CLINICAL PHARMACOLOGY REVIEW

NDA	21-227
Drug	Caspofungin
Date of Submission	01/31/08
Trade Name	Cancidas™
OCP Reviewer	Dakshina M. Chilukuri, Ph.D.
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OND division	ODE IV; DSPTP
Sponsor	Merck Inc.
Submission Type	Supplemental New Application
Formulation	IV Infusion
Indication	Empiric therapy for fungal infections, Invasive aspergillosis, Candidemia and invasive candidiasis and Esophageal Candidiasis,
Dosage and Administration	70 mg/m^2 loading dose on Day 1 followed by 50 mg/m^2 QD
Date of Review	07/08/08

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1. Executive Summary

The applicant is seeking approval of Cancidas™ (caspofungin), an antifungal agent belonging to the echinocandin class for intravenous (IV) administration in pediatric patients between the ages of 3 months – 17 years. The sponsor has sought to approve Cancidas in pediatric patients for all the indications for which it is approved in adults. The proposed dosage regimen is a loading dose of 70 mg/m^2 followed by a maintenance dose of 50 mg/m^2 for duration of treatment based on the patients' response.

Caspofungin is a semisynthetic cyclic lipopeptide belonging to an echinocandin class of antifungal agents. Caspofungin was previously approved in 2000 for the treatment of the following fungal infections in adults. (1) invasive aspergillosis in adults who are refractory to or intolerant of other fungal agents (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole); (2) invasive candidiasis (candidemia and other

Candida infections) in adult patients; (3) esophageal candidiasis in adult patients; and (4) empirical treatment of suspected fungal infections in febrile, neutropenic adult patients.

As part of the pediatric development program, in response to a Pediatric Written Request (PWR) issued by the FDA, the pharmacokinetics of caspofungin were assessed in pediatric patients 0-17 years of age using a staged approach. Per this approach, the pharmacokinetics of caspofungin were first assessed in children 2 through 17 years of age (Study 033). Once the pharmacokinetics and safety of caspofungin were confirmed in this older age group, the pharmacokinetics of caspofungin were then assessed in younger children 3 months to 2 years of age (Study 042), followed by an assessment in infants/neonates less than 3 months of age (Study 058). Based on these pharmacokinetic studies, the safety and efficacy of caspofungin in pediatric patients were assessed in each of the infectious disease indications previously studied and approved in adults. Two separate safety/efficacy studies were conducted. The first study (Study 043) was an open-label, non-comparative trial of caspofungin against documented *Candida* or *Aspergillus* infections (esophageal candidiasis, invasive candidiasis, or salvage treatment of invasive aspergillosis) in pediatric patients 3 months through 17 years of age. The second study (Study 044) was a comparator-controlled study to assess the safety and efficacy of caspofungin as empirical therapy for pediatric patients 2 through 17 years of age with persistent fever and neutropenia. The different age groups for the 2 safety/efficacy groups were chosen based on the epidemiology of fungal infections in these various patient populations.

The systemic exposure following administration of a loading dose of 70 mg/m^2 and a maintenance dose of 50 mg/m^2 was comparable between pediatric patients aged 3 months – 17 years and adults. The steady-state AUC_{24} and C_{24h} were similar between adults and pediatric patients across all the studies conducted in the pediatric WR. The C_{1h} was significantly higher across all pediatric age groups compared to adults. The safety profile in pediatric patients was similar to adults indicating that the increased C_{1h} does not result in elevated safety concerns in pediatric patients. There was no evidence of a relationship between exposure and the safety event of thrombocytopenia (change in platelet counts from baseline) that was selected as a potential concern by the reviewing medical officers (Dr. Yuliya Yasinskaya and Dr. Julie-Ann Crewalk).

The similarity in systemic exposure (AUC and C_{24}) between pediatric patients and adults observed in studies 033 and 042 indicated that the effectiveness of caspofungin in the treatment of fungal infections would be similar to that previously observed in adults. This hypothesis is confirmed from the results obtained in studies 043 and 044 which indicated that the caspofungin dose selected from studies 033 and 042 is effective and safe across the age range of 3 months – 17 years and all disease indications. The results of the safety and efficacy trials indicated that caspofungin when administered at a loading dose of 70 mg/m^2 followed by a maintenance dose of 50 mg/m^2 is comparable to adults.

Based on the comparable systemic exposures seen in pediatric patients between the ages of 3 months -17 years and adults and the demonstration of effectiveness and safety of

caspofungin in the pediatric patients in the 2 clinical studies, the review team will approve caspofungin in pediatric patients 3 months-17 years at a dosage regimen of 70 mg/m^2 as a loading dose followed by 50 mg/m^2 as the maintenance dose. The sponsor has requested [redacted]

No outstanding clinical pharmacology issues were identified with caspofungin in this current NDA submission.

1.1. Recommendation

The clinical pharmacology information submitted to NDA 21-227 for caspofungin is acceptable from the perspective of the Office of Clinical Pharmacology (OCP).

1.2. Phase 4 Commitments

Not applicable

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Dakshina M. Chilukuri, Ph.D.
Reviewer, DCP4/OCP

Concurrence _____.
Philip M. Colangelo, Pharm.D., Ph.D.
Team Leader, DCP4/OCP

2. Summary of Clinical Pharmacology and Biopharmaceutics findings

Clinical Study 033:
This was a multicenter, open-label, sequential dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of 2 doses of caspofungin (50 mg/m^2 daily and 70 mg/m^2 daily) in clinically stable children or adolescents with a history of underlying hematological or solid organ malignancies, bone marrow or peripheral stem cell transplantation, or aplastic anemia. The maximum caspofungin daily dose was not to exceed 70 mg/day. This study was conducted in pediatric patients from 2 different age groups: children between the ages of 2 to 11 years and adolescents between the ages of 12 to 17 years. Intravenous caspofungin was given as a daily dose infused over a 1-hour period to patients with new onset fever and neutropenia [absolute neutrophil count (ANC) <500/mm^3]. Plasma was collected for pharmacokinetic analyses from these patients using a 7-point plasma schedule on Days 1, 4, and 9: pre-dose, at the completion of the 1-hour infusion (within 5 minutes after the end of the infusion), at 2 hours (1 hour after the end of infusion), 4 hours (3 hours after the end of infusion), 8 hours, 12 hours, and 24 hours post-initiation of study drug infusion (trough before the next day's dose). Plasma concentration trough (pre-dose, or $C_{24\ hr}$) samples were also collected on Days 3, 7, 12, 14, 21, and 28.

The steady-state $AUC_{24\ hr}$ geometric mean ratio (GMR) for children aged between **2-11 years** receiving **50 mg/m^2/day** relative to adult historical controls was 1.11. The steady-state $C_{1\ hr}$ and $C_{24\ hr}$ GMR for children relative to adult historical controls were 1.66 and 0.72, respectively. The rate of decline in the mean plasma concentration-time profiles during the β-phase appeared to be faster (~8.2 hours) in children relative to adults (13 hours).

The steady-state $AUC_{24\ hr}$ GMR for children aged between **2-11 years** receiving **70 mg/m^2/day** relative to adult historical controls was 1.05. The steady-state $C_{1\ hr}$ and $C_{24\ hr}$ GMR for children relative to adult historical controls were 1.57 and 0.74, respectively. The rate of decline in the mean plasma concentration-time profiles during the β-phase appeared to be faster (~8.2 hours) in children relative to adults (13 hours).

The steady-state $AUC_{24\ hr}$ GMR for adolescents aged between **12-17 years** receiving **50 mg/m^2/day** relative to adult historical controls was 1.13. The steady-state $C_{1\ hr}$ and $C_{24\ hr}$ GMR for adolescents relative to adult historical controls were 1.37 and 1.07, respectively. The rate of decline in the mean plasma concentration-time profiles during the β-phase appeared to be comparable (~11.2 hours) in adolescents relative to adults (13 hours).

Clinical Study 042
This was a multicenter, open-label study to investigate the safety, tolerability, and pharmacokinetics of caspofungin at a dose of 50 mg/m^2 daily in young children 3 to 24 months of age. Clinically stable, immuno-compromised pediatric patients between the ages of 3 and 24 months with a history of underlying hematological or solid organ malignancies and documented fever and neutropenia received caspofungin at or around

the onset of empirical antibacterial therapy. Plasma pharmacokinetic samples were obtained on Days 1 and 4 using a 7-point plasma profile: pre-dose, at the completion of the 1-hour infusion, at 2 hours (1 hour after the end of infusion), at 4 hours (3 hours after the end of infusion), 8 hours, 12 hours, and 24 hours post-initiation of caspofungin infusion (trough before next day's dose. Trough (pre-dose) samples were also collected on Day 3 (and Days 7, 14, and 28, when applicable).

The steady-state $AUC_{24\ hr}$ GMR for young children aged between **3-24 months** relative to adult historical controls was 1.26. The steady-state $C_{1\ hr}$ and $C_{24\ hr}$ GMR for young children relative to adult historical controls were 1.83 and 0.81, respectively. The rate of decline in the mean plasma concentration-time profiles during the β-phase appeared to be faster (~8.8 hours) in young children relative to adults (13 hours).

Clinical Study 058:
Protocol 058 was a multicenter, sequential-panel, open-label, noncomparative study to investigate the safety, tolerability, and pharmacokinetics of caspofungin in neonates and infants <3 months of age. Neonates and infants <3 months of age with documented (culture-confirmed) or highly suspected *Candida* infections were enrolled in one of the two sequential treatment panels (Panel A [Single Dose] or Panel B [Multiple Dose]). In both panels, all patients received caspofungin at 25 mg/m^2 in combination with an intravenous amphotericin B formulation (amphotericin B deoxycholate or a lipid preparation of amphotericin B) and administered over approximately 1 hour as a single daily infusion. Patients enrolled in Panel B received multiple doses of caspofungin at 25 mg/m^2 daily, and the minimum duration of caspofungin in Panel B was expected to be 4 days. Blood for plasma pharmacokinetic sampling was collected at pre-dose (at screening), 1 hour and 24 hours post caspofungin infusion on Day 1 in all patients, and 1 hour and 24 hours post caspofungin infusion on Day 4 (corresponding to peak and trough concentrations, respectively) in Panel B patients only.

The steady-state C_{1hr} and C_{24hr} GMR were 1.18 and 1.21 for neonates and infants relative to adult historical controls. The Day 1 C_{1hr} and C_{24hr} GMR were 1.07 and 1.36 for neonates and infants relative to adult historical controls.

Clinical Study 043
This was a multicenter, open-label, non-comparative study to evaluate the safety, tolerability and efficacy of caspofungin in approximately 50 children or adolescents (ages 3 months to 17 years) with documented *Candida* or *Aspergillus* infection at the time of enrollment. All patients received caspofungin monotherapy at 50 mg/m^2 daily following a 70-mg/m^2 loading dose on Day 1. The maximum daily dose was not to exceed 70 mg/day. Intravenous caspofungin was infused over a 1-hour period. Blood samples were collected on Days 4, 7, and 14, for measurement of peak and trough caspofungin plasma concentrations. In addition, a blank (negative control) specimen was collected at screening. At certain study sites, blood samples for caspofungin drug level assays were collected at 5 time-points (pre-dose, 1 hour, 2 hour, 4 hour, and 24 hour) on Day 4.

The mean steady-state $AUC_{24\ hr}$, C_{1h} and C_{24h} in this study were 172.42 µg-hr/mL, 18.76 µg/mL and 3.48 µg/mL, respectively.

Clinical Study 044

This was a multi-center, double-blind, randomized, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin versus liposomal amphotericin B (AmBisome™) in the empiric treatment of patients with persistent fever and neutropenia. The patient population under study were pediatric patients aged 2 to 17 years, who had received chemotherapy for leukemia, lymphoma, or other cancers, or had undergone bone marrow or peripheral stem-cell transplantation, and were persistently neutropenic and febrile. At least 75 patients were to be enrolled in this study. Patients were assigned to receive daily intravenous doses of caspofungin (50 mg/m^2/day following a 70-mg/m^2 loading dose on Day 1; maximum 70 mg/day) or AmBisome™ (3 mg/kg/day). If study therapy was well tolerated but fever persisted for 5 or more days, and the patient's clinical condition deteriorated, the dosage of study drug could be increased (70 mg/m^2/day for caspofungin and 5 mg/kg/day for AmBisome™) at the discretion of the investigator. The maximum dose of caspofungin was 70 mg/day for both standard and high doses. Caspofungin or matching placebo was given intravenously as a single daily dose infused over ~1 hour. This was followed by AmBisome™ or matching placebo given intravenously as a single daily dose infused over 2 hours. Pharmacokinetic samples were collected at all study sites pre-infusion and within 5 minutes after the end of caspofungin/placebo infusion on Days 4, 7, and 14. At a subset of study sites, 5-point plasma sampling for pharmacokinetics (pre-dose, 1 hour, 2 hour, 4 hour, and 24 hour) was also done on Day 4.

The steady-state $AUC_{24\ hr}$, C_{1h} and C_{24h} in this study were 165.36 µg-hr/mL, 17.08 µg/mL and 3.14 µg/mL, respectively.

3. Question Based Review

3.1. General Attributes of the Drug

3.1.1. What are the proposed dosage(s) for various indications?

Cancidas is to be administered in pediatric patients (3 months to 17 years of age) by slow IV infusion over approximately 1 hour. Dosing in pediatric patients (3 months to 17 years of age) should be based on the patient's body surface area. For all indications, a single 70-mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg daily). Duration of treatment should be individualized to the indication, as described for each indication in adults. If the 50-mg/m^2 daily dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg). Although an increase in efficacy with 70 mg/m^2 daily has not been demonstrated, limited safety data suggest that an increase in dose to 70 mg/m^2 daily is well tolerated.

3.2. General Clinical Pharmacology

3.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In response to a Written Request issued by the FDA the sponsor conducted three (3) clinical pharmacology studies and two (2) safety/efficacy studies. The clinical pharmacology studies were designed to enable a determination of the caspofungin dose that would result in similar systemic exposures compared to adults. The expectation behind this was that the disease pathophysiology and the fungal pathogens are similar between pediatric and adult patients. Thus, when the systemic exposures between pediatric and adult patients are matched then it is anticipated that similar effectiveness and safety results would be seen in both patient populations. Moreover, taking into consideration that it is first important to establish the safety of caspofungin in older children, the clinical pharmacology studies were designed to first evaluate the safety, tolerability and PK of caspofungin in children 2-17 years of age. Subsequent to this, the safety, tolerability and PK were evaluated in patients 3 months -24 months and later in patients 0-3 months. Thus this sequential stepwise manner of evaluating the safety, tolerability and PK in pediatric patients was implemented. The purpose of evaluation the PK in these patients was to evaluate and the characterize the dose needed to achieve comparable exposures with adults.

Subsequent to the clinical pharmacology studies, the safety and efficacy of caspofungin was assessed in each of the infectious disease indications previously studied and approved in adults. To accomplish this goal, 2 separate safety/efficacy studies were conducted. The first study was an open-label, non-comparative trial of caspofungin against documented *Candida* and *Aspergillus* infections [esophageal candidiasis, invasive candidiasis, or salvage treatment of invasive aspergillosis] in pediatric patients 3 months through 17 years of age (Protocol 043). The second study was a comparator-controlled study of caspofungin *versus* liposomal amphotericin B (AmBisome™) to assess the safety and efficacy of caspofungin as empirical therapy for pediatric patients 2 to 17

years of age with persistent fever and neutropenia (Protocol 044). In Tables 1 and 2 are presented the results of the clinical efficacy/safety studies.

Table 1. Proportion of patients who received caspofungin and had a favorable response at the primary efficacy time point in Protocol 043

	Caspofungin Treatment Group					
	Pediatric Study (Protocol 043)			Adult Studies		
Treatment Indication	Protocol	n/m	Observed Response % (95% CI)	Protocol	n/m	Observed Response % (95% CI)
Invasive Aspergillosis	043 50 mg/m^2‖	5/10	50% (18.7, 81.3)	019 50 mg# 50 mg# (EP)‡	46/96 37/83	47.9% (37.6, 47.9) 44.6% (33.7, 55.9)
Invasive Candidiasis	043 50 mg/m^2‖	30/37	81.1% (64.8, 92.0)	014 50 mg#	80/109	73.4% (65.1, 81.7)
Esophageal Candidiasis	043 50 mg/m^2‖	1/1	100% (NA)	020 50 mg	66/81	81.5% (71.3, 89.2)

n/m = Number of patients with a favorable response / Number of patients in the analysis.
‖ Patients received a loading dose of caspofungin 70 mg/m^2 (maximum dose for treatment period =70 mg/day) on Day 1.
Patients received a loading dose of caspofungin 70 mg on Day 1.
‡ EP = Expert Panel assessment

Table 2. Proportion of patients who received caspofungin and had a favorable response in Protocol 044

	Pediatric Study (Protocol 044)		Adult Study (Protocol 026)	
Endpoint	Caspofungin 70/50 mg/m^2 (N = 56) Observed Response n/m (%) (95% CI)	AmBisome™ 3.0 mg/kg (N = 25) Observed Response n/m (%) (95% CI)	Caspofungin 70/50 mg (N=556) Observed Response m/n† (%) (95% CI)	AmBisome™ 3.0 mg/kg (N=539) Observed Response m/n† (%) (95% CI)
Favorable Response (overall)	**23/56 (41.1) (28.2, 54.0)**	7/25 **(28.0) (10.4, 45.6)**	**190/556 (34.2) (30.2, 38.1)**	**181/539 (33.6) (29.6, 37.6)**
Successful treatment of baseline infection†	0/1 (0.0)	----	14/27 (51.9) (33.0, 70.7)	7/27 (25.9) (9.4, 42.5)
Absence of breakthrough fungal infection	56/56 (100)	24/25 (96.0) (88.3, 100)	527/556 (94.8) (92.9, 96.6)	516/539 (95.7) (94.0, 97.4)
Survival to 7-day follow-up	56/56 (100)	25/25 (100)	515/556 (92.6) (90.5, 94.8)	481/539 (89.2) (86.6, 91.9)
Completed therapy or non-endpoint discontinuation	51/56 (91.1) (83.6, 98.5)	21/25 (84.0) (69.6, 98.4)	499/556 (89.7) (87.2, 92.3)	461/539 (85.5) (82.6, 88.5)
Resolution of fever during neutropenia	24/56 (42.9) (29.9, 55.8)	8/25 (32.0) (13.7, 50.3)	229/556 (41.2) (37.1, 45.3)	223/539 (41.4) (37.2, 45.5)

† Only patients with a baseline infection are included in this analysis.
N = Number of Modified Intention-to-Treat patients in the treatment group.
n/m = Number of patients with a favorable response / Number of patients in the analysis.

3.2.2. What are the characteristics of the exposure-response relationship for efficacy and safety?

Exposure-efficacy

In previous submissions for adult patients, the relationship between caspofungin exposure and effectiveness was explored both by the sponsor as well as the FDA. However, no PK/PD parameter was found to predict outcome. In this pediatric submission the sponsor

attempted to characterize the PK/PD relationship in pediatric patients enrolled across 4 studies, 033, 042, 043 and 044. The results of these analyses are given below.

Of the three PK parameters examined ($AUC_{0\text{-}24hr}$, C_{1hr}, and C_{24hr}) for each disease indication (empirical therapy, invasive aspergillosis, and invasive candidiasis), none was found to be a significant factor for predicting efficacy outcome within the range of available pharmacokinetic parameter values. The analysis determined the fold change in the odds (probability of a favorable outcome/probability of an unfavorable outcome) per unit change (on the log scale) in these pharmacokinetic parameters. For instance, for every unit increase (on the log scale) of $AUC_{0\text{-}24hr}$ based on the analysis for patients with empirical therapy in Table 3, the odds increase 0.18 times on average. Or, expressed on the original scale, the odds increase 0.18 times for every 2.72-fold (e = 2.72) increase of $AUC_{0\text{-}24hr}$. In all the cases, the 95% confidence intervals for the odds ratio estimates were wide and extended both below and above 1.

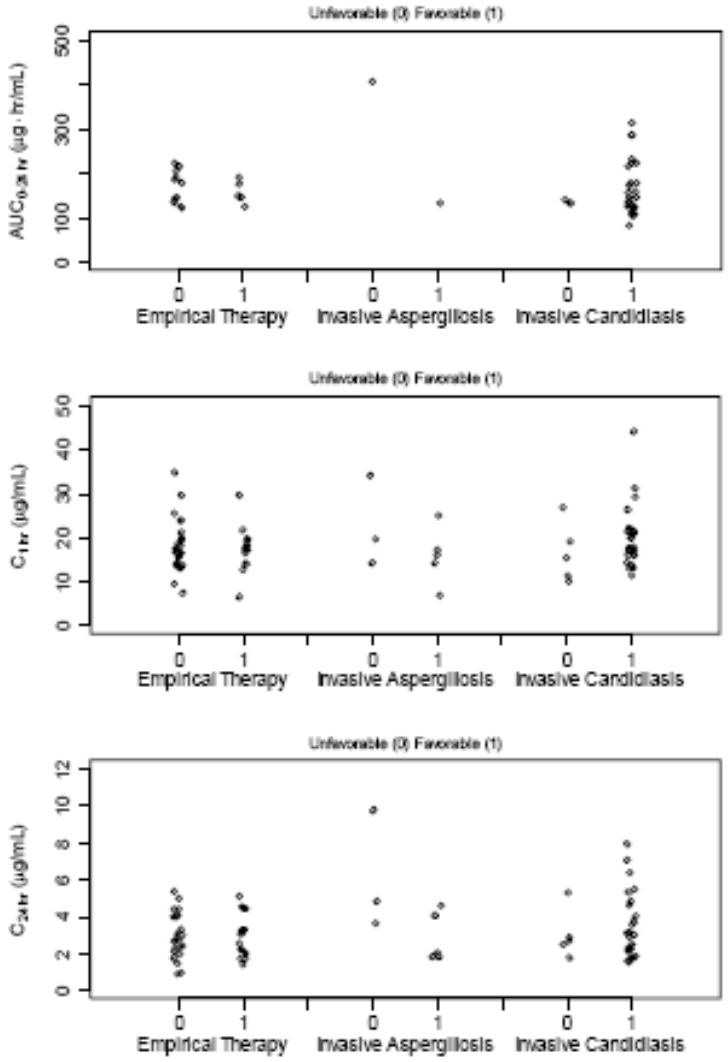
In addition to the pharmacokinetic parameters, three hybrid parameters ($AUC_{0\text{-}24hr}$: MIC, C_{1hr}:MIC, and C_{24hr}:MIC), incorporating both pharmacokinetics and in vitro susceptibility data, were examined as potential predictors of overall response at the end of caspofungin therapy in pediatric patients with invasive candidiasis (from Protocol 043, evaluable-patients population). Table 3 contains summary statistics from the logistic regression model for these hybrid parameters. Of the three hybrid parameters examined, none was found to be a significant factor for predicting overall response in pediatric patients with invasive candidiasis. Scattergrams comparing the individual PK data in patients with favorable versus unfavorable treatment outcomes are provided in Figure 1.

Table 3. Potential for patient PK parameters to predict favorable outcome in pediatric patients by disease indications (Protocols 043 and 044)

Parameter†	N Favorable Outcome	N Total	Odds Ratio (95% CI)‡	p-Value
Empirical Therapy (Protocol 044)				
$AUC_{0\text{-}24\,hr}$ (µg•hr/mL)	5	16	0.18 (0.00, 38.36)	0.529
$C_{1\,hr}$ (µg/mL)	14	38	0.66 (0.09, 4.76)	0.677
$C_{24\,hr}$ (µg/mL)	15	40	1.24 (0.28, 5.43)	0.774
Invasive Aspergillosis (Protocol 043)				
$AUC_{0\text{-}24\,hr}$ (µg•hr/mL)	1	2	-	-
$C_{1\,hr}$ (µg/mL)	5	8	0.08 (0.00, 9.02)	0.300
$C_{24\,hr}$ (µg/mL)	5	8	0.01 (0.00, 12.19)	0.216
Invasive Candidiasis (Protocol 043)				
$AUC_{0\text{-}24\,hr}$ (µg•hr/mL)	23	26	5.39 (0.07, 400.25)	0.444
$AUC_{0\text{-}24\,hr}$: MIC (hr)	21	24	0.47 (0.10, 2.26)	0.349
$C_{1\,hr}$ (µg/mL)	23	28	9.49 (0.27, 333.88)	0.216
$C_{1\,hr}$: MIC	21	25	0.99 (0.31, 3.14)	0.983
$C_{24\,hr}$ (µg/mL)	24	29	1.67 (0.19, 14.36)	0.642
$C_{24\,hr}$: MIC	21	25	0.94 (0.34, 2.55)	0.898

† Time averaged (Day 3 and greater).
‡ Fold change in odds (probability of a favorable outcome/probability of an unfavorable outcome) per unit increase (on the log scale) in parameter.

Figure 1. Scattergrams of individual steady-state PK values in pediatric patients with favorable and unfavorable treatment outcomes by disease indication (Protocols 043 and 044)



Exposure-safety:

Overall, no major safety concerns were identified by the clinical review team and the adverse event profile in pediatric patients was similar to that observed previously in adults. However, based on discussion with the clinical review team during the review, thrombocytopenia was identified as a safety event that needs further evaluation. Thus, the relationship between exposure (C_{1h}) and platelet count (change from baseline) was explored by the clinical pharmacology review team. Also, the effect of duration of therapy on platelet count was studied to understand the effect of treatment on platelet count. In Figures 2 and 3 are plotted the relationship between C_{1h} and platelet count (change from baseline) and in Figure 4 the effect of duration of treatment on platelet

count (change from baseline) are plotted from Study 043 in a representative set of patients. As seen below in the figures, the relationship between C_{1h} and platelet count (change from baseline) appears to be flat and also as shown in Figure 4, the duration of treatment of caspofungin does not appear to affect the platelet count (change from baseline).

Figure 2. Relationship between C_1 and platelet count (change from baseline) in Study 043

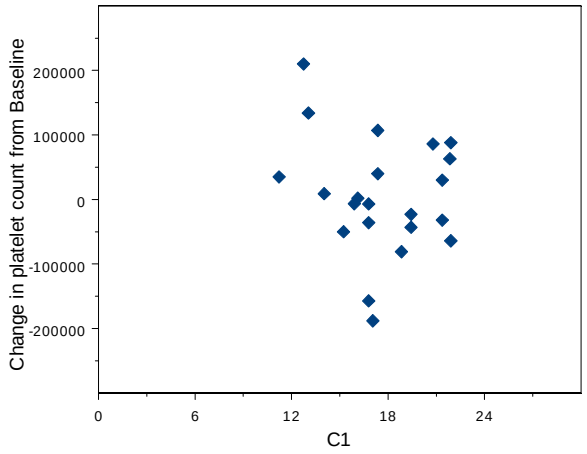


Figure 3. Relationship between C_1 and platelet count (change from baseline) in Study 044

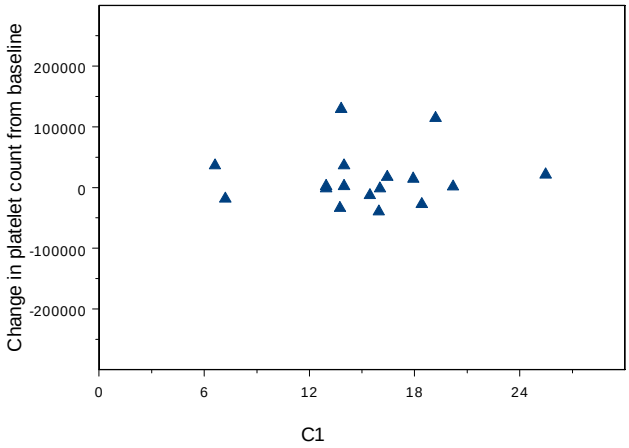
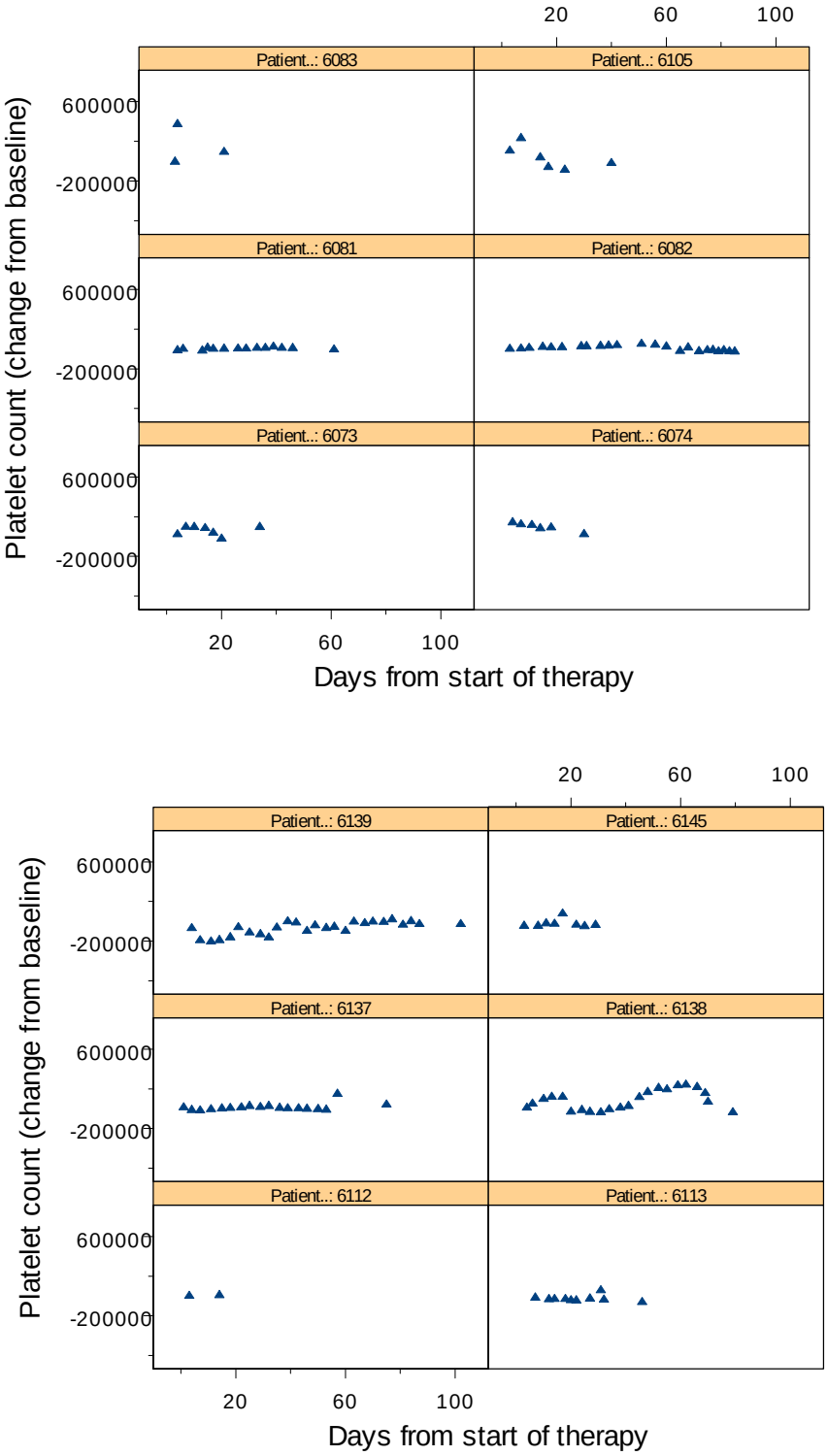


Figure 4. Effect of duration of treatment on platelet count (change from baseline) in Study 043 for selected patients



3.2.3. What are the single- and multiple-dose PK parameters in pediatric patients?

Initially the sponsor chose a dose of 1 mg/kg/day for administration to pediatric patients 2-11 years. A comparison of the pharmacokinetics in children (ages 2 to 11 years) receiving caspofungin at a dose of 1.0 mg/kg/day and adults receiving caspofungin at a dose of 50 mg/day is given below in Table 4.

Table 4. PK parameters of caspofungin following administration of 1 mg/kg/day in patients 2-11 years compared to adults.

Age groups	**AUC_{0-24} (µg-h/mL)**	**GMR**	**C_1 µg/mL**	**GMR**	**C_{24} µg/mL**	**GMR**
2-11 Years	56.33	0.54	8.38	0.89	0.63	0.31
Adults	103.38	-	9.39	-	2.01	-

Notes: 1. AUC, C_1 and C_{24} are presented as least square means
2. GMR was calculated as a ratio of PK parameter in pediatric patients compared to adults

As seen above in Table 4, the systemic exposure in pediatric patients 2-11 years obtained after administration of 1 mg/kg/day was significantly lower than that observed in adults. Based on this, the sponsor hypothesized that the correct way to administer caspofungin in pediatric patients is based on BSA of the pediatric patients. Hence all subsequent dosing of Cancidas in pediatric patients was performed on the basis of BSA.

The pharmacokinetic parameters of caspofungin following IV administration of 50 mg/ m^2/day to pediatric patients in Studies 033 and 042 are given below.

Table 5. PK parameters of caspofungin following administration of 50 mg/m^2/day in patients 3 months-17 years obtained in studies 033 and 042.

Age groups	AUC_{0-24} (µg-h/mL)	GMR	C_1 µg/mL	GMR	C_{24} µg/mL	GMR
12-17 Years	117.19	**1.13**	12.9	**1.37**	2.15	**1.07**
2-11 Years	115.23	**1.11**	15.61	**1.66**	1.46	**0.72**
3-24 months	130.29	**1.26**	17.21	**1.83**	1.64	**0.81**
Adults	103.38	-	9.39	-	2.01	-

Notes: 1. AUC, C_1 and C_{24} are presented as least square means
2. GMR was calculated as a ratio of PK parameter in pediatric patients compared to adults

Table 6. PK parameters (arithmetic mean ± SD) of caspofungin following administration of 50 mg/m^2/day in patients 3 months-17 years obtained in studies 033 and 042.

Age groups	N	AUC_{0-24} (µg·hr/mL)	C_1 (µg/mL)	C_{24} (µg/mL)
12-17 Years	8	124.9 ± 50.4	14.0 ± 6.9	2.4 ± 1.0
2-11 Years	9	120.0 ± 33.4	16.1 ± 4.2	1.7 ± 0.8
3-24 months	8	131.2 ± 17.7	17.6 ± 3.9	1.7 ± 0.7
Adults	7	87.3 ± 30.0	8.7 ± 2.1	1.7 ± 0.7

As seen above in Tables 5 and 6, there is a difference in the systemic exposure estimates of caspofungin across all doses when calculated as the least square mean (Table 5) compared to the arithmetic mean (Table 6). Based on the comparison of the least square mean and GMRs, the systemic exposure in pediatric and adult patients are comparable. However, based on comparisons made with arithmetic mean, the difference in systemic exposure between pediatric and adult patients appears larger. Despite these differences, however, it should be noted that the safety data in pediatric patients is comparable to adults and there were no safety concerns in pediatric patients. These differences in exposure between pediatric and adult patients is not likely to result in clinically significant outcomes.

Following administration of a loading dose of 70 mg/m^2 on Day 1 and a maintenance dose of 50 mg/m^2 QD, the PK profiles of caspofungin in patients in Protocols 043 and 044 are given below:

Figure 5. Mean Concentration Profiles on Day 4 for Subjects (n= 35) in Protocol 043

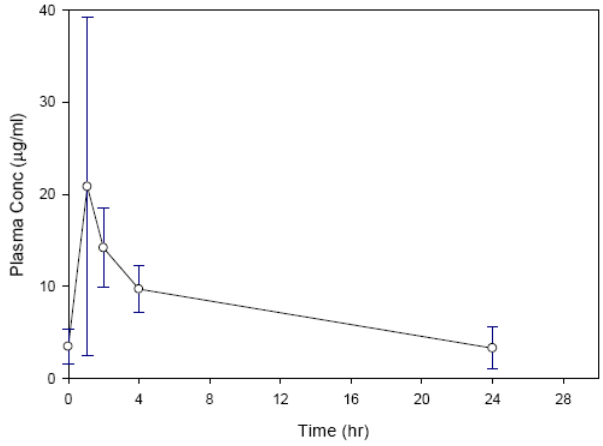


Figure 6. Mean Concentration Profiles on Day 4 for Subjects (n= 43) in Protocol 044

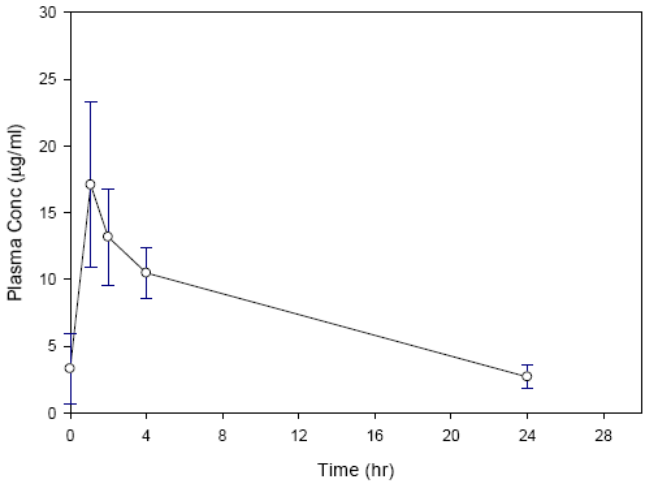


Table 7. The PK parameters (mean±SD) of IV caspofungin administered as a 70 mg/m^2 loading dose followed by a maintenance dose of 50 mg/m^2 observed in the two safety/efficacy studies (Studies 043 and 044) are given below.

Age groups	AUC_{0-24} (µg-h/mL)	C_1 µg/mL	C_{24} µg/mL
12-17 years	168.7 ± 49.5 (N=16)	16.89 ± 7.2 (N=25)	3.6±1.1 (N=26)
2-11 years	165.8±59.1 (N=29)	18.2±5.9 (N=52)	3.0±2.1 (N=52)
3 months-2 years	223.5 (N=2)	24.1 (N=2)	4.4 (N=2)

As seen in Tables 6 and 7, the AUC_{0-24}, C_{1h} and C_{24} in pediatric patients 3-24 months appears to be higher than that of patients between the ages of 2-17 years. However, it should be noted that in Studies 043 and 044 data from only 2 patients in the age range of 3-24 months was available and thus the higher exposure seen in those 2 patients may be unreliable in comparison with the older pediatric patients. The PK parameters compared across studies and across age groups are all at steady-state and it should not matter that in protocols 033 and 042 a loading dose was not given to patients while in protocols 043 and 044 a loading dose was given. Thus, it is unclear why a difference in exposure is seen across the 2 sets of studies, particularly in patients 2-11 years and 12-17 years of age. This difference however, is not expected to be important in the context of dosing, since the safety data from all the pediatric studies indicated that Cancidas when given at a loading dose of 70 mg/m^2 followed by a maintenance dose of 50 mg/m^2/day is safe and comparable to the safety data previously seen in adults.

3.2.4. Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation?

In order to understand the relationship between caspofungin clearance and patient covariates such as body weight, age and BSA, summary plots are presented below. Clearance estimates were derived from the geometric mean $AUC_{0\text{-}24}$ at steady-state. Clearance values were estimated for all patients receiving caspofungin in P033, P042, P043, and P044 in whom the necessary pharmacokinetic parameter values were available. The following plots may be of interest as they illustrate the consistency of BSA-normalized clearance across the pediatric age range and further support a BSA-scaled dosing regimen for pediatric patients receiving caspofungin.

The plots pooling data across all studies are presented first (Figures 7-12). The clearance values appeared to be reasonably proportional to BSA, while there appears to be some curvature in the relationship of clearance with age or body weight. Similarly, the BSA-normalized clearance appears to be more consistent across the age range than the weight-normalized clearance. These observations support the use of BSA-scaled dosing of caspofungin in pediatric patients.

Figure 7. Caspofungin clearance increases as a function of age (Studies 033, 042, 043 and 044).

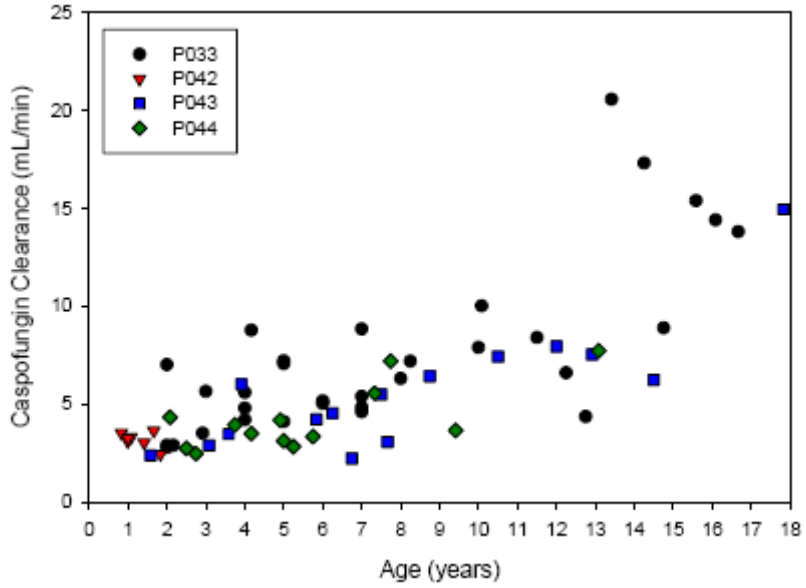


Figure 8. Caspofungin clearance increases as a function of body weight (Studies 033, 042, 043 and 044)

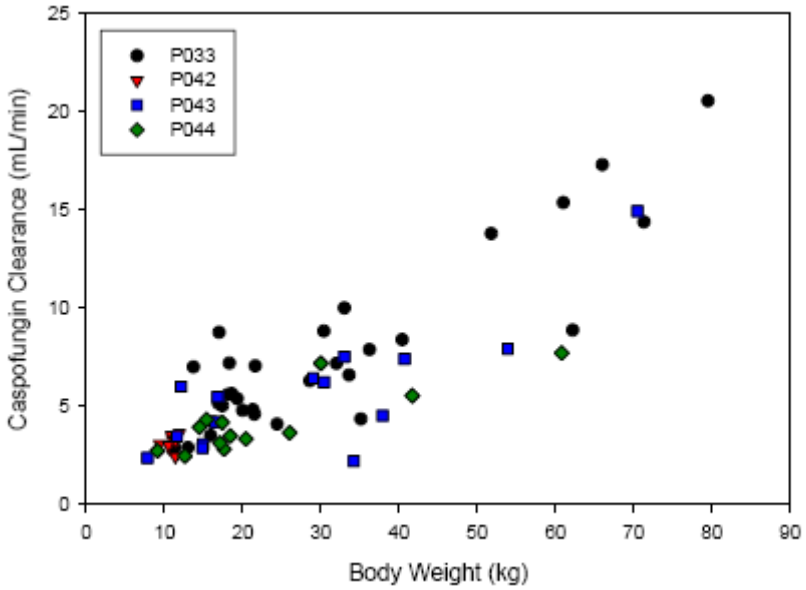


Figure 9. Caspofungin clearance increases as a function of BSA (Studies 033, 042, 043 and 044

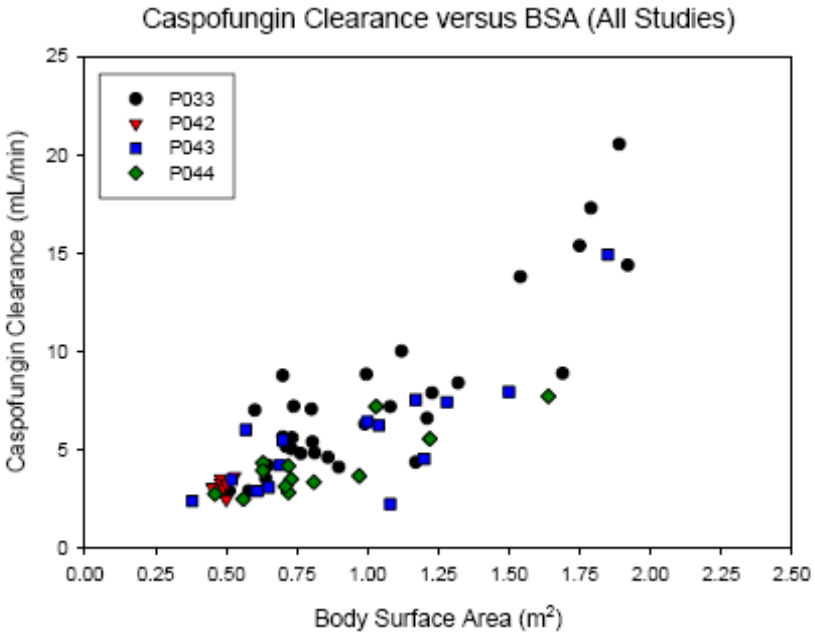


Figure 10. Body-weight normalized caspofungin clearance as a function of age (Studies 033, 042, 043 and 044)

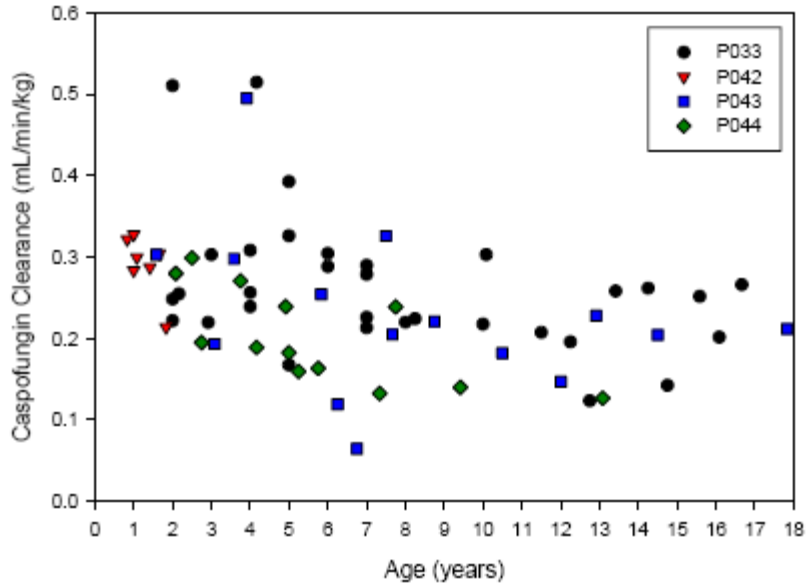


Figure 11. BSA-normalized caspofungin clearance as a function of age (Studies 033, 042, 043 and 044)

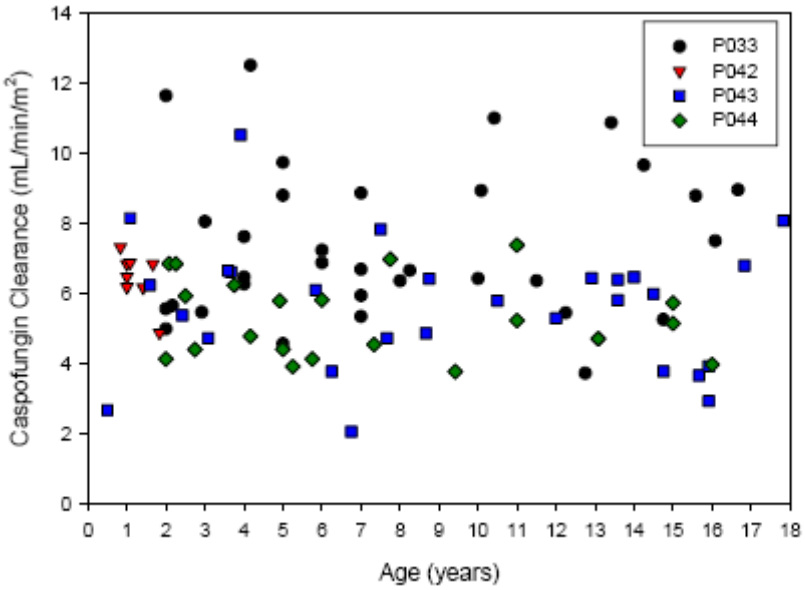
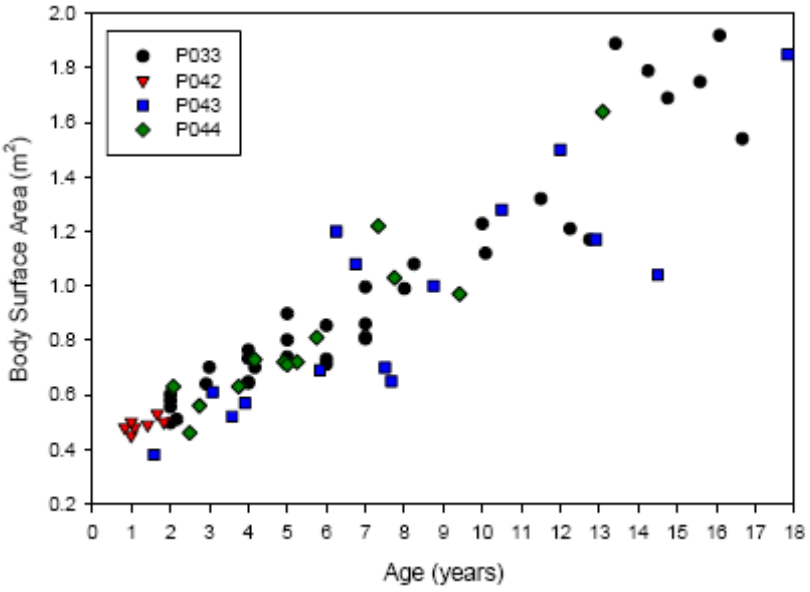


Figure 12. Relationship between age and BSA



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4. Appendices

A. Package insert (Proposed Labeling) : Available separately

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/s/

Dakshina Chilukuri
7/8/2008 05:43:14 PM
BIOPHARMACEUTICS

Phil Colangelo
7/11/2008 03:23:38 PM
BIOPHARMACEUTICS