a number of patients who had clinical and/or radiographic progression of their disease while receiving standard antifungal therapy. A

majority of patients had been treated for >14 days prior to study entry and a number had received multiple agents. These patients who were both refractory to and/or intolerant of therapy or who were refractory to more than 1 agent had very limited therapeutic alternatives. Patients with hematological malignancies and solid tumors, as well as recipients of bone marrow or organ transplants, have responded favorably to caspofungin therapy. Documented improvement during caspofungin therapy has occurred during periods of neutropenia or following aggressive chemotherapeutic regimens for cancer relapse.

The favorable response rate for Protocol 019 is dramatic considering the population included in the study. This is supported by a comparison to a historical control group identified through a retrospective chart review of patients with IA, treated from 1995 to 1998 with at least 7 days of standard antifungal therapy (Protocol 028/029). Two hundred six patients were identified in the refractory or intolerant population as the historical control group, and 17% of these patients had a favorable response at the end of standard antifungal therapy. In the historical control group, 4 factors were identified as independent predictors of outcome: disseminated disease, neutropenia, bone marrow transplant, and use of high-dose corticosteroids (≥ 20 mg prednisolone equivalents/day). Because an imbalance in these factors across the study populations could influence the overall response to therapy, an analysis using logistic regression was performed to formally compare the results of noncomparative *Aspergillus* study (Protocol 019) with those of the historical control group from Protocol 028/029, with adjustment for potential imbalances. In the logistic regression analysis, the odds ratio for the response to caspofungin in Protocol 019, compared to response to standard therapy in Protocol 028/029, was >3 and the lower bound of the 95% confidence interval was >1 in all models tested. These results indicate that, in this comparison, caspofungin was more commonly associated with a better outcome than standard therapy, supporting the overall effectiveness of caspofungin in this disease. Based on the results of the noncomparative *Aspergillus* study (Protocol 019) and a comparison to those in the Historical Control Study (Protocol 028/029), caspofungin acetate can be expected to confer substantial clinical benefit to patients with IA who are refractory to or intolerant of standard antifungal therapy.

In addition to its compelling antifungal effect, caspofungin has been generally well tolerated. The results from over 500 patients and volunteers treated with multiple doses of caspofungin acetate have been documented. Among patients enrolled in Phase II/III studies, 338 patients have received multiple doses of caspofungin for the treatment of either IA or esophageal and/or oropharyngeal candidiasis. Caspofungin has been generally well tolerated in these patients, with very few serious drug-related adverse experiences or drug-related adverse experiences leading to discontinuation of therapy. In addition, caspofungin was generally well tolerated in patients who received long-term therapy (≥ 28 days) and in a limited number of patients who received repeated courses of treatment. In randomized, double-blind Phase II studies in which amphotericin B was the comparator, nephrotoxicity and systemic infusion-related events in the caspofungin arm of the study were uncommon and caspofungin appeared to be better tolerated than

amphotericin B. In the Phase III *Candida* esophagitis trial (Protocol 020), the safety profile of caspofungin was similar to that of intravenous fluconazole with regard to drug-related adverse experiences and drug-related adverse experiences leading to discontinuation of therapy. Transaminase elevations have occurred in the Phase II/III trials during caspofungin administration with an incidence similar to that observed with comparator agents (amphotericin B, fluconazole). These transaminase elevations were generally <5-fold the upper limit of normal, transient, and rarely led to discontinuation of therapy. While transaminase elevations did occur, the interpretation of these laboratory values is confounded by concurrent diseases, concomitant medications, and elevated baseline values.

Based on the structure of caspofungin, potential risks include adverse experiences as a result of histamine release. High doses of caspofungin did produce signs of histamine release in rats and monkeys during bolus infusion. No signs of histamine release occurred in the 5-, 14-, or 27-week studies in monkeys where caspofungin was administered using a 20-minute infusion. Histamine-release reactions were not noted, despite careful monitoring, in clinical pharmacology studies or in patients with *Aspergillus* or *Candida* infections in clinical studies.

In a study evaluating the metabolism of caspofungin (Protocol 010), there was evidence of low levels of irreversible binding of degradates of caspofungin acetate to plasma proteins. These findings raise the concern of potential adverse effects associated with the presence of caspofungin's degradates. To address this concern, the results of the preclinical toxicology studies and clinical trials were carefully examined for safety issues related to irreversible binding to plasma proteins. The final findings of the preclinical toxicology studies, extending up to 27 weeks, showed that there were no adverse effects related to the long-lived degradates in monkeys. Safety monitoring for systemic reactions, as well as for hematologic, hepatic, and renal abnormalities in the caspofungin clinical trials showed no suggestion of adverse experiences related to covalent binding. Adverse experiences, such as fever, rash, and eosinophilia have occurred uncommonly and only in clinical scenarios where such findings are often encountered (most notably, severely immunocompromised patients with advanced HIV infection). There was no constellation of findings suggestive of allergic reactions that emerged in the clinical trials. Thus, there has been no evidence in clinical trials or preclinical toxicology studies to date to suggest adverse experiences are associated with the presence of caspofungin's degradates.

Finally, clinical studies evaluating drug interactions between caspofungin and commonly used drugs in patients with malignancies or transplant recipients, such as tacrolimus, mycophenolate mofetil, amphotericin B, and itraconazole, have not shown clinically significant drug interactions. Lack of interactions with other commonly administered agents is an important consideration given the large number of concomitant medications that may be required in the treatment of patients with malignancies or transplants.

One clinically significant interaction was noted when caspofungin was administered with cyclosporin A (CsA). Volunteers who received 2 doses of CsA and multiple doses of

Caspofungin Acetate
FDA Advisory Committee Meeting Background
Summary of Benefits and Risks

-171-

casposfungin experienced elevations in ALT and AST of 2- to 3-fold the upper limit of normal that resolved when both drugs were discontinued. In addition, the levels of casposfungin were higher in patients who received concomitant CsA than in those who received casposfungin alone. There was no effect on CsA pharmacokinetics. As a result of the mild transaminase elevations seen in this Phase I study, CsA was excluded from casposfungin clinical trials. One patient enrolled in Protocol 019, however, had received concomitant CsA and casposfungin, because no other therapeutic options were available; there were no transaminase elevations observed during 9 days of therapy with frequent monitoring. The ultimate implications of the observations in the Phase I trial for long-term concomitant administration require further study.

In summary, casposfungin acetate has shown compelling efficacy as salvage treatment for IA in patients refractory to or intolerant of standard antifungal therapy, a patient population with few therapeutic options. Casposfungin has also been very well tolerated in clinical trials even in seriously ill patients. A significant clinical benefit, coupled with a generally favorable safety profile, strongly favors the use of casposfungin for the treatment of IA in patients refractory to or intolerant of other therapy. In the context of currently available treatment options, both the activity and safety profiles of casposfungin are very favorable.

10. Conclusions

10.1 Pharmacotoxicology Conclusions

1. The NOELs for elevations in serum transaminase values after intravenous treatment with caspofungin for 27 weeks are 1.5 mg/kg/day in rhesus monkeys and >7.2 mg/kg/day in rats.
2. Since one rat dosed with 1.8 mg/kg showed signs of histamine release on Day 1 of the 27-week intravenous toxicity study, the overall NOEL for signs of histamine release in rats is 0.5 mg/kg/day.
3. Although injection site irritation was seen in rats and monkeys at lower dosages and concentrations, it was not seen in the high-dosage group (5.0 mg/kg/day; 0.625 mg/mL) in the 5-week intravenous toxicity study in monkeys administered the lyophilized formulation containing degradates.
4. In the definitive developmental toxicity studies in the rat and rabbit, the sole treatment-related developmental or reproductive findings occurred at a maternally toxic dose (due to histamine release), and consisted of a decrease in mean fetal body weight in the rat (with secondary very slight increases in incomplete ossification of the torso and/or skull) and an increase in cervical rib formation, both with a NOEL of 2 mg/kg/day.
5. In a postweaning evaluation study in rats, the NOEL for effects on the F₁ and F₂ generation was >5 mg/kg/day.
6. The NOEL for fertility and general performance in the fertility studies in male and female rats was >5 mg/kg/day.
7. In toxicokinetic studies using a dose of 5 mg/kg/day in rats and rabbits, the maternal exposure levels were slightly greater than the human plasma AUC of approximately 137 µg•hr/mL. In rats and rabbits, the placenta acted as a barrier to drug entry into the fetus to some degree; however, significant fetal exposure did occur at the NOEL dose for developmental toxicity of >6 mg/kg/day for rabbits and at the highest dose tested in the developmental toxicity studies in rats (5 mg/kg/day). In rats, the drug concentrations in milk indicated a transfer of drug from the plasma to the milk. In both the rat and rabbit, plasma elimination was slower in the fetus than in the dam.
8. Based upon the results of the studies discussed above, with the establishment of no-effect dosage levels for all drug-related findings, the available preclinical data support the conclusion that caspofungin may be safely administered to humans for the treatment of disseminated aspergillosis infection.

10.2 Microbiology Conclusions

1. Caspofungin prevents the synthesis of β (1,3)-D-glucan, an essential cell wall component in many pathogenic fungi.

2. Caspofungin has in vitro activity against *Aspergillus* isolates using the NCCLS proposed M38-P microbroth dilution protocol with either RPMI-1640 or AM-3 medium. The M38-P MIC endpoint of substantial (50 to 80%) inhibition of growth correlates well with the caspofungin concentration which induces morphological changes in *Aspergillus* isolates.
3. Caspofungin causes death and lysis of the growing hyphal tips and branching segments of *A. fumigatus* based on fluorescent stains designed to distinguish viable from dead cells.
4. Caspofungin is highly efficacious in animal survival models of disseminated aspergillosis and was also efficacious in a pulmonary aspergillosis survival model in rats as a therapeutic or prophylactic agent. In all in vivo studies, the efficacy of caspofungin was comparable to that achieved with AmB.
5. Caspofungin has potent in vitro activity in broth microdilution assays against a wide range of *Candida* spp. including isolates that are resistant to azole antifungals, flucytosine or AmB.
6. Caspofungin is fungicidal against *Candida* spp. based on growth inhibition kinetic studies and tissue sterilization in animal models of disseminated candidiasis.
7. Caspofungin resistance is a very rare event in the laboratory occurring at a rate of approximately 1 in 108 when selected on agar plates with *C. albicans*.
8. Caspofungin has potent in vivo efficacy in a range of animal models of disseminated candidiasis in both immunocompetent and immunosuppressed mice. Caspofungin also sterilizes kidneys in mouse models of disseminated candidiasis even in the setting of impaired host response. The efficacy of caspofungin is similar to that of AmB.
9. Results from in vitro and in vivo tests of caspofungin in combination with AmB against *Aspergillus*, *Candida*, and *Cryptococcus* isolates suggest that this combination is additive or indifferent compared to each compound alone; no evidence of antagonism has been observed. In vivo studies examining the efficacy of caspofungin in combination with FCZ against *C. albicans* show no antagonism.

10.3 Pharmacokinetics Conclusions

1. Distribution, rather than excretion or biotransformation, is the predominant mechanism controlling caspofungin plasma clearance. Biotransformation of caspofungin is slow. The major metabolic pathways are peptide hydrolysis and *N*-acetylation.
2. Following IV administration of [³H]caspofungin, the radioactivity is distributed widely throughout the body of rats. Liver contains the highest level of radioactivity and hepatic uptake is very slow. Kinetically, the equilibration of the drug between blood and liver tissue is not established rapidly (>24 hours).

3. There is a low level of irreversible binding of radioactivity (3 to 7 pmol/mg protein) in plasma following single dose administration of [³H]caspofungin. In vitro experiments suggest that the chemical degradation of caspofungin to L-747969 involves the formation of 2 potentially reactive intermediates which appear to bind irreversibly to plasma proteins.
4. The radiolabeled dose is excreted almost equally into the urine and feces after IV dosing in rats, monkeys, and humans. Less than 5% of the dose is excreted as unchanged drug in the urine.
5. Caspofungin is not a substrate for P-glycoprotein, nor is it a potent inhibitor of P-glycoprotein. Caspofungin is a poor substrate for CYP isozymes. At clinically relevant concentrations, caspofungin does not inhibit major human CYP isozymes.
6. Administration of a 70-mg loading dose on Day 1 followed by 50 mg caspofungin daily maintains mean caspofungin plasma concentrations above a 1-µg/mL target throughout treatment.
7. No clinically meaningful effects on caspofungin pharmacokinetics were observed for age, gender, race, renal insufficiency, mild hepatic insufficiency and underlying disease or condition. Pending additional results from a multiple dose study, a dose reduction to 35 mg following the 70-mg loading dose is recommended for patients with moderate hepatic insufficiency.
8. Itraconazole, tacrolimus, mycophenolate, and probably amphotericin B have no effect on the pharmacokinetics of caspofungin. Coadministration of a single dose or 2 doses of cyclosporin A moderately increases (~35% for AUC) plasma concentrations of caspofungin.
9. Caspofungin has no effect on the pharmacokinetics of itraconazole, amphotericin B, cyclosporin A and mycophenolic acid, the pharmacologically active metabolite of mycophenolate. Caspofungin slightly decreases (~20% for AUC) whole blood concentrations of tacrolimus.

10.4 Clinical Efficacy Conclusions

1. Caspofungin 50 mg IV daily, following a 70-mg loading dose on Day 1, is effective in the treatment of well-documented invasive aspergillosis in patients refractory to or intolerant of other therapy, based on the assessments of an Expert Panel.
2. Caspofungin is associated with favorable outcomes in patients with an expected poor prognosis, including those refractory to initial therapy, with disseminated disease, who are neutropenic, or are recipients of allogeneic transplants or high-dose corticosteroids.
3. Caspofungin is effective in the treatment of invasive aspergillosis when compared to a historical control group receiving standard therapy. Using logistic regression, an odds ratio of >3 in favor of caspofungin is seen after adjusting for potential imbalances in prognostic factors. The lower bound of the 95% CI is >1 in all cases.

In this analysis, caspofungin was at least as effective as standard therapy, supporting the overall effectiveness of caspofungin.

4. Documented relapse of invasive aspergillosis is uncommon up to 4 weeks after completion of IV caspofungin therapy.
5. Favorable clinical and microbiological responses are seen in patients with infections due to *A. fumigatus*, *A. flavus*, and *A. niger*. In these patients, there is no apparent correlation between caspofungin minimum inhibitory concentrations at 24 hours in RPMI medium or AM3 medium and outcome.
6. In Phase II studies, caspofungin at 35, 50, and 70 mg IV daily is effective in the treatment of esophageal and oropharyngeal candidiasis.
7. In the Phase II studies of esophageal and oropharyngeal candidiasis, caspofungin at 50 or 70 mg IV daily appears more effective than 35 mg and appears at least as effective as amphotericin B.
8. Most esophageal and oropharyngeal *Candida* infections are caused by *C. albicans*, but there is no apparent difference in clinical or microbiological outcome in patients with mixed infections or infections due to *non-albicans Candida spp.* when compared to those with *C. albicans* alone.

10.5 Clinical Safety Conclusions

1. Caspofungin 50 mg is generally well tolerated in healthy subjects and patients with invasive *Aspergillus* and *Candida* infections who received several concomitant medications. There are few serious drug-related adverse experiences or discontinuations in therapy due to drug-related adverse experiences.
2. The most common drug-related clinical adverse experiences in patients receiving caspofungin 50 mg are fever and phlebitis/thrombophlebitis and/or infused vein complications. Most of these adverse experiences are mild and do not lead to discontinuation of therapy. The evaluation of fever is confounded by the patients' underlying advanced AIDS diseases and its presence at baseline in some patients.
3. The most common drug-related laboratory adverse experiences in patients receiving caspofungin 50 mg are increased ALT, increased AST, decreased hemoglobin, and decreased hematocrit. Most of the increases in ALT and AST are <5-fold the ULN, transient, and do not limit therapy. The evaluation of these adverse experiences is also confounded by the patients' underlying diseases and their presence at baseline in some patients.
4. There is no evidence of dose-related toxicities (range: 35 to 70 mg).
5. The safety profile of caspofungin does not appear to change with extended therapy (up to 162 days).
6. Coadministration of cyclosporin A with caspofungin is not recommended based on mild increases in ALT/AST in Phase I studies. Implications for multiple-dose safety require further studies.

10.6 Recommended Dosing Conclusions

1. The recommended dosing regimen for the treatment of IA in patients refractory to or intolerant of other therapies is 50 mg daily IV, following a 70-mg loading dose on Day 1.
2. Caspofungin in the Noncomparative *Aspergillus* Study showed compelling efficacy (41% favorable response) in patients with IA who were refractory to or intolerant of other therapies.
3. No dose adjustments are necessary in the elderly or on the basis of gender or race.
4. No dosage adjustment is recommended for patients with mild-to-moderate renal insufficiency. Caspofungin is not cleared by hemodialysis, so there is no need for a supplementary dose after dialysis.
5. No dosage adjustment is recommended for patients with mild hepatic insufficiency. A dose reduction is recommended for moderate hepatic insufficiency to 35 mg caspofungin daily, following a 70 mg loading dose on Day 1, based on results of a single dose study which indicate that the effect of moderate hepatic insufficiency is somewhat more pronounced than in patients with mild dysfunction.
6. No dosage adjustments are necessary when caspofungin is coadministered with itraconazole, amphotericin B, mycophenolate mofetil, or tacrolimus. Standard monitoring of tacrolimus blood concentrations should be used to determine whether patients receive concurrent caspofungin require dosage adjustments of tacrolimus.
7. Coadministration of cyclosporin A cannot be recommended until additional data regarding multiple dose administration in patients are available, due to the mild transient elevations in ALT and AST that were seen in some subjects in Phase I studies (as described in Section 7.4).

APPENDIX 1

Listing of Differences Between Final Assessments of the Expert Panel and Investigator Assessments

Initial 58 Patients

Diagnosis of Infection

- AN 446—Diagnosed with probable pulmonary aspergillosis by investigator; definite pulmonary aspergillosis by Expert Panel.
- AN 476—Investigator enrolled with presumptive diagnosis and later stated patient did not meet criteria for diagnosis. Expert Panel considered patient not to have met criteria for diagnosis.

Reason for Enrollment

Allocation Number	Investigator Reason	Expert Panel Reason
0019	Refractory	Refractory to prophylactic dosage
0248	Refractory	Refractory to prophylactic dosage
0412	Intolerant	Refractory

Evaluation of Outcome

Allocation Number	Investigator Response	Expert Panel Response
0216	Complete response	Failure
0217	Partial response	Failure
0297	Partial response	Failure
0063	Stable disease	Partial response
0016	Complete response	Partial response
0019	Complete response	Partial response
0061	Complete response	Partial response
0248	Complete response	Partial response
0316	Complete response	Partial response
0328	Complete response	Partial response
0509	Complete response	Partial response
0471	Partial response	Unassessable
0017	Stable disease	Failure
0486	Stable disease	Failure
0056	Failure	Stable disease

APPENDIX 1 (Cont.)

Listing of Differences Between Final Assessments of the Expert Panel and Investigator Assessments

Additional 11 Patients:

Diagnosis of Infection

- AN 510—Diagnosed with probable pulmonary aspergillosis by investigator and later found to have rhizopus; Expert Panel considered patient not to have met criteria for diagnosis.
- AN 511—Diagnosed with probable pulmonary aspergillosis by investigator; Expert Panel considered patient to have probable pulmonary aspergillosis at entry and “other fungal infection” at final diagnosis.

Reason for Enrollment

- There were no differences between the investigator and Expert Panel assessment for the 11 additional patients.

Evaluation of Outcome

- AN 291—Assessed as complete response by the investigator; Expert Panel determined patient had a partial response.

References:

Preclinical Pharmacotoxicology

1. Garrison JC. Histamine, bradykinin, 5-hydroxytryptamine, and their antagonists. In: Gilman AG, Rall TW, Nies AS and Taylor P, eds. The pharmacological basis of therapeutics. 8th ed. New York: Pergamon Press, 1990:574-99.

Human Pharmacokinetics

1. Squires K, Riddler S, Havlir D, et al. Co-administration of indinavir (IDV) 1200 mg with nelfinavir (NFV) 1250 mg in a twice daily regimen: preliminary safety, PK activity [Abstract]. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, IL 1999:Session 48.
2. Skowron G, Leoung G, Kerr B, et al. Lack of pharmacokinetic interaction between nelfinavir and nevirapine. AIDS 1998;12:1243-4.
3. Merry C, Barry MG, Mulcahy F, et al. The pharmacokinetics of combination therapy with nelfinavir plus nevirapine. AIDS 1998;12:1163-7.

Clinical Efficacy and Safety

1. Denning DW, Lee JY, Hostetler JS, et al. NIAID mycoses study group multicenter trial of oral itraconazole therapy for invasive aspergillosis. Am J Med 1994;97:135-44.
2. Package Circular: AmBisome[®] (amphotericin B) liposome for injection: January 1998.
3. Package Circular: ABELCET[®] (amphotericin B lipid complex injection): October 1996.
4. Package Circular: AMPHOTEC[®] (Amphotericin B) cholesteryl sulfate complex for injection: August 1997.
5. Package Circular: Sporanox Oral Solution (Janssen) (Itraconazole): 1997.
6. USA Package Circular: Fungizone[®] Intravenous: amphotericin B for injection USP: 1993.

References (Cont.)

7. Ellis M, Spence D, de Pauw B, et al. An EORTC international multicenter randomized trial (EORTC number 19923) comparing two dosages of liposomal amphotericin B for treatment of invasive aspergillosis. *Clin Infect Dis* 1998;27:1406-12.
8. Leenders ACAP, Daenen S, Jansen RLH, et al. Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. *Br J Haematol* 1998;103:205-12.
9. Stevens DA, Lee JY. Analysis of compassionate use itraconazole therapy for invasive Aspergillosis by the NIAID Mycoses Study Group criteria. *Arch Intern Med* 1997;157:1857-62.
10. White MH, Anaissie EJ, Kusne S, et al. Amphotericin B colloidal dispersion vs. amphotericin B as therapy for invasive aspergillosis. *Clin Infect Dis* 1997;24:635-42.
11. Cevenbergh P, Jacobs F, Kentos A, et al. Compassionate use of amphotericin B lipid complex (Abelcet) in life-threatening fungal infections: report of 30 courses. *Clin Microbiol Infect* 1998;4(4):192-8.
12. Denning DW. Therapeutic outcome in invasive aspergillosis. *Clin Infect Dis* 1996;23:608-15.
13. Ascioğlu S, de Pauw B, Bennett JE, et al. Analysis of definitions used in clinical research on Invasive Fungal Infections (IFI): consensus proposal for new, standardized definitions. 39th ICAAC; 1999; San Francisco, CA, 1999.
14. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999;340(10):764-71.
15. Outcome of therapy for invasive aspergillosis 1995 to 2000.

Figure 1: In Vitro Effects of Caspofungin on *A. fumigatus* Using a Viability Stain

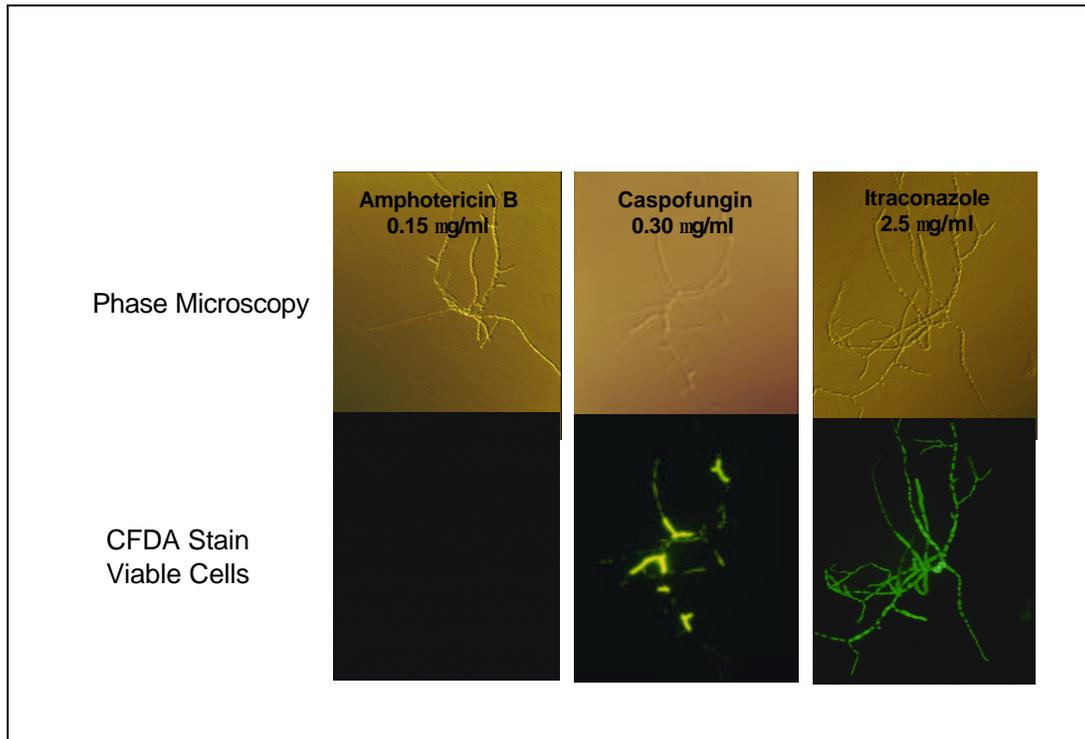


Figure 2: In Vitro Effects of Caspofungin on *A. fumigatus* Using Mortality Stain

