CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-227

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	**21-227**
Generic	**Caspofungin Acetate**
(Brand®)	**Cancidas®**
Submission Date:	**April 03, 2000, July 28, 2000, August 14, 2000, September 20, 2000, October 31, 2000, November 16, 2000, November 21, 2000, December 15, 2000, January 15, 2000, January 18, 2000**
Type of Submission:	**New Drug Application**
Reviewer:	**Houda Mahayni**

I. Executive Summary

What is the clinical indication and how were the doses selected for Phase II and III studies?

In this NDA submission, the active moiety caspofungin acetate (MK-0991), is being evaluated for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

The first dose in humans was derived based on achieving a target concentration of 1μg/mL that had been selected based on the in vitro susceptibility of clinically relevant fungal isolates. In the initial, rising-multiple-dose study (002), 15, 35, and 70 mg doses were evaluated. The results demonstrated that trough concentrations on Day 14 exceeded the target concentration for a 70 mg daily regimen and approached the target concentration for a 35 mg daily regimen.

The 35 mg dose was shown later to be suboptimal in the Phase II dose-ranging study (004). On the basis of these results, the regimens 50 and 70 mg daily were selected for evaluation in the initial Phase II efficacy study.

Did the sponsor attempt to characterize the exposure-response relationship for caspofungin?

The Sponsor did not attempt to characterize an exposure-response relationship for the drug for the aspergillosis indication sought in this NDA (21-227). However, the sponsor did attempt to find a PK/PD relationship for the drug in the candidiasis indication for which the sponsor will submit an NDA in the future.

Although candidiasis is not the intended indication for this submission, this study served as proof of concept for the antifungal property of Cancidas®. In the dose-ranging efficacy study (Protocol 004), doses of 35, 50, and 70 mg were effective in the treatment of esophageal and oropharyngeal candidiasis. The pharmacokinetic data showed that the geometric mean estimates for $AUC_{0\text{-}24\ hr}$ and $C_{24\ hr}$ after the 35-mg dose were ~30% lower than those for the 50 mg dose. Numerically, but not statistically, 50 and 70 mg doses were associated with a greater proportion of patients with a favorable outcome than the 35 mg dose. In the primary modified-intention-to-treat (MITT) analysis, 73.5% of patients receiving 35 mg had a favorable overall outcome, while 91.2% and 82.9% of patients receiving 50 and 70 mg, respectively, had a favorable outcome. $C_{24\ hr}$ was found to be a significant predictor for clinical outcome (p=0.0226) while a similar relationship was not seen with $AUC_{0\text{-}24\ hr}$ (p=0.057). $C_{1\ hr}$ was not a significant predictor.

The breakpoint for the antifungal activity, based on $C_{24\ hr}$, using tree regression method was 1.4 μg/mL in contrast to 1.0 μg/mL from *in vitro* data. The average C_{24} observed in candidiasis patients is 1.65 μg/mL after administration of 35 mg, 2.06 μg/mL after administration of 50 mg dose, and 3.82 μg/mL after administration of 70 mg dose of caspofungin.

As a result, the Sponsor is proposing 50 mg and 70 mg doses of caspofungin for achieving C_{24} values that will be acceptable for treatment of aspergillosis.

What are the basic characteristics (drug class, and mechanism of action) of caspofungin?

It is an echinocandin, a new class of antifungals that is not chemically related to existing antifungal drugs. Caspofungin inhibits the synthesis of β(1,3)-D-glucan, an integral component of the cell wall of many fungi, including *Candida* and *Aspergillus*, and the cyst form of *Pneumocystis carinii.*

What are the dosage form, strengths and regimen?

It is a parenteral product administered as a 1 hour intravenous infusion. It is available at 50 mg/vial and 70 mg/vial; The dosage regimen is 70 mg loading dose followed by 50 mg of caspofungin given once daily. Duration of treatment will be based upon the severity of the patient's underlying disease, status of recovery from immunosuppression, and clinical response.

What are the basic pharmacokinetic characteristics of caspofungin?

Caspofungin pharmacokinetics display a slight deviation from linearity which is observed by dose-dependent differences in the accumulation of caspofungin and was not detected after single 5 to 100 mg doses of caspofungin. The degree of accumulation on Day 14, based on comparison of AUC values, for 15, 35 and 70 mg daily caspofungin doses is 1.24, 1.33 and 1.50, respectively. Indicating effective elimination half-lives of 10, 12, and 15 hrs which is consistent with the estimated effective half-life of 9 to 11 hrs from single dose studies (in which also, a 40-50 hr disposition half-life was detected for the terminal phase).

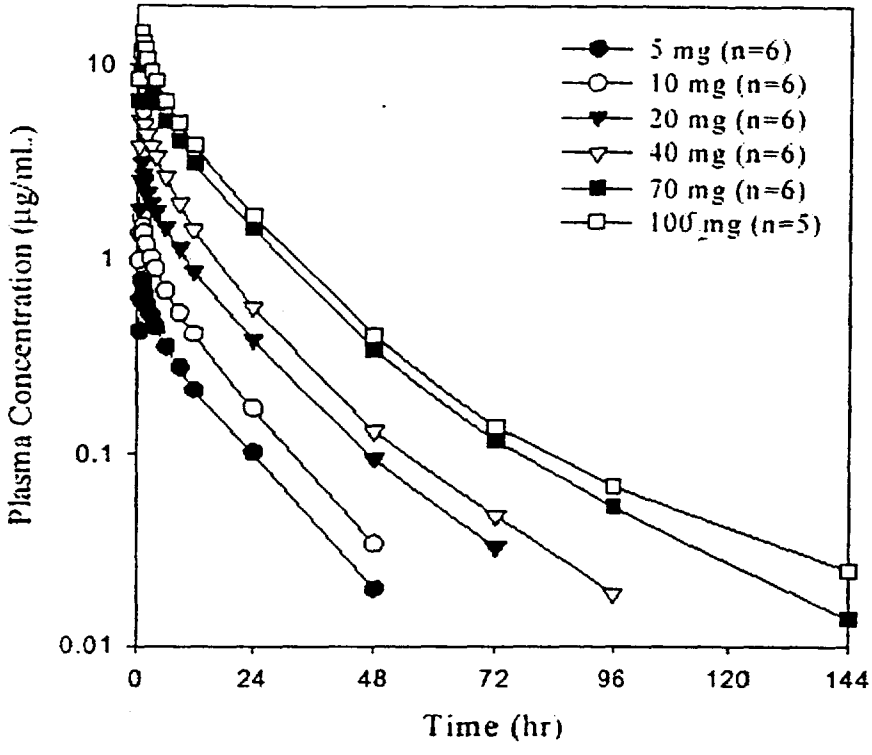
The degree of accumulation is higher based on comparison of trough values than the AUCs. The trough (C_{24}) values show approximately a 2-fold increase by Day 14 and Day 21(although Day 21 values are slightly higher than Day 14 trough values) compared to Day 1 in healthy volunteers, and up to a 4-fold increase in patients. In all submitted studies, the degree of accumulation is higher when assessed based on C_{24} values.

A concern is the continuing increase in trough values, albeit small, even by Day 21 which suggests a very slow rate controlling process in reaching steady-state. Given the difference in the magnitude of accumulation based on AUC and C_{24} values, it is difficult to estimate C_{24} values when caspofungin doses will be given for periods longer than those studied in this submission. This leads to an uncertainty regarding when and whether steady-state will be attained based on trough concentrations. Under the recommendations section, the Sponsor will be requested to provide trough concentrations after long term (exceeding 1 month) use of caspofungin in any clinical trial.

The following is a concentration-time profile of caspofungin after administration of a single dose as 1hour IV infusion (Figure 1, page 3)

Figure 1

Mean Plasma Concentration Profiles of MK-0991 Following Single 1-Hour Intravenous Infusions of 5 to 100 mg to Healthy Male Subjects



As apparent at the 20 mg and the higher doses, decline in caspofungin concentrations is triphasic. The third disposition(terminal elimination) phase may be due to slow release of drug from tissues. The disposition phase half-lives are 1-2 hours, 9-11 hours, and 40-50 hours for Alpha, Beta and Gamma phases, respectively.

The geometric mean values of caspofungin clearance for 5, 10, 20, 40, 70 and 100 mg doses were 10.36, 11.02, 10.77, 11.99, 9.85 and 12.43 mL/min, respectively.

Distribution, Metabolism and Routes of Excretion

Caspofungin does not have a large distribution volume as the steady-state volume of distribution of caspofungin is 9.67 L. Caspofungin is extensively bound to albumin (~97%) and based on blood/plasma partitioning ratio of ~0.74, it is not taken up extensively by red blood cells. The major metabolic pathways of caspofungin involve peptide hydrolysis and N-acetylation. Caspofungin degrades chemically to L-747969, a ring-opened peptide, which is the major component of extractable radioactivity in plasma seen at later time points (5 days after a single dose). L-747969 does not have antifungal activity and it is expected to form throughout the body.

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) were seen in vivo during later time points (Days 5 to 20) in the clinical disposition study. Additional metabolism of caspofungin appears to involve the hydrolysis of this hexapeptide into its constitutive amino acids or their degradation products.

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, indicating that the clearance of M1 and M2 is fast relative to the formation and/or release rate. It is unclear whether the polar hydrolysis metabolites M1 and M2 are formed directly from caspofungin or through L-747969 and/or the protein adducts. 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, indicating that little biotransformation occurs during the first day or 2 postdose.

Caspofungin is excreted unchanged at low levels in urine (1.44% of dose). The appearance of low amounts of radioactivity in feces by the second day following administration, at which time radioactivity in plasma is largely intact drug, suggest that there may be a low rate of biliary excretion of unchanged drug as well. Renal clearance of caspofungin is very slow, averaging 0.15 mL/min and 0.16 mL/min on Day 14 of daily dosing at 70mg.

A striking feature of the radioactivity recovery 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. The spontaneous degradation of caspofungin to L-747969, as well as the formation of M1 and M2, are slow processes too that may contribute to the delayed recovery of radioactivity. Extensive binding of L-747969 to liver tissues may also slow its release from liver or further biotransformation. The impact of this binding was further discussed with the medical officer who indicated that the ALT and AST changes in the clinical trials were not significant.

After administration of a $[H]^3$-labeled 70 mg of caspofungin dose, over a collection period of 27 days, approximately 75% of the radiolabeled dose (34 % in feces and 41 % in urine) was recovered.

Caspofungin And Special Populations: What Are The Dosing Recommendations For Caspofungin In These Populations?

To ensure efficacy, the Sponsor is recommending dosing adjustments only in cases where the exposure is reduced by 30% or more from the control (such that the concentrations would be comparable to or less than those from the 35 mg dose). This is acceptable.

The Sponsor is not recommending a dosing adjustment for increases in exposure that are within the following boundaries. The Sponsor has defined clinically significant increase in exposure by the 90% CI interval which will have a lower limit significantly greater than 1 and an upper limit greater than 1.5. The submitted information at 50 mg and 70 mg doses in the Section 6 of this NDA is not adequate to support the upper limit of this confidence interval. The clinical impact of increase in exposure was discussed with the MO and this reviewer believes that the upper limit of this 90% CI is an acceptable indicator of clinically significant increase in caspofungin exposure.

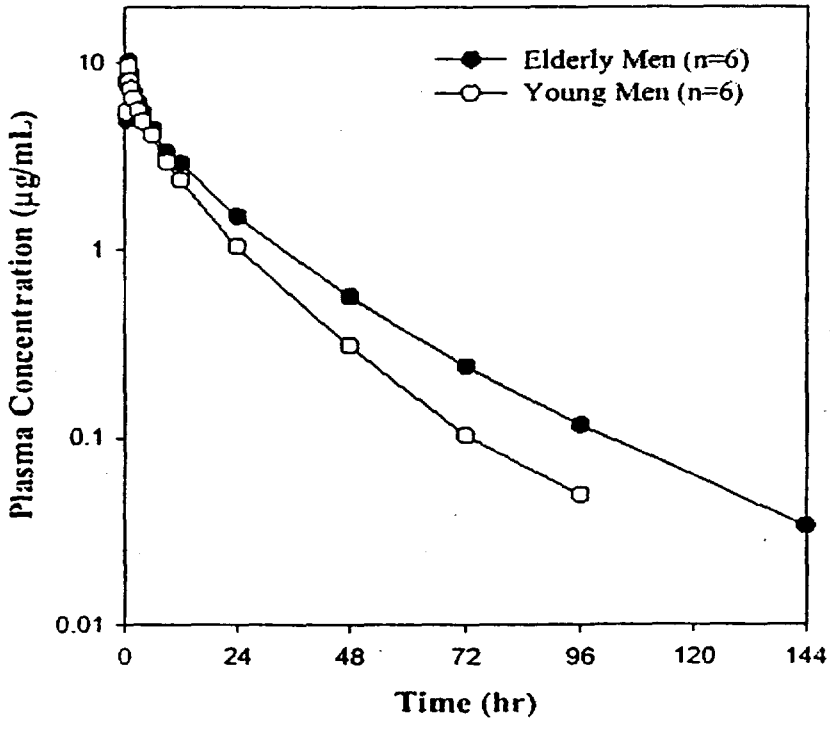
The following section summarizes the pertinent dosing information in the special populations.

Elderly:

The following figure illustrates plasma caspofungin concentration-time profiles in elderly (n=6) and young (n=6) subjects following administration of a single 70 mg dose.

Figure 3

Mean MK-0991 Plasma Profiles in Elderly and Young Men Administered Single 70-mg Doses in Protocol 022



The geometric mean clearance of caspofungin in elderly is 9.48 mL/min as compared to 12.48 mL/min in young subjects. The geometric mean ratio of clearance in healthy elderly men when compared to healthy young men is 0.76 and the 90% CI for this ratio is 0.64 to 0.90.

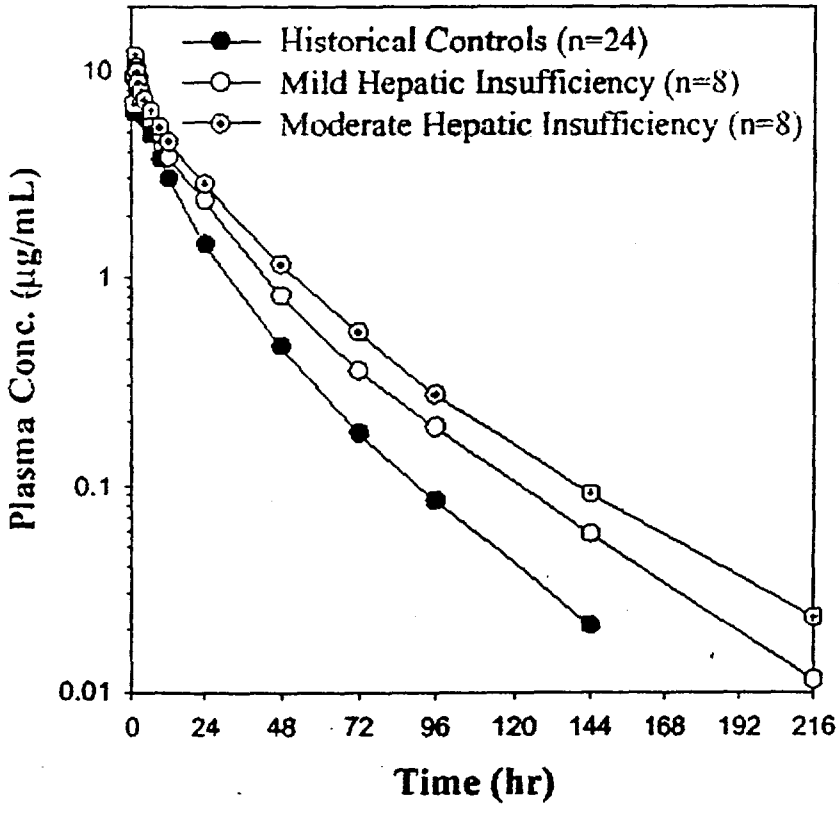
The decrease seen in clearance in the elderly as compared to young subjects is considered small (a reduction in the point estimate of about 25%). There would be no need to reduce caspofungin dose in the elderly.

Hepatic impairment

The following figure illustrates plasma caspofungin concentration time profiles in healthy subjects, and mild and moderate hepatic insufficiency patients following administration of a single 70 mg dose of caspofungin.

Figure 5

Mean MK-0991 Plasma Profiles in Healthy Subjects and Mild and Moderate Hepatic Insufficiency Patients Administered Single 70-mg Doses



The geometric mean clearance of caspofungin is 6.33 mL/min in subjects with mild hepatic insufficiency and 5.55 in subjects with moderate hepatic insufficiency as compared to controls 9.77 mL/min.

The geometric mean ratio of caspofungin clearance in subjects with mild hepatic impairment when compared to controls is 0.65 and the 90% CI for this estimate is 0.55 to 0.76. The geometric mean ratio of caspofungin clearance in subjects with moderate hepatic impairment when compared to controls is 0.57 with a range of [redacted] for the 90% CI.

The geometric mean ratio of caspofungin AUC values in subjects with mild hepatic impairment when compared to controls is 1.55 and the 90% CI for this estimate is 1.32 to1.86. The geometric mean ratio of AUC values of caspofungin in subjects with moderate hepatic impairment when compared to controls is 1.76 with a range of [redacted] for the 90% CI.

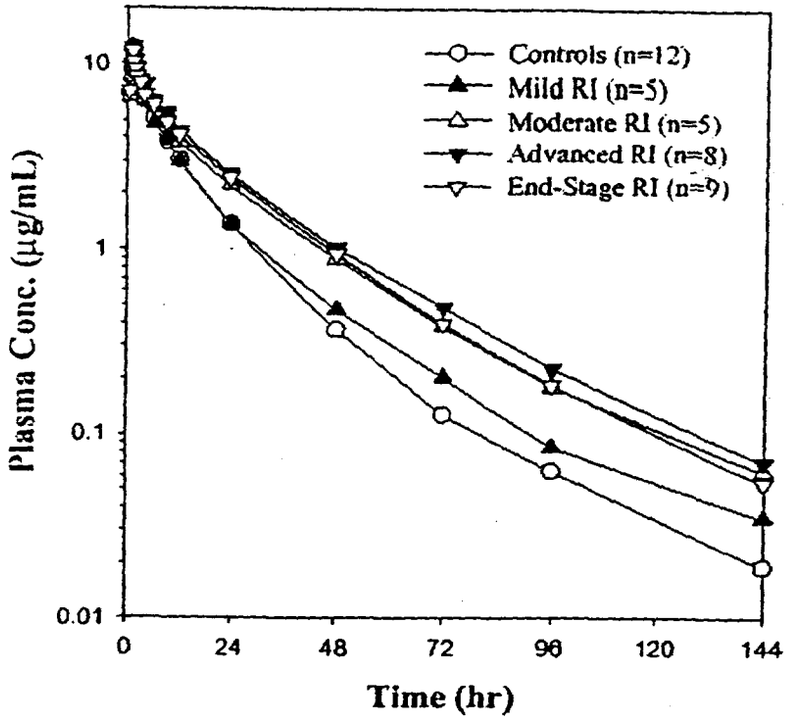
Dose adjustment is needed in the moderate hepatic insufficiency patients. The dosing recommendation is 35 mg daily after 70 mg Loading dose. From the results obtained in the single dose study, dosage adjustment is also needed in the mild group. The sponsor is performing a multiple dose study in mild hepatic insufficiency patients to confirm results obtained in the single dose study. The preliminary results, geometric mean ratio and (90% CI) received so far from the multiple dose study in the mild hepatic insufficiency group compared to matched healthy control: $AUC_{0\text{-}24}$, and C_{24} are 1.19 (1.03, 1.37) and 1.42 (1.14, 1.77). These results are obtained on day 14 after receiving 70 mg loading dose and 50 mg dose daily. Based on these preliminary results dosage adjustment in mild hepatic insufficiency group is not needed.

Renal impairment

The following figure illustrates plasma caspofungin concentration-time profiles in controls, mild, moderate, advanced, and end-stage renal insufficiency subjects after receiving a single 70 mg dose of caspofungin.

Figure 3

Mean MK-0991 Plasma Profiles in the Pooled Controls and Patients With Varying Degrees of Renal Insufficiency Administered a Single 70-mg Dose



APPEARS THIS WAY
ON ORIGINAL

The geometric mean clearance of caspofungin is 9.72 mL/min in Mild RI, 7.08 mL/min in Moderate RI, 6.24 mL/min in Advanced RI, and 7.17 mL/min in End-Stage RI as compared to 9.31 mL/min in the control group. The geometric mean ratio (90% CI) of caspofungin clearance in mild, moderate, advanced, and end-stage renal insufficiency subjects when compared to controls are: 1.04(0.85, 1.28), 0.76 (0.62, 0.94), 0.67 (0.56, 0.80), 0.77(0.65, 0.92), respectively.

The geometric mean ratio (90% CI) of caspofungin AUC values in mild, moderate, advanced, and end-stage renal insufficiency subjects when compared to controls are: 0.96 (0.78, 1.17), 1.31 (1.07, 1.62), 1.49 (1.24, 1.79), 1.30(1.09, 1.56), respectively. Given the overlapping range of confidence intervals, the effect of renal impairment on caspofungin exposure is similar in subjects with moderate, advanced(severe) and end-stage renal impairment and clearance of caspofungin is approximately 30% less in these subjects compared to the clearance values in the control group. Overall impact of this reduction in clearance is not expected to warrant a dosage adjustment in subjects with renal impairment.

Is there a pediatric formulation and dosing recommendation?

The Sponsor is working on a pediatric formulation which will be available at a later date. On June 13, 2000, the Sponsor submitted a detailed outline of the proposed program in the pediatric population.

Drug-Drug Interactions and dosing recommendations:

The following drugs (CYP450 substrates/inhibitors) were studied with caspofungin: Cyclosporin, Amphotericin B, FK-506(tacrolimus), itraconazole, and mycophenolate.

Although caspofungin C_{24} changed 2 fold, the increase in AUC_{0-24} was approximately 35%. This change was considered clinically insignificant (based on discussion with the medical officer), and therefore, no dosage adjustment is recommended.

For FK-506, the geometric mean ratio (90% CI) of AUC_{0-12}, C_{max}, and C_{12} are 0.80 (0.72, 0.89), 0.84 (0.75, 0.95), and 0.75 (0.63, 0.86), respectively. This should not be of concern since tracrolimus trough concentrations are usually monitored.

No remarkable changes (±20%) of the point estimate were observed for AUC_{0-24}, C_1, and C_{24} when caspofungin was administered with amphotericin B, itraconazole, and mycophenolate.

A summary of pharmacokinetic parameters from the cyclosporin and tacrolimus interaction studies is presented in the following table.

Summary of Results From Caspofungin Drug Drug Interaction Studies:

Interacting Drugs	Protocol No	Comparison	Parameters	GMR 90% CI
MD, MK-0991(70 mg) SD, CsA (4 mg/kg) N=18	013 Cyclosporin	The effect of cyclosporin on caspofungin	AUC_{0-24} C_{1hr} C_{24}	**1.34 (1.17, 1.54)** **1.04 (0.91, 1.18)** **1.65 (1.37, 1.98)**
		The effect of caspofungin on cyclosporin	$AUC_{0-\infty}$ C_{max}	1.00 (0.87, 1.15) 0.88 (0.68, 1.13)
MD, MK-0991(70 mg) SD,CsA(3mg/kg BID) N=34	017 Cyclosporin	The effect of cyclosporin on caspofungin	AUC_{0-24} C_{1h} C_{24hr}	**1.35 (1.21,1.49)** **0.91(0.82, 1.00)** **2.01(1.69, 2.34)**
		The effect of caspofungin on cyclosporin	AUC_{0-12} C_{max} C_{12}	1.02 (0.93,1.11) 1.08(0.79, 1.22) 1.15(1.04, 1.28)
MD,MK-0991 (50 mg) SD,FK-506(0.1mg/kg) N=34	017 FK-506	The effect of tacrolimus on caspofungin	AUC_{0-24} C_1 C_{24}	1.05(0.96, 1.15) 1.02 (0.92, 1.13) 1.10 (0.94, 1.28)
MD, MK-0991(70 mg) SD,FK-506(0.1 mg/kg)			AUC_{0-24} C_1 C_{24}	1.00 (0.96, 1.04) 0.94 (0.87, 1.02) 1.00 (0.92, 1.09)
		The effect of capsofungin on tacrolimus	AUC_{0-12} C_{max} C_{12}	**0.80 (0.72, 0.89)** **0.84 (0.75, 0.95)** **0.75 (0.63, 0.86)**

A summary of pharmacokinetic parameters from all of the interaction studies is on page 50 of the review.

Discussion point:

The sponsor is proposing the following statement in the label: "When coadministering CANCIDAS with efavirenz, nelfinavir, nevirapine, phenytoin, rifampin, dexamethasone, or carbamazepine, an increase in the daily dose of CANCIDAS to 70 mg, following the usual 70-mg loading dose, should be considered".

Although there may be a need to increase the daily caspofungin dose so that efficacy is not compromised when these agents are coadministered with caspofungin, there is no data in this submission to support that increasing caspofungin dose to 70 mg daily is going to be adequate. As a Phase IV commitment, the Sponsor will be requested to characterize the extent of interaction between caspofungin and rifampin (as it is highly likely to be the greatest inducer of caspofungin metabolism) so that appropriate dosing recommendations can be made for coadministration of caspofungin with drugs that can induce its metabolism.

It is this reviewer's opinion that until the appropriate dosing recommendation can be made, the label should alert the health care provider that there may be a loss of efficacy when caspofungin is given with the above listed drugs and therefore, use of these drugs with caspofungin should be avoided.

II. General Comments

- In Both types of studies, the special population and drug-drug interaction, subjects were not dosed to steady state.

- Accumulation was also still occurring up to the third week of dosing and up till then steady-state was still not achieved.

- The sponsor used different a priori criteria in the individual studies for making decisions than the ones used in our Guidances (DDI, Liver, Renal). The sponsor later chose the 90% CI limit to be (0.7, 1.5) with the caveat that not only the upper limit has to be greater than 1.5, but the lower limit also has to be significantly greater than **one** to conclude a significant change in PK.

- Although there was an increase in the levels of capsofungin in the renal insufficiency patients, no dosage adjustment recommendation was provided because caspofungin renal clearance is slow and its elimination is evenly divided between urine and feces. In addition, the increased levels seen in the renal insufficiency study was discussed with the medical officer (Dr. Navarro). Her response was that although the database she had seen in the clinical studies had limited number of patients with renal insufficiency (N=12), there was no major indication to point to any safety concerns.

- Caspofungin levels were increased in the presence of CsA. This issue was also discussed with the medical officer and she stated that there was no safety concerns in patients who are given caspofungin and CsA concomitantly.

III. Comments to firm

- **The Sponsor is requested to fully characterize caspofungin steady-state pharmacokinetics by conducting either a stand alone pharmacokinetic study or by utilizing sparse sampling technique for sample collection during conduct of a long term clinical study.**
- **The Sponsor needs to address the potential interaction between caspofungin and mixed inhibitors/inducers such as efavirenz, nelfinavir, nevirapine, phenytoin, rifampin, dexamethasone, or carbamazepine so that appropriate dosing recommendations can be made with these drugs.**
- **The sponsor is requested to adopt the OCPB labeling as provided in this review.**

IV. Labeling Comments

- The label should alert the health care provider that there may be a loss of efficacy when caspofungin is given with mixed inducers/inhibitors, and therefore, use of these drugs with caspofungin should be avoided.
- The sponsor is requested to adopt other minor labeling changes as provided on the following pages.

OCPB LABELING
CLINICAL PHARMACOLOGY
Pharmacokinetics

Distribution
Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour IV infusions. A short α -phase occurs immediately postinfusion, followed by a β-phase (half-life of 9 to 11 hours) that characterizes much of the profile and exhibits clear log-linear behavior from 6 to 48 hours postdose during which the plasma concentration decreases **10 folds** An additional, longer half-life phase, χ -phase **(half-life of 40-50 hours)**, also occurs Distribution, rather than excretion or biotransformation, is the dominant

mechanism influencing plasma clearance. Caspofungin is extensively bound to albumin (~97%), and distribution into red blood cells is minimal. Mass balance results showed that approximately 92% of the **administered radioactivity** was distributed tissues **by** 36 to 48 hours after a single 70-mg dose of [^{3}H] caspofungin acetate. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration.

Metabolism

Caspofungin is slowly metabolized by hydrolysis and N-acetylation. Caspofungin also undergoes spontaneous chemical degradation to an open-ring peptide compound, L-747969. At later time points (5 to 20 days postdose), there is a low level (3 to 7 pico moles/mg protein, or 0.6 to 1.3% of administered dose) of covalent binding of radiolabel in plasma following single-dose administration of [^{3}H] caspofungin acetate, which may be due to two reactive intermediates formed during the chemical degradation of caspofungin to L-747969. Additional metabolism involves hydrolysis into constitutive amino acids and their degradates, including dihydroxyhomotyrosine and N-acetyl-dihydroxyhomotyrosine. These two tyrosine derivatives are found only in urine, suggesting rapid clearance of these derivatives by the kidneys.

Excretion

In a single-dose radiolabeled pharmacokinetic study, plasma, urine, and feces were collected over 27 days. Plasma concentrations of radioactivity and of caspofungin were similar during the first 24 to 48 hours postdose; thereafter drug levels fell more rapidly. Radiolabel remained quantifiable through Day 27, whereas caspofungin concentrations fell below the limit of quantitation after 6 to 8 days postdose. **After single intravenous administration of excretion of and its metabolites in humans were 35% of dose in feces and 41% of dose in urine.** A small amount of caspofungin is excreted unchanged in urine (~1.4% of dose). Renal clearance of parent drug is low (~0.15 mL/min) **and total clearance of caspofungin is 12 mL/min.**

Special Populations

Gender

Plasma concentrations of caspofungin in healthy men and women were similar following a single 70-mg dose. After 13 daily 50-mg doses, caspofungin plasma concentrations in women were elevated slightly (approximately **22 % in area under the curve [AUC]**) relative to men. No dosage adjustment is necessary based on gender.

Geriatric

Plasma concentrations of caspofungin in healthy older men and women (65 years of age) were increased slightly (approximately 28% in area under the curve [AUC]) compared to young healthy men **after single 70 mg dose of caspofungin**. Age is not a significant determinant of caspofungin pharmacokinetics in patients with fungal infections. No dosage adjustment is necessary for the elderly (see PRECAUTIONS, *Geriatric Use*).

Race

Regression analyses of patient pharmacokinetic data indicated that no clinically significant differences in the pharmacokinetics of caspofungin were seen among Caucasians, Blacks, **and** Hispanics. No dosage adjustment is necessary on the basis of race.

Renal Insufficiency

In a clinical study of single 70-mg doses, caspofungin pharmacokinetics were similar in volunteers with mild renal insufficiency (creatinine clearance 50 to 80 mL/min) and control subjects. Moderate (creatinine clearance 31 to 49 mL/min), advanced (creatinine clearance 5 to 30 mL/min), and end-stage (creatinine clearance <10 mL/min and dialysis dependent) renal insufficiency moderately increased caspofungin plasma concentrations after single-dose administration (range: 30 to 49% for AUC). However, in patients with invasive aspergillosis who received multiple daily doses of CANCIDAS 50 mg, there was no significant effect of mild to advanced renal impairment on caspofungin trough concentrations. No dosage adjustment is necessary for patients with renal insufficiency. Caspofungin is not dialyzable, thus supplementary dosing is not required following hemodialysis.

Hepatic Insufficiency

Plasma concentrations of caspofungin after a single 70-mg dose in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) were increased by approximately 55% **in AUC** compared

to healthy control subjects. In a 14-day multiple-dose study (70 mg on Day 1 followed by 50 mg daily thereafter), plasma concentrations in patients with mild hepatic insufficiency were increased modestly (19 to 25% **in AUC**) on Days 7 and 14 relative to healthy control subjects. No dosage adjustment is recommended for patients with mild hepatic insufficiency. Patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9) who received a single 70-mg dose of CANCIDAS had an average plasma caspofungin increase of 76% **in AUC** compared to control subjects. A dosage reduction is recommended for patients with moderate hepatic insufficiency (see DOSAGE AND ADMINISTRATION). There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9).

Pediatric Patients

CANCIDAS has not been adequately studied in patients under 18 years of age.

PRECAUTIONS

Drug Interactions

Studies *in vitro* show that caspofungin acetate is not an inhibitor of any enzyme in the cytochrome P450 (CYP) system. In clinical studies, caspofungin did not induce the CYP3A4 metabolism of other drugs. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes.

Clinical studies in healthy volunteers show that the pharmacokinetics of CANCIDAS are not altered by itraconazole, amphotericin B, mycophenolate, or tacrolimus. CANCIDAS has no effect on the pharmacokinetics of itraconazole, amphotericin B, or the active metabolite of mycophenolate. CANCIDAS reduced the blood AUC of tacrolimus (FK-506, Prograf ®) by approximately 20% **peak** blood concentration (C_{max}) by 16%, and 12-hour blood concentration (C_{12hr}) by 26% in healthy subjects when tacrolimus (2 doses of 0.1 mg/kg 12 hours apart) was administered on the 10th day of CANCIDAS 70 mg daily, as compared to results from a control period in which tacrolimus was administered alone. For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are recommended.

In two clinical studies, cyclosporin (one 4 mg/kg dose or two 3 mg/kg doses) increased the AUC of caspofungin by approximately 35%.

The results from regression analyses of patient pharmacokinetic data suggest that coadministration of inducers of drug clearance and/or mixed inducer/inhibitors with CANCIDAS may result in clinically meaningful reductions in caspofungin concentrations. This is based on results from a small number of patients who were administered the inducers and/or mixed inducer/inhibitors efavirenz, nelfinavir, nevirapine, phenytoin, rifampin, dexamethasone, or carbamazepine prior to and/or concomitant with caspofungin. There are presently no data from formal drug interaction studies to evaluate **regression analyses of patient pharmacokinetic data** and it is not known which drug clearance mechanism involved in caspofungin disposition may be inducible.

When coadministering CANCIDAS with efavirenz, nelfinavir, nevirapine, phenytoin, rifampin, dexamethasone, or carbamazepine, an increase in the daily dose of CANCIDAS to 70 mg, following the usual 70-mg loading dose, should be considered **in patients who are not clinically responding**.

Patients with Hepatic Insufficiency

Patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment. For patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), after the initial 70-mg loading dose, CANCIDAS 35 mg daily is recommended. There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Clinical studies of CANCIDAS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Although the number of elderly patients was not large enough for a statistical analysis, no overall differences in safety or efficacy were observed between these and younger patients. Plasma concentrations of caspofungin in healthy older men and women (65 years of age) were increased slightly (approximately 28% in AUC) compared to young healthy men. No dose adjustment is recommended for the elderly; however, greater sensitivity of some older individuals cannot be ruled out.

DOSAGE AND ADMINISTRATION

General Recommendations
A single 70-mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. CANCIDAS should be administered by slow IV infusion of approximately 1 hour. Duration of treatment should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. Do not mix or co-infuse CANCIDAS with other medications. DO NOT USE DILUENTS CONTAINING DEXTROSE (...-D-GLUCOSE).

[redacted]

Hepatic Insufficiency
Patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment. However, for patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), after the initial 70-mg loading dose, CANCIDAS 35 mg daily is recommended. There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9) (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Special Populations.*).

V. Recommendations

- **This submission (NDA 21-227) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and has been found to be acceptable for meeting the OCPB requirements.**
- **The Sponsor is requested to provide information on caspofungin trough concentrations in patients who will be taking caspofungin for extended periods.**
- **The Sponsor needs to address the potential interaction between caspofungin and mixed inhibitors/inducers such as efavirenz, nelfinavir, nevirapine, phenytoin, rifampin, dexamethasone, or carbamazepine so that appropriate dosing recommendations can be made with these drugs.**
- **The sponsor is requested to adopt the OCPB labeling as provided in this review.**

VI. Signatures

/S/

Houda Mahayni, R.Ph., Ph.D.
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics
FT/RD initialed by Funmi Ajayi, Ph.D., Team Leader /S/

CC: NDA 21-227 (orig., 1 copy), HFD-590(Navarro, Chan), HFD-880(Ajayi, Mahayni), Central Document Room
11/21/00

CP/B briefing (11/30/00) attendees: Larry Lesko, Jerry Collins, Hank Malinowski, John Lazor, Paul Hepp, Funmi Ajayi, Houda Mahayni, Robert Kumi, Joette Meyer, Rigo Roca, Owen McMaster, Dorota Matecka, Gene Holbert.

Pharmacometrics Review

NDA 21-227
Drug Name: CANCIDAS™ (caspofungin acetate) FOR INJECTION
Sponsor: Merck & Co., Inc.
Submission Date: 7/28/2000
Primary Reviewer: Houda Mahayni, Ph.D.
Pharmacometrics Scientist: Dan Wang, Ph.D.

SUMMARY

1. Pharmacokinetics ($AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, $C_{24\ hr}$) and Clinical Outcome Relationships

a. Oropharyngeal and esophageal candidiasis (Reference 19 - Protocols 003, 004 and 007)

Three dose levels (35, 50 and 70 mg) were studied. $C_{24\ hr}$ was found to be a significant predictor for clinical outcome (p=0.0226), while $AUC_{0\text{-}24\ hr}$ is marginally significant (p=0.057). $C_{1\ hr}$ was not a significant predictor. The breakpoint obtained for $C_{24\ hr}$ using tree regression was 1.4 μg/mL (Figure A) in contrast to 1.0 μg/mL from *in vitro* data.

Figure A

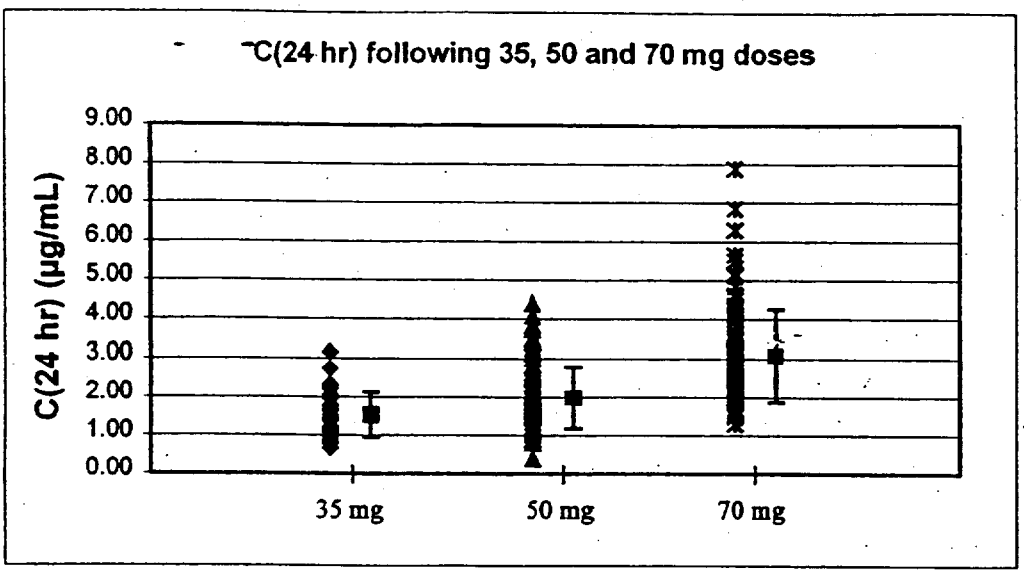
Probability of favorable clinical outcome (Tree regression)

The average $C_{24\ hr}$ observed in candidiasis patients is 2.06 μg/mL. Based on the breakpoint of 1.4 μg/mL, a reduction of more than 30% in $C_{24\ hr}$ will cause significant decrease in favorable clinical outcome. This result is consistent with the statistical analysis result summarized below.

The pharmacokinetic data showed that the geometric mean estimates for $AUC_{0\text{-}24\ hr}$ and $C_{24\ hr}$ in patients are ~30% lower for the 35-mg dose than for the 50 mg dose. In the dose-ranging efficacy study (Protocol 004), doses of 35, 50, and 70 mg were effective in the treatment of esophageal and oropharyngeal candidiasis. Numerically, but not statistically, 50 and 70 mg doses were associated with a greater proportion of patients with a favorable outcome than the 35 mg dose. In the primary modified-intention-to-treat (MITT) analysis, 73.5% of patients receiving 35 mg had a favorable overall outcome, while 91.2% and 82.9% of patients receiving 50 and 70 mg, respectively, had a favorable outcome. This argues that the lower bound of the interval defining a clinically significant change in AUC0-24 hr or C24 hr should be 0.7.

$C_{24\ hr}$ values at different dose levels are shown in Figure B.

Figure B

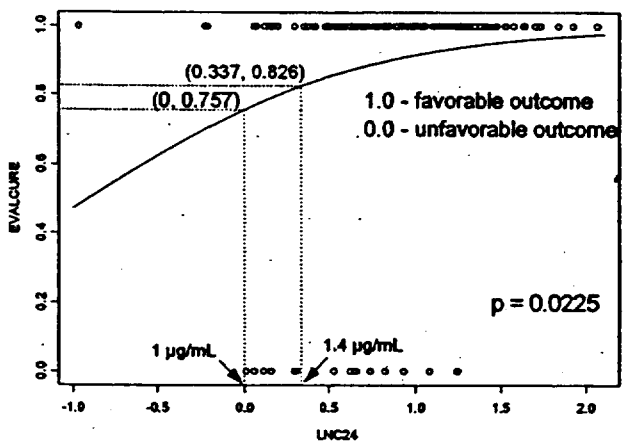


It is observed from Figure B that percentage of $C_{24\ hr}$ less than 1.4 µg/mL following 35 mg dose is more than the other two dosing groups.

Based on the above analyses, the $C_{24\ hr}$ greater than 1.4 µg/mL should be targeted rather than 1.0 µg/mL for localized candidiasis.

Figure C shows the probability of favorable clinical outcome as a function of $C_{24\ hr}$.

Figure C



Although candidiasis is not the intended indication for this submission, this study served as proof of concept. This is particularly important when the study for the intended indication has a low successful rate (<50%) because of severity of the disease and other complicated factors. This study also established concentration-response relationship in localized candidiasis patients, which provided the basis for dose adjustment if the application for candidiasis indication is submitted in the future.

b. Aspergillosis (Reference 20 - Protocol 019)

The 70 mg loading dose with 50 mg daily dose were studied. Only $C_{1\ hr}$ and $C_{24\ hr}$ were measured in this study. Neither $C_{1\ hr}$ nor $C_{24\ hr}$ was found to be a significant factor for predicting treatment outcome within the range of pharmacokinetic parameter values available. It should be noted that unlike the studies for candidiasis indication, only one dose was studied for aspergillosis indication, which may not be able to provide the concentration range that is wide enough to establish the concentration-response relationship.

2. Pharmacokinetics ($AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, $C_{24\ hr}$) and Adverse Event Relationships

With the possible exception of nausea, the occurrence of adverse experiences or laboratory abnormalities examined in this analysis is not increased by higher MK-0991 plasma concentrations over the range of pharmacokinetic parameters observed. $AUC_{0\text{-}24\ hr}$ is marginally significant ($p = 0.078$) predictor of nausea in one analysis but in the other. Although the odds ratio was high for both studies, the reviewer believes that no conclusion can be made from the data available.

3. Covariates as a Predictor of Patient Pharmacokinetics

a. Weight

Body weight was found to be a covariate for $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$ and $C_{24\ hr}$ in Reference 19 and for $C_{1\ hr}$ but not for $C_{24\ hr}$ in Reference 20. The results of the analysis comparing a patient /subject weighing 50 kg relative to a patient/subject weighing 70 kg in different patient population and in healthy subjects are summarized in the table below.

Population	Geometric Mean Ratio (95% Confidence Interval)		
	$AUC_{0\text{-}24\ hr}$	$C_{1\ hr}$	$C_{24\ hr}$
Candidiasis	1.29 (1.17, 1.43)	1.20 (1.10, 1.30)	1.29 (1.14, 1.45)
Aspergillosis	NA[1]	1.36 (1.18, 1.56)	NS[2]
Healthy Subjects	1.11 (1.02, 1.21)	1.14 (1.07, 1.21)	NS

[1]Not available
[2]Not significant

b. Gender

Gender effect was not consistent among the two patient populations. For candidiasis patients, on average $AUC_{0\text{-}24\ hr}$ and $C_{1\ hr}$ were increased 17% in women relative to men

but different was not significant for $C_{24\ hr}$. For aspergillosis patients, gender was a significant covariate for $C_{24\ hr}$ but not $C_{1\ hr}$. On average, $C_{24\ hr}$ was increased 38% in women relative to men. No information is available for healthy subjects regarding gender effect.

c. Serum albumin level

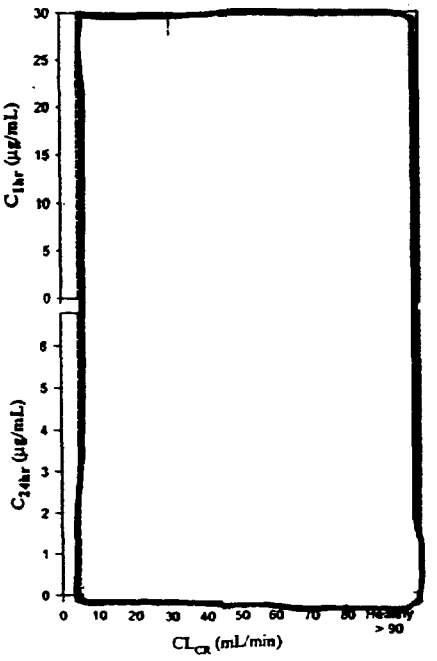
Serum albumin level was a significant determinant of $C_{1\ hr}$ but not $AUC_{0\text{-}24\ hr}$ and $C_{1\ hr}$ in candidiasis patients. The ratio (95% CI) of $C_{1\ hr}$ in a patient with serum albumin of 3.5 g/dL relative to a patient with serum albumin of 5.0 g/dL is predicted to be 0.87 (0.76, 0.98). The 13% decrease in $C_{1\ hr}$ does not warrant a dose adjustment based on serum albumin level.

d. Renal Status

Renal status was a significant determinant of $C_{1\ hr}$ but not $C_{24\ hr}$ in aspergillosis patients. On average, $C_{1\ hr}$ is 31% elevated in patients with mild renal insufficiency and 54% elevated in patients with moderate renal insufficiency relative to patients with normal renal function. Inconsistent with the results in mild and moderate renal insufficiency, $C_{1\ hr}$ in patients with advanced renal insufficiency was not statistically significantly different from that in patients with normal renal function. One would have expected a pharmacokinetic effect of renal insufficiency to be more pronounced in more severe disease rather than less. A scattergram of individual pharmacokinetic values versus creatinine clearance is shown in the figure on next page.

These scattergrams suggest that pharmacokinetic variability is increased in patients with renal insufficiency relative to patients with normal renal function. A few high values in the mild and moderate patients appear to be driving much of the distinction found between these groups and normal patients. The lower end of the range of individual parameter values does not appear to vary much with renal status, particularly for $C_{1\ hr}$.

Scattergrams of Individual Pharmacokinetic Values
Versus Renal Status in Patients in Protocol 019



4. Concomitant Medications

The analysis for the effect of concomitant medications on MK-0991 pharmacokinetics was more for screening for unanticipated drug interactions than quantifying the effect of drug interactions. Patients in these analyses received many concomitant medications. No adjustments for multiplicity were made in this exploratory analysis.

Several drugs and drug classes were found to have significant effect on MK-0991 PK based on this analysis. The results of the analysis can be found in this review. The pharmacometrics reviewer leaves the primary reviewer to interpret the results of these analyses along with other traditional drug interaction studies.

5. Comparison of Pharmacokinetics in Patients and Healthy Subjects

On average, there is a trend of decrease in $C_{1\ hr}$ and increase in $C_{24\ hr}$ in patients relative to healthy subjects.

On Day 1, $C_{1\ hr}$ was reduced 19% and $C_{24\ hr}$ increased 39% on average in patients with localized candidiasis relative to healthy subjects. $C_{1\ hr}$ was reduced 26% in patients with aspergillosis, while $C_{24\ hr}$ increased 13% although not statistically significant.

Following multiple dose, only $C_{1\ hr}$ had a statistically significant reduction in patients with localized candidiasis and aspergillosis (17% and 19%, respectively) compared to healthy subjects. Although not statistically significant, there was a 16% and 23% increase in average $C_{24\ hr}$ in patients with localized candidiasis and aspergillosis, respectively.

Summary of review of Studies Reference 19 and 20 (Reference 19 - Population pharmacokinetics and pharmacodynamics of MK–0991 in phase II patients with oropharyngeal and esophageal candidiasis (Protocols 003, 004, and 007), Reference 20 - Population pharmacokinetics and pharmacodynamics of MK–0991 in phase II patients with aspergillosis (Protocol 019))

Objectives – the objectives of this PK/PD analysis was 1) to investigate the relationship between MK-0991 pharmacokinetics and both treatment outcome and the occurrence of adverse experiences in different patient populations; 2) to investigate the effect of patient characteristics (covariates) on MK-0991 pharmacokinetics in patient population; 3) to screen for unanticipated drug interactions; and 4) to characterize MK-0991 pharmacokinetics in patients and compare to pharmacokinetics in healthy subjects.

Study Design - Patients with *Candida* esophagitis and/or oropharyngitis receiving daily 1-hour, constant-rate, intravenous (I.V.) infusions of 35, 50, or 70 mg MK-0991 in three Phase II studies (Protocols 003, 004, and 007). Patients with invasive aspergillosis receiving 50 mg MK-0991 daily with a 70-mg loading dose administered on Day 1 in a Phase II study (Protocol 019). The pharmacokinetic data in patients obtained through trough sampling in Protocol 003 on Days 7, 10, and 13, 5-point plasma profile sampling in Protocol 004 (predose, 1, 2, 4-6, and 24 hours on Days 1 and 6 or 9, 1 to 2 additional trough samples, and a washout sample obtained during the 3- to 4-day follow-up visit), and extensive profile sampling in Protocol 007 (predose, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 8, 12, and 24 hours were obtained on Days 1, 9, and 14 were pooled in the analysis). Additional trough samples were obtained predose on Days 4, 7, 12, and 13 and a washout sample was obtained at the 3- to 4-day follow-up visit. In Protocol 019, a series of predose and end-of-infusion plasma samples for MK-0991 assay were obtained on Days 1, 2, 4, 7, 14, 28, and every two weeks thereafter while on MK-0991.

Pharmacokinetic Analysis - Analyses were conducted using the two-step method. Individual pharmacokinetic parameters were first determined for each patient, and then statistical models were used to evaluate the relationships between those parameters and various pharmacodynamic measures or patient covariates. The pharmacokinetic analysis method used by the sponsor is acceptable. The pharmacokinetic parameters used in the population pharmacokinetic analysis were $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, and $C_{24\ hr}$ on Day 1 and time averaged over the period Day 3 to Day 14. The time-averaged parameters in a given patient were determined as the geometric mean of all values obtained between Days 3 and 14. Time-averaged parameters were calculated because the study days on which pharmacokinetics sampling was performed differed somewhat between Protocols 003, 004, and 007, and among the patients enrolled in Protocol 019. By determining the time-averaged parameter valued over a period in which the parameters were expected to be reasonably stable, a common parameter for three studies was obtained.

Statistic analysis - Parameters on Day 1 were only analyzed in the comparison of the pharmacokinetics of healthy subjects to patients with *Candida* infections. All pharmacokinetic parameters were natural log-transformed prior to analysis, and all tests were two-sided and assumed a significance level of α of 0.05.

The first statistical analysis examined the effect of patient pharmacokinetics on treatment outcome. Treatment outcome was defined as a favorable or unfavorable overall response in evaluable patients at the end of I.V. therapy. Since the dependent variable for this analysis was binary and the independent variable was a continuous pharmacokinetic parameter, a univariate logistic regression model was constructed for each time-averaged parameter. An odds ratio (95% confidence interval (CI)) measuring the association between the log-transformed pharmacokinetic parameter and treatment outcome was determined from each model. More specifically, this was interpreted as the change in odds for a successful treatment outcome per 2.72-fold change in the pharmacokinetic parameter on the original scale (since a change of one unit on the natural log scale back-transforms to a fold change of e=2.72 on the original scale). Identical methods were used to analyze the effect of MK-0991 pharmacokinetics on clinically important adverse experiences or laboratory abnormalities.

Covariates effects on MK-0991 population pharmacokinetics was examined using linear regression. Because more than one dose of MK-0991 was evaluated in Protocols 003, 004, and 007, dose was also included as a factor in each regression model. Regarding the interpretability of the parameters from each regression, if the covariate was quantitative, then the estimate and 95% CI for the regression coefficient β_1 was reported. The coefficient β_1 was determined from the regression model as follows,

$$\ln(y) = \beta_0 + \beta_1 x,$$

where ln (y) is the natural log-transformed pharmacokinetic parameter of interest and x is the continuous covariate. The expected change in the pharmacokinetic parameter on the original scale for two covariate values of interest (e.g., x2-x1) could then be determined from the regression model as follows,

$$\ln(y_2) - \ln(y_1) = \ln\left(\frac{y_2}{y_1}\right) = \beta_1(x_2 - x_1).$$

Thus, exponentiating both sides, the following ratio is obtained:

$$\frac{y_2}{y_1} = \exp(\beta_1(x_2 - x_1)).$$

Ninety-five percent (95%) CIs for this ratio could then be obtained by performing the same calculation on the limits of the 95% CI for the regression coefficient, β_1. If the covariate was qualitative, then geometric mean ratios (95% CIs) for each level of the covariate versus all other levels of the covariate (e.g., Females/Males or Blacks/Non-Blacks) were determined from the least square means of the statistical model. After the analysis of each covariate separately, those variables of clinical and statistical significance were then used to construct a more extensive multiple regression model. It was decided *a priori* that a concomitant medication would be analyzed only if five or more patients in Protocols 003, 004, 007 and 019 received the medication for 90-100% of the time while on I.V. therapy.

Patient pharmacokinetics was compared with the pharmacokinetics of healthy subjects from Protocols 002, 008, 013, 016, 017, 021, and 023. A linear model with factors for patient status (healthy subject, patient), dose, gender, weight, and dose by status interaction was used for this analysis; gender and weight were identified and included due to the results of the patient covariate analysis. Differences in least square means from this model for the effect of status were then back-transformed to obtain geometric mean ratios to compare the pharmacokinetics of healthy subjects to the pharmacokinetics of patients averaging over all doses as well as for each dose; p-values from this model were also presented.

Results

1. Pharmacokinetics

Summary statistics describing the pharmacokinetic results in the three local candidiasis studies (Ref. 19) and one aspergillosis study (Ref. 20) are provided in Tables 1 and 2, respectively.

Table 1. Cross-Study Comparison of Plasma Pharmacokinetics of MK-0991 Following Daily 1-Hour Infusions to Patients with Localized Candidiasis

Dose (mg/day)	Protocol	N	$AUC_{(0\text{-}24\ hr)}$† (µg·hr/mL)	$C_{1\ hr}$† (µg/mL)	$C_{24\ hr}$† (µg/mL)
35	004	28	80.31 (22.10)	7.45 (1.64)	1.65 (0.57)
50	003	22	-	-	2.19 (0.95)
	004	32	111.49 (30.58)	9.87 (2.37)	2.26 (0.81)
	007	6	86.74 (23.80)	8.63 (1.77)	1.72 (0.64)
70	003	20	-	-	3.89 (1.41)
	004	31	155.90 (36.21)	13.42 (2.71)	3.16 (0.58)
	007	6	176.62 (75.19)	14.64 (3.61)	4.40 (2.33)

† Time average of all values obtained between Days 3 and 14. Summary statistics reported are arithmetic means (standard deviation).

Table 2. Pharmacokinetics of MK-0991 in patients with aspergillosis (Protocol 019)

Dose	Day 1		Day 3 – 14		Day 3+	
	C_{1hr} (µg/mL) (N = 48)	$C_{24\ hr}$ (µg/mL) (N = 20)	C_{1hr} (µg/mL) (N = 49)	$C_{24\ hr}$ (µg/mL) (N = 51)	C_{1hr} (µg/mL) (N = 50)	$C_{24\ hr}$ (µg/mL) (N = 51)
70 mg loading dose, 50 mg daily dose	10.16 (5.14)	1.81 (0.91)	9.68 (4.60)	2.25 (1.19)	9.82 (4.19)	2.33 (1.20)

The pharmacokinetic parameters ($C_{1\ hr}$ and $C_{24\ hr}$) appear to be similar across all 4 studies. For most patients in Protocol 019, steady-state was achieved with the first dose (70 mg loading dose plus 50 mg daily dose) and were maintained thereafter throughout therapy.

2. Patient Pharmacokinetics as a Predictor of Treatment Outcome

1) Reference 19 (protocol 003, 004 and 007, patients with oropharyngeal and esophageal candidiasis)

Table 3 contains summary statistics from the logistic regression model of patient pharmacokinetics as a predictor of overall treatment outcome in evaluable patients at the end of I.V. therapy. The definition of a favorable overall outcome included assessment of both endoscopic response and symptomatic response. Pharmacokinetic data were log-transformed prior to regression analysis.

Table 3

Potential for Patient Pharmacokinetic Parameters (Log-Transformed) to Predict Favorable Treatment Outcome at the End of I.V. Therapy in Evaluable Patients with Localized Candidiasis

Parameter	N Favorable Outcome	N Total	Odds Ratio (95% CI)[†]	p-value
$AUC_{0\text{-}24\ hr}$ (μg•hr/mL)	86	99	4.67 (0.90, 24.23)	0.067
$C_{1\ hr}$ (μg/mL)	86	99	1.83 (0.32, 10.58)	0.501
$C_{24\ hr}$ (μg/mL)	126	142	3.48 (1.16, 10.42)	0.026

[†] Change in odds for a successful treatment outcome per unit increase (on the log scale) in pharmacokinetic parameters.

The histogram of the PK parameters indicated that $AUC_{0\text{-}24\ hr}$ and $C_{24\ hr}$ follow lognormal distribution, while $C_{1\ hr}$ follows normal distribution. Therefore, C1 hr data were re-analyzed by the reviewer using unlog-transformed data. The p-value for C_{1hr} was 0.462.

The results of the analysis suggest that $C_{24\ hr}$ is the only significant predictor for the clinical outcome, while $AUC_{0\text{-}24\ hr}$ is marginally significant. The odds ratios are interpreted as the change in odds for a successful treatment outcome per unit change in these pharmacokinetic parameters. For instance, for every unit increase (on the log scale) of$C_{24\ hr}$ based on the analysis in Table 3, the chance of a positive treatment outcome increases 3.48 times.

Scattergrams comparing the individual pharmacokinetic data in patients with favorable versus unfavorable treatment outcome are provided in Figure 1. Figure 2 illustrates the trend in treatment outcome versus $C_{24\ hr}$ and $AUC_{0\text{-}24}$ hr identified by the analysis.

In Figure 2, the sponsor used $C_{24\ hr}$ of 1.5 μg/mL and $AUC_{0\text{-}24\ hr}$ of 75 μg.hr/mL as breakpoints. No explanation of how were these values selected. The reviewer thus conducted a tree regression analysis. The results are summarized in the Figure 3. The breakpoints were found to be 1.4 μg/mL and 70.4 μg.hr/mL for $C_{24\ hr}$ and $AUC_{0\text{-}24\ hr}$, respectively.

Figure 4. Probability of favorable clinical outcome vs. Ln($C_{24\ hr}$)

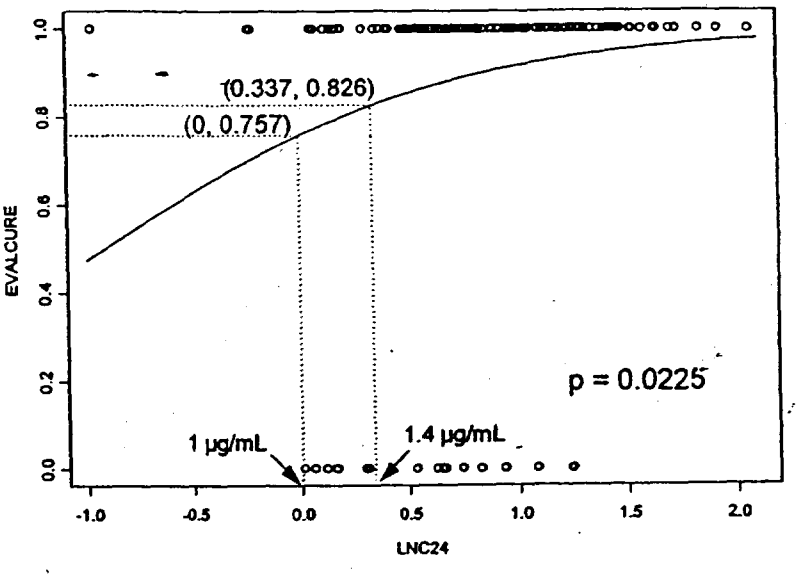
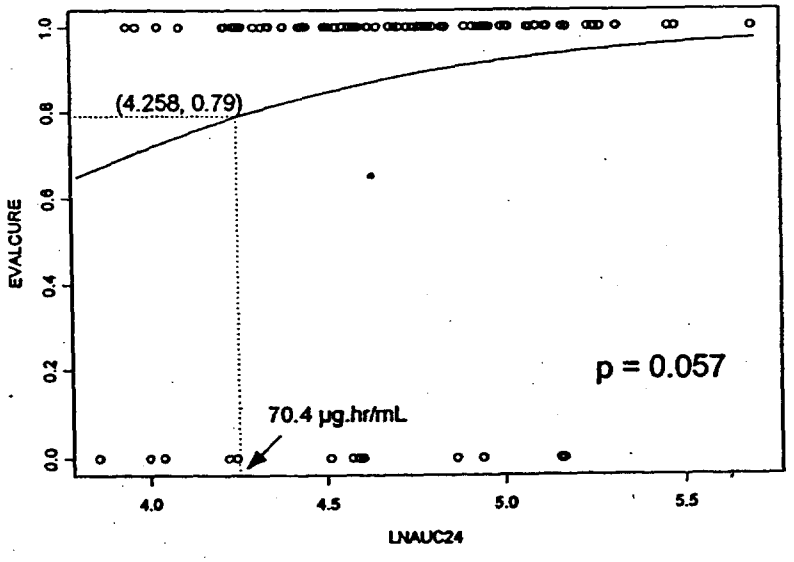


Figure 5. Probability of favorable clinical outcome vs. Ln($AUC_{0\text{-}24\ hr}$)



It is shown from Figure 4 that the favorable clinical outcome rate at 1.0 µg/mL, the breakpoint obtained from *in vitro* data, is about 76%, and at 1.4 µg/mL, the breakpoint obtained from *in vivo* data, is about 83%. During the internal discussion, the medical officer indicated that 1.4 µg/mL might be a better breakpoint that could be used in dose adjustment for the indication studied.

2) Reference 20 (Protocol 019, patients with aspergillosis)

Table 5 contains summary statistics from the logistic regression model of time averaged patient pharmacokinetics (Day 3 to end of IV therapy) as a predictor of overall treatment outcome in evaluable patients at the end of I.V. therapy. A favorable overall outcome included both complete and partial responses, as defined by resolution or clinically meaningful improvement, respectively, of attributable symptoms, signs, and radiographic or bronchoscopic abnormalities, if present at enrollment.

Table 5

Potential for Patient Pharmacokinetic Parameters (Log-transformed) to Predict Favorable Treatment Outcome at the End of I.V. Therapy in Evaluable Patients with Aspergillosis

Parameter†	N Favorable Outcome	N Total	Odds Ratio (95% CI)‡	p-value
$C_{1\ hr}$ (µg/mL)	24	48	0.52 (0.11, 2.34)	0.392
$C_{24\ hr}$ (µg/mL)	24	51	1.09 (0.36, 3.27)	0.882

† Time averaged (Day 3 to end of I.V. therapy).
‡ Change in odds for a successful treatment outcome per unit increase (on the log scale) in pharmacokinetic parameters.

Neither $C_{1\ hr}$ nor $C_{24\ hr}$ was found to be a significant factor for predicting treatment outcome within the range of pharmacokinetic parameter values available. Scattergrams comparing the individual pharmacokinetic data in patients with favorable versus unfavorable treatment outcome are provided in Figure 6.

Figure 6

Scattergrams of Individual MK-0991 Pharmacokinetic Values in Patients in Protocol 019 with Favorable and Unfavorable Treatment Outcomes

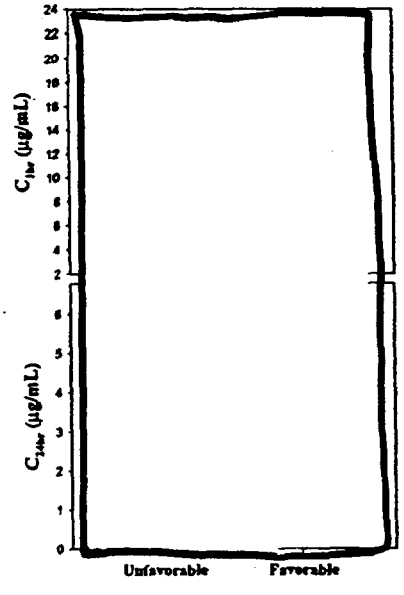
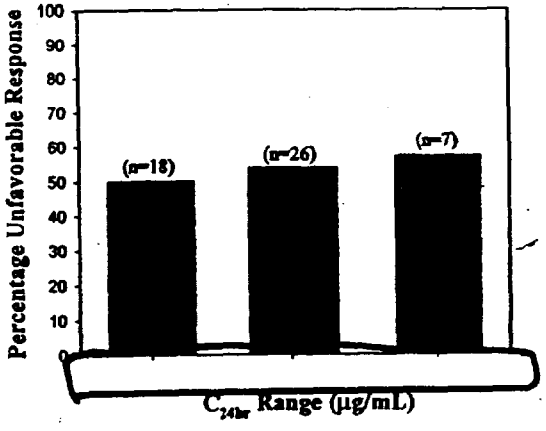


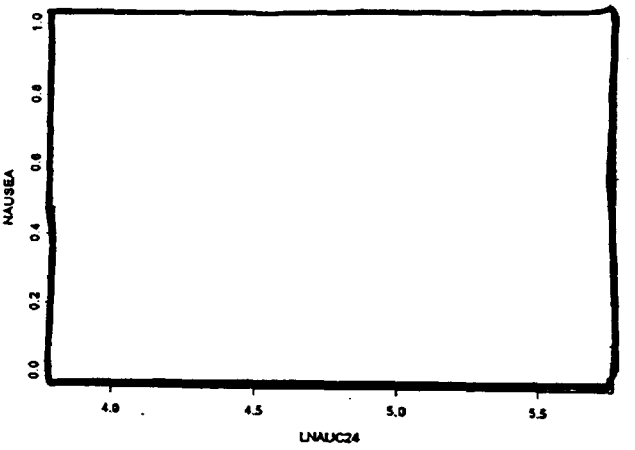
Figure 7

Percentage of Unfavorable Responses Versus $C_{24\ hr}$ in *Aspergillus* Patients in Protocols 019



of the occurrence of these adverse experiences. The reviewer reanalyzed the data for Reference 19 in which $AUC_{0\text{-}24\ hr}$ was marginally significant. The result of the analysis is shown in Figure 8. The p-value obtained from this analysis is a little different from the sponsor's.

Figure 8



Over all, the results suggest that, with the possible exception of nausea, the occurrence of adverse experiences or laboratory abnormalities examined in this analysis is not increased by higher MK-0991 plasma concentrations over the range of pharmacokinetic parameters observed.

4. Covariates as a Predictor of Patient Pharmacokinetics

Reference 19 (Protocol 003, 004 and 005)

A combination of univariate and multiple regression approaches was used to identify patient characteristics that were significantly correlated with pharmacokinetics. Dose was adjusted for in all analyses. Table 8 lists the covariates included in the initial univariate analysis. P-values less than 0.05 were obtained for weight, creatinine clearance, serum albumin level, and gender for at least one pharmacokinetic parameter.

On the basis of the univariate assessment, weight, creatinine clearance, serum albumin level, and gender were examined in a second step involving development of a multiple linear regression model which accounted for the effect of each covariate, as well as dose, within the same model. From the set of covariates included, stepwise (backward) regression was used to construct the final multiple regression model. Covariates found not to be a significant determinant of the pharmacokinetic parameter of interest were eliminated from the model in a stepwise fashion such that the final model consisted solely of covari-ates demonstrated to be significant in the mulitple regression model. Table 9 presents the results of the final multiple linear regression model. Weight, gender, and albumin level were the only covariates found to be significant determinants of one or more of the MK-0991 pharmacokinetic parameters analyzed.

Table 8

Listing of Covariates Examined in Univariate Analysis

Covariate	Covariate Range† or Comparison	Median or N_1/N_2‡
<u>Continuous</u>		
Age		34.0 years
Weight		55.0 kg
BMI		20.1 kg/m^2
CD4 Count		33.0 mm^{-3}
Creatinine C		87.8 mL/min
Serum Albumin		3.7 g/dL
<u>Categorical</u>		
Gender	Female/Male	32/113
Race	Asian/Non-Asian	1/144
	Black/Non-Black	16/129
	Caucasian/Non-Caucasian	30/115
	Hispanic/Non-Hispanic	61/84
	Mestizo/Non-Mestizo	36/109
	Other/Non-Other	1/144
HIV Status	Positive/Negative	130/15

† Covariate range for $C_{24\ hr}$ provided, range may be smaller for AUC or $C_{1\ hr}$ (see Appendix K, Table K-4).
‡ Median and N_1/N_2 for $C_{24\ hr}$ provided, values may differ slightly for AUC or $C_{1\ hr}$ (see Appendix K, Tables K-3 and K-4).
BMI = body mass index.

Table 9

Potential for Covariates to Predict Patient Pharmacokinetics (Multiple Regression Analysis)

Parameter†	Covariate	Covariate Range/ Comparison	Median	N_1/N_2	β_1 Estimate (95% CI) GMR (95% CI)‡	p-value
$AUC_{0\text{-}24\ hr}$ (µg-hr/mL)	Weight		55.0	101	-0.0113 (-0.0162, -0.0063)	<0.001
	Gender	Female/Male	-	22/79	1.17 (1.04, 1.33)	0.011
	Dose	35 mg/70 mg	-	28/35	0.47 (0.41, 0.53)	<0.001
		50 mg/70 mg	-	38/35	0.67 (0.60, 0.75)	<0.001
$C_{1\ hr}$ (µg/mL)	Weight		55.0	101	-0.0064 (-0.0107, -0.0020)	0.005
	Gender	Female/Male	-	23/78	1.17 (1.06, 1.30)	0.003
	Albumin	2.1 to 5.0 g/dL	3.9	101	0.0846 (0.0052, 0.1641)	0.037
	Dose	35 mg/70 mg	-	28/35	0.52 (0.47, 0.58)	<0.001
		50 mg/70 mg	-	38/35	0.70 (0.64, 0.77)	<0.001
$C_{24\ hr}$ (µg/mL)	Weight		34.0	144	-0.0127 (-0.0187, -0.0067)	<0.001
	Dose	35 mg/70 mg	-	28/56	0.46 (0.39, 0.54)	<0.001
		50 mg/70 mg	-	60/56	0.61 (0.54, 0.70)	<0.001

† Time averaged (Day 3 to Day 14).
‡ Geometric mean ratio of the comparison is provided if the covariate is categorical. The estimate (95% CI) of the slope (β_1 in Section IV.D.) of the linear relationship between the covariate and the log-transformed pharmacokinetic parameter is provided if the covariate is continuous.

Weight was found to be a statistically significant determinant of $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, and $C_{24\ hr}$. Because this covariate was continuous, the analysis determined an estimate (95% CI) for β_1, the slope of the linear relationship between the covariate and log-transform pharmacokinetic parameter of interest. Based on the statistical model, the current analysis

predicts that the ratio (95% CI) of $AUC_{0\text{-}24\ hr}$, $C_{1\ hr}$, and $C_{24\ hr}$ in a patient weighing 50 kg relative to a patient weighing 70 kg would be 1.29 (1.17, 1.43), 1.20 (1.10, 1.30), and 1.29 (1.14, 1.45), respectively. Variability of PK parameters was higher in lighter patients relative to heavier patients. The analysis of healthy subject's data showed that weight was a significant determinant of $AUC_{0\text{-}24\ hr}$ and $C_{1\ hr}$, but not $C_{24\ hr}$. Based on the β_1 estimate obtained from the statistical model, the ratio (95% CI) of $AUC_{0\text{-}24\ hr}$ and $C_{1\ hr}$ in a subject weighing 70 kg relative to a subject weighing 90 kg is predicted to be 1.11 (1.02, 1.21) and 1.14 (1.07, 1.21), respectively.

Gender was a significant covariate for $AUC_{0\text{-}24\ hr}$ and $C_{1\ hr}$, but not $C_{24\ hr}$. On average $AUC_{0\text{-}24\ hr}$ and $C_{1\ hr}$ were increased 17% in women relative to men. Gender analysis for healthy subjects is not available because there was one female in the study.

Serum albumin level was a significant determinant of $C_{1\ hr}$, but not $AUC_{0\text{-}24\ hr}$ and $C_{24\ hr}$. Based on the β_1 estimate obtained from the statistical model, the ratio (95% CI) of $C_{1\ hr}$ in a patient with serum albumin of 3.5 g/dL relative to a patient with serum albumin of 5.0 g/dL is predicted to be 0.87 (0.76, 0.98).

Dose proportionality was observed in the patient population studied.

Reference 20 (Protocol 019)

Same covariate analyses were conducted for Protocol 019. The results of multiple regression analysis were listed in Table 10.

Table 10

Potential for Covariates to Predict Patient Pharmacokinetics
(Multiple Regression Analysis)

Parameter†	Covariate	Covariate Range/ Comparison	Median	N_1/N_2	β_1 Estimate (95% CI)/ GMR (95% CI)‡	p-value
$C_{1\ hr}$ (μg/mL)	Weight	[redacted]	66.8	49	-0.0152 (-0.0221, -0.0083)	<0.001
	Renal Status	Mild RI/Normal	–	14/16	1.31 (1.00, 1.73)	0.050
		Moderate RI/Normal	–	9/16	1.54 (1.13, 2.10)	0.008
		Advanced RI/Normal	–	10/16	1.24 (0.92, 1.68)	0.156
$C_{24\ hr}$ (μg/mL)	Gender	Female/Male	–	20/31	1.38 (1.04, 1.82)	0.024

† Time averaged (Day 3 to Day 14).
‡ Geometric mean ratio of the comparison is provided if the covariate is categorical;, the estimate (95% CI) of the slope (β_1 in Section IV.D.) of the linear relationship between the covariate and the log-transformed pharmacokinetic parameter are provided if the covariate is continuous.
RI = renal insufficiency.

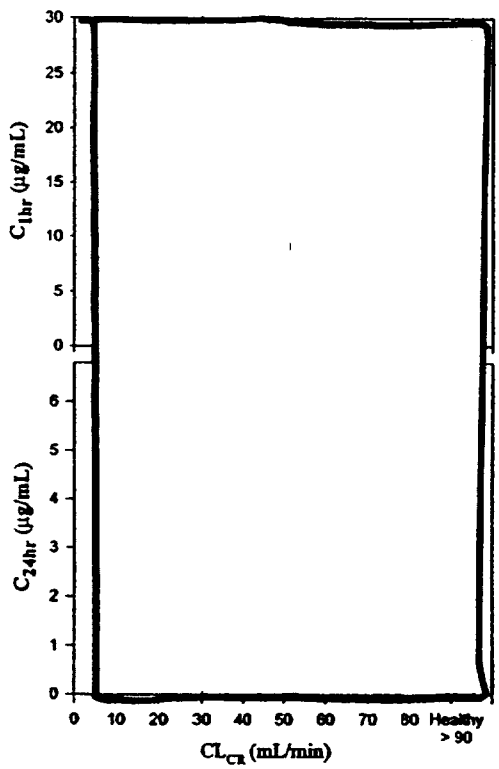
Weight, gender, and renal status were the only covariates found to be statistically significant determinants of $C_{1\ hr}$ or $C_{24\ hr}$. Weight was found to be a significant determinant of $C_{1\ hr}$ but not $C_{24\ hr}$. The ratio (95% CI) of average $C_{1\ hr}$ in a patient weighing 50 kg relative to a patient weighing 70 kg would be 1.36 (1.18, 1.56).

Gender was a significant covariate for $C_{24\ hr}$ but not $C_{1\ hr}$. On average, $C_{24\ hr}$ was increased 38% in women relative to men.

Renal status was a significant determinant of $C_{1\ hr}$ but not $C_{24\ hr}$. In this categorical analysis, patients were grouped into four classifications (normal function and mild, moderate, and advanced renal insufficiency) based on their creatinine clearances, which were estimated by the [redacted] method. The results indicate that, on average, $C_{1\ hr}$ is 31% elevated in patients with mild renal insufficiency and 54% elevated in patients with moderate renal insufficiency relative to patients with normal renal function. Inconsistent with the results in mild and moderate renal insufficiency, $C_{1\ hr}$ in patients with advanced renal insufficiency was not statistically significantly different from that in patients with normal renal function. One would have expected a pharmacokinetic effect of renal insufficiency to be more pronounced in more severe disease rather than less. A scattergram of individual pharmacokinetic values versus creatinine clearance is shown in Figure 9.

Figure 9

Scattergrams of Individual Pharmacokinetic Values Versus Renal Status in Patients in Protocol 019



These scattergrams suggest that pharmacokinetic variability is increased in patients with renal insufficiency relative to patients with normal renal function. A few high values in the mild and moderate patients appear to be driving much of the distinction found between these groups and normal patients. The lower end of the range of individual parameter values does not appear to vary much with renal status, particularly for $C_{1\ hr}$.

5. Concomitant Medications

Screening for unanticipated drug interactions was conducted for both studies. Due to the severity of the underlying diseases in most patients, as well as their fungal infections, patients in these analyses received many concomitant medications. Concomitant medications or grouped classes of medications, such as CYP3A4 inhibitors or protease inhibitors, were included in the analyses if pharmacokinetic data were available in at least five individuals receiving the drug or class throughout MK-0991 therapy. No adjustments for multiplicity were made in this exploratory analysis. Therefore, significant p-values found in this context are guides to generate hypotheses for possible meaningful drug interactions and should not be interpreted in isolation as an indication of a true drug interaction or lack of interaction. Overlapping administration of the various concomitant medications confounds clear interpretation of the results. Additional factors, such as underlying conditions and differences in the general health of the patients, are likely to be correlated with the use of certain drugs and thus may also confound interpretation.

The results of the drug interaction analyses for Reference 19 are provided in Table 11, Table 12, and Table 13; and in Table 14 and 15 for Reference 20.

The pharmacometrics reviewer leaves the primary reviewer to interpret the results of these analyses along with other traditional drug interaction studies.

Table 11. (Reference 19)

Effect of Concomitant Medications on $AUC_{(0\text{-}24\ hr)}$

Concomitant Medication	N with ≥ 90% Coverage	N Total	GMR (95% CI)[1]	p-value
Azithromycin	8	100	0.86 (0.70, 1.05)	0.144
Clarithromycin	6	99	0.87 (0.69, 1.10)	0.246
Dapsone	8	101	0.88 (0.71, 1.08)	0.206
Ethambutol	7	100	0.77 (0.62, 0.95)	0.017
Isoniazid	22	99	0.92 (0.81, 1.05)	0.226
Prior Isoniazid[2]	21	99	0.93 (0.81, 1.06)	0.260
Acyclovir	6	98	0.89 (0.71, 1.12)	0.323
Ganciclovir	5	101	0.85 (0.66, 1.10)	0.225
Didanosine	5	98	0.95 (0.74, 1.22)	0.698
Zalcitabine	5	101	0.93 (0.72, 1.20)	0.559
Zidovudine	10	100	1.02 (0.85, 1.22)	0.833
Lamivudine	13	98	0.87 (0.74, 1.02)	0.085
Stavudine	10	98	0.73 (0.61, 0.87)	<0.001
Indinavir	8	99	0.80 (0.63, 1.00)	0.054
Nelfinavir	8	100	0.73 (0.60, 0.88)	0.002
Acetaminophen	16	84	0.82 (0.72, 0.94)	0.005
Albuterol	5	98	0.90 (0.70, 1.16)	0.410
CYP3A4 Inhibitor	14	97	0.74 (0.63, 0.86)	<0.001
Prior Inducer[3]	5	97	0.68 (0.54, 0.86)	0.002

[1] GMR = geometric mean ratio (≥90% coverage/no coverage).
[2] Use during the 14 days preceding MK-0991 therapy.
[3] Inducer included in analysis with n=4, due to the large effect obtained with prior inducers.

Table 12 (Reference 19)

Effect of Concomitant Medications on $C_{1\,hr}$

Concomitant Medication	N with ≥ 90% Coverage	N Total	GMR (95% CI)[†]	p-value
Azithromycin	8	100	0.96 (0.81, 1.14)	0.638
Clarithromycin	6	100	0.99 (0.82, 1.21)	0.960
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dapsone	8	101	0.95 (0.80, 1.13)	0.551
Ethambutol	7	100	0.89 (0.74, 1.07)	0.210
Isoniazid	22	99	0.90 (0.80, 1.00)	0.049
Prior Isoniazid[‡]	21	99	0.88 (0.79, 0.99)	0.030
Acyclovir	6	98	0.96 (0.79, 1.17)	0.696
Ganciclovir	5	101	0.99 (0.80, 1.23)	0.930
Didanosine	5	98	1.06 (0.86, 1.31)	0.593
Zalcitabine	5	101	1.01 (0.82, 1.26)	0.893
Zidovudine	10	100	1.07 (0.92, 1.25)	0.370
Lamivudine	13	98	1.00 (0.87, 1.15)	0.976
Stavudine	10	98	0.89 (0.77, 1.04)	0.153
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Indinavir	6	99	0.97 (0.79, 1.18)	0.764
Nelfinavir	8	100	0.88 (0.74, 1.04)	0.130
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Acetaminophen	17	85	0.86 (0.77, 0.97)	0.012
Albuterol	5	98	0.99 (0.80, 1.22)	0.888
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Inducer[§]	4	97	0.68 (0.54, 0.85)	0.001
CYP3A4 Inhibitor	14	97	0.91 (0.80, 1.05)	0.188
Prior Inducer[‡]	5	97	0.80 (0.66, 0.98)	0.033

[†] GMR = geometric mean ratio (≥ 90% coverage/no coverage).
[‡] Use during the 14 days preceding MK-0991 therapy.
[§] Inducer included in analysis with n=4, due to the large effect obtained with prior inducers.

Table 13 (Reference 19)

Effect of Concomitant Medications on $C_{24\,hr}$

Concomitant Medication	N with ≥ 90% Coverage	N Total	GMR (95% CI)[†]	p-value
Azithromycin	9	143	0.84 (0.64, 1.10)	0.196
Clarithromycin	6	143	0.90 (0.65, 1.24)	0.520
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dapsone	9	144	0.76 (0.58, 0.99)	0.041
Ethambutol	7	144	0.72 (0.54, 0.97)	0.030
Isoniazid	29	143	0.91 (0.77, 1.06)	0.229
Prior Isoniazid[‡]	27	141	0.92 (0.78, 1.09)	0.348
Acyclovir	7	140	1.06 (0.79, 1.42)	0.691
Ganciclovir	5	145	0.85 (0.60, 1.20)	0.343
Didanosine	7	140	0.88 (0.66, 1.17)	0.375
Zalcitabine	5	145	0.93 (0.65, 1.32)	0.669
Zidovudine	14	140	0.94 (0.76, 1.16)	0.533
Lamivudine	15	140	0.84 (0.68, 1.04)	0.107
Stavudine	10	142	0.68 (0.54, 0.87)	0.003
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Indinavir	6	142	0.77 (0.58, 1.06)	0.105
Nelfinavir	8	144	0.68 (0.51, 0.89)	0.005
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Pyrimethamine	5	141	1.05 (0.74, 1.50)	0.784
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ranitidine	5	143	0.92 (0.64, 1.31)	0.636
Loperamide	5	142	0.88 (0.62, 1.25)	0.476
Albuterol	6	141	0.93 (0.67, 1.28)	0.641
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Inducer	8	141	0.80 (0.60, 1.05)	0.112
CYP3A4 Inhibitor	14	140	0.70 (0.57, 0.87)	0.001
Prior Inducer[‡]	7	139	0.69 (0.52, 0.93)	0.014

[†] GMR = geometric mean ratio (≥90% coverage/no coverage).
[‡] Use during the 14 days preceding MK-0991 therapy.

6. Comparison of Pharmacokinetics in Patients and Healthy Subjects

The pharmacokinetics in patients were compared to the pharmacokinetics obtained in healthy young adults who received the same dosing regimen in Protocol 021. Formal comparisons of the pharmacokinetics in patients and healthy subjects were conducted as described in the statistical methods section. In these analyses, a general linear statistical model adjusted for differences in weight and gender between the groups compared, since prior results had indicated that these factors could be significant.

Reference 19

Tables 16 and 17 display the results for single dose (Day1) and multiple dose pharmacokinetics, respectively. On Day 1, $C_{1\ hr}$ was reduced 19% and $C_{24\ hr}$ increased 39% on average in patients with localized candidiasis relative to healthy subjects. No significant difference in AUC0-24 hr was identified. Following multiple dose, only $C_{1\ hr}$ was significantly different (17% reduction) in patients compared to healthy subjects, although a modest reduction of 12% in the 70-mg AUC0-24 hr in patients achieved statistical significance in the dose comparison. There was a trend towards greater C24 hr (16%) in patients than healthy subjects, which approached significance in the overall analysis. The comparison of pharmacokinetic profiles of patients and healthy subjects indicate that relative to healthy subjects. Patients appear to have a somewhat more pronounced α-phase evident immediately postinfusion and a somewhat slower decline during the β-phase, particularly on Day 1. These small differences in end-of-infusion and trough concentrations tend to balance each other, such that the AUC is similar between patients and subjects.

Table 16

Comparison of Pharmacokinetics Between Healthy Subjects and Patients on Day 1 of Multiple Dosing When Adjusting for Differences in Weight and Gender

Parameter	N (Patients/ Subjects)	Geometric Mean		GMR (95% CI)†	p-value
		Patients	Subjects		
$AUC_{0\text{-}24\ hr}$	84/52	64.86 (61.17, 68.78)‡	68.38 (62.86, 74.39)‡	0.95 (0.85, 1.06)	0.328
35 mg	23/5	46.53 (42.61, 50.81)	45.94 (38.43, 54.92)	1.01 (0.83, 1.24)	0.901
50 mg	32/15	65.65 (60.74, 70.95)	67.76 (60.60, 75.76)	0.97 (0.85, 1.11)	0.646
70 mg	29/32	89.34 (82.24, 97.06)	102.72 (95.44, 110.56)	0.87 (0.78, 0.97)	0.016
$C_{1\ hr}$	102/52	7.20 (6.77, 7.65)‡	8.92 (8.08, 9.84)‡	0.81 (0.71, 0.91)	0.001
35 mg	27/5	5.40 (4.92, 5.93)	5.79 (4.70, 7.13)	0.93 (0.74, 1.18)	0.559
50 mg	38/15	7.30 (6.72, 7.92)	9.38 (8.23, 10.68)	0.78 (0.67, 0.91)	0.002
70 mg	37/32	9.46 (8.68, 10.32)	13.07 (11.98, 14.25)	0.72 (0.64, 0.82)	<0.001
$C_{24\ hr}$	86/52	1.31 (1.19, 1.44)‡	0.94 (0.82, 1.09)‡	1.39 (1.16, 1.66)	<0.001
35 mg	24/5	0.96 (0.83, 1.11)	0.66 (0.49, 0.90)	1.45 (1.03, 2.05)	0.035
50 mg	33/15	1.28 (1.12, 1.46)	0.89 (0.73, 1.08)	1.44 (1.14, 1.81)	0.002
70 mg	29/32	1.83 (1.59, 2.11)	1.43 (1.27, 1.63)	1.28 (1.05, 1.55)	0.013

† Geometric mean ratio (patients/subjects).
‡ Values averaged across all doses.

Table 17

Comparison of Pharmacokinetics Between Healthy Subjects and Patients for Time-Averaged Pharmacokinetic Parameters (Days 3-14) When Adjusting for Differences in Weight and Gender

Parameter	N (Patients/ Subjects)	Geometric Mean		GMR (95% CI)†	p-value
		Patients	Subjects		
$AUC_{0\text{-}24\ hr}$	101/85	103.19 (96.76, 110.05)‡	110.48 (100.57, 121.35)‡	0.93 (0.83, 1.05)	0.234
35 mg	28/5	71.26 (65.01, 78.12)	69.54 (56.75, 85.22)	1.02 (0.82, 1.29)	0.834
50 mg	38/38	101.57 (93.34, 110.52)	112.71 (103.13, 123.17)	0.90 (0.80, 1.01)	0.079
70 mg	35/42	151.82 (138.52, 166.39)	172.02 (157.30, 188.12)	0.88 (0.78, 1.00)	0.043
$C_{1\ hr}$	101/85	9.37 (8.89, 9.87)‡	11.32 (10.48, 12.22)‡	0.83 (0.75, 0.91)	<0.001
35 mg	28/5	6.79 (6.29, 7.32)	7.22 (6.11, 8.53)	0.94 (0.78, 1.14)	0.521
50 mg	38/38	9.23 (8.61, 9.90)	11.50 (10.69, 12.36)	0.80 (0.73, 0.88)	<0.001
70 mg	35/42	13.12 (12.18, 14.13)	17.46 (16.23, 18.79)	0.75 (0.68, 0.83)	<0.001
$C_{24\ hr}$	144/85	2.10 (1.93, 2.27)‡	1.81 (1.57, 2.09)‡	1.16 (0.98, 1.37)	0.082
35 mg	28/5	1.45 (1.26, 1.66)	1.09 (0.80, 1.50)	1.32 (0.93, 1.88)	0.118
50 mg	60/38	1.97 (1.77, 2.19)	1.86 (1.63, 2.13)	1.06 (0.90, 1.25)	0.490
70 mg	56/42	3.22 (2.89, 3.59)	2.91 (2.54, 3.33)	1.11 (0.93, 1.31)	0.236

† Geometric mean ratio (patients/subjects).
‡ Values averaged across all doses.

Reference 20

Table 18 displays the results of the analysis for Reference 20. On average, $C_{1\ hr}$ was reduced 26% on Day 1 and 19% after multiple doses in patients relative to healthy subjects. These differences were statistically significant for both comparisons. No statistically significant differences were identified for $C_{24\ hr}$. However, there is a trend of higher $C_{24\ hr}$ in patients compared to healthy subjects.

Table 18

Comparison of Pharmacokinetics Between Healthy Subjects and Patients Adjusting for Differences in Weight and Gender

Parameter	N (Patients/ Subjects)	Geometric Mean		GMR (95% CI)‡	p-value
		Patients	Subjects		
Day 1					
$C_{1\ hr}$ (µg/mL)	48/16	9.22 (8.19, 10.38)	12.44 (10.18, 15.22)	0.74 (0.59, 0.94)	0.013
$C_{24\ hr}$ (µg/mL)	37/16	1.68 (1.45, 1.95)	1.49 (1.19, 1.86)	1.13 (0.86, 1.48)	0.367
Day 3-14†					
$C_{1\ hr}$ (µg/mL)	49/16	8.81 (7.97, 9.75)	10.92 (9.18, 13.00)	0.81 (0.66, 0.99)	0.037
$C_{24\ hr}$ (µg/mL)	51/16	2.04 (1.80, 2.32)	1.66 (1.32, 2.08)	1.23 (0.95, 1.60)	0.115

† Time-averaged (Day 3 to Day 14).
‡ Geometric mean ratio (patients/subjects).

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