

# Pharmacokinetics of Antifungal Agents in Pediatric Patients

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**Dosage / Dosage Interval**



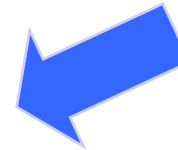
**Disease-  
related  
Factors**



**Pharmacokinetics**

Absorption  
Distribution  
Metabolization  
Elimination

**Growth and  
Development**



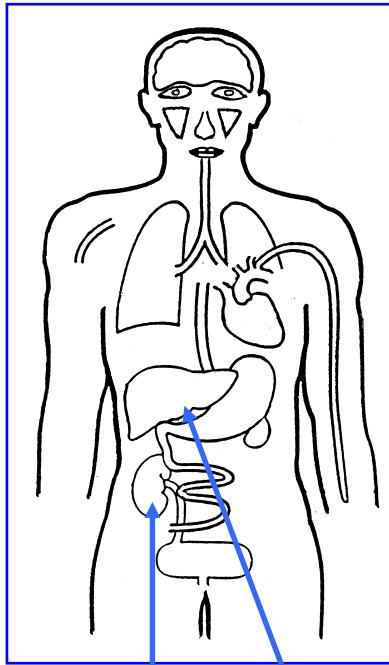
**Concentration at Target Site**



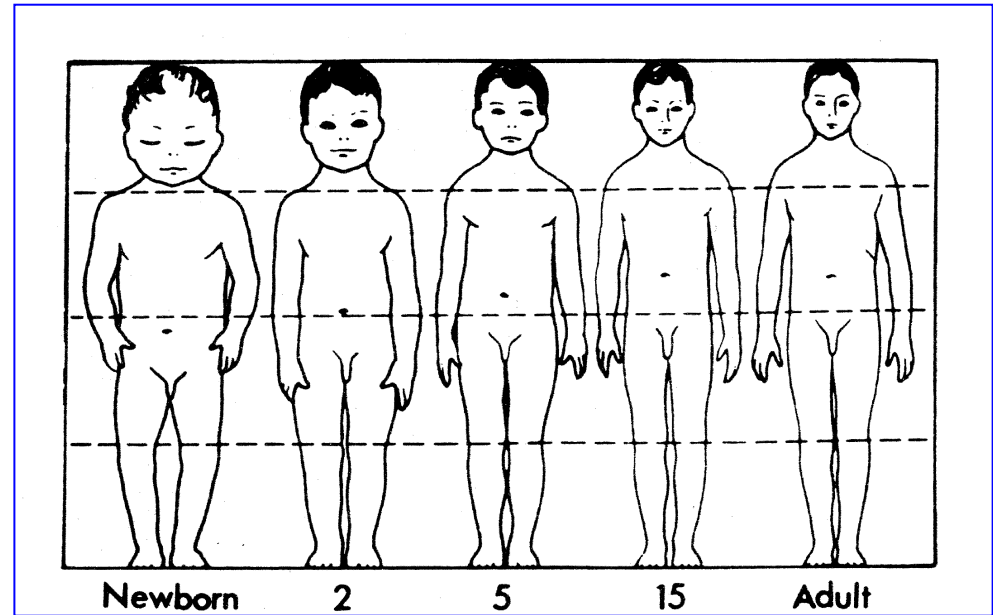
**Pharmacological Effects**

Efficacy  
Toxicity

## Changes in body mass and body composition



**Maturation processes  
of excretory organs**



**Scaling of dosing regimens based on body weight  
or body surface area generally inappropriate**

# Pediatric Antifungal Arsenal

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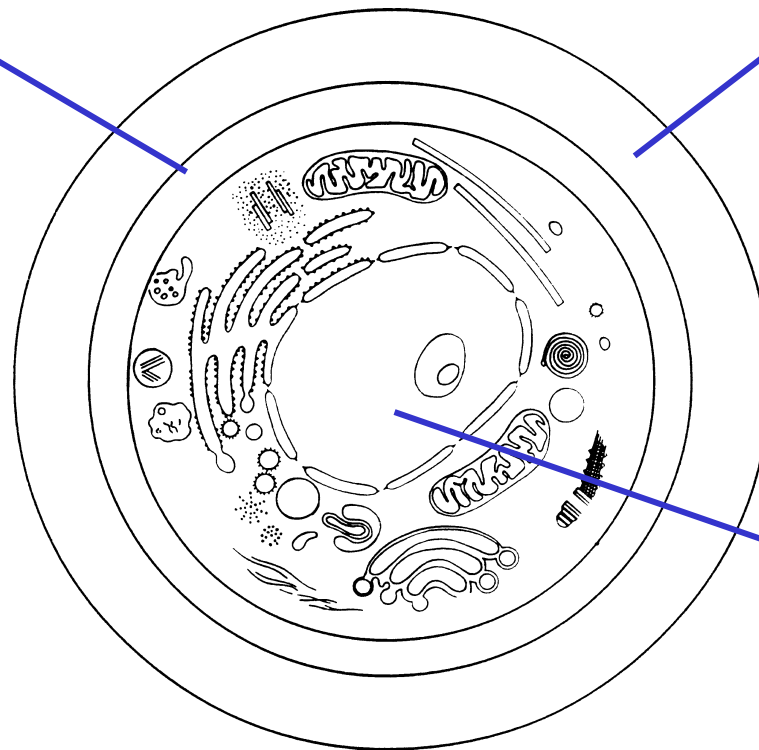
## Cell membrane

### - Polyenes

- > D-AmB
- > L-AmB
- > ABLC

### - Triazoles

- > Fluconazole
- > Itraconazole
- > Voriconazole
- > Posaconazole



## Cell wall

### - Echinocandins

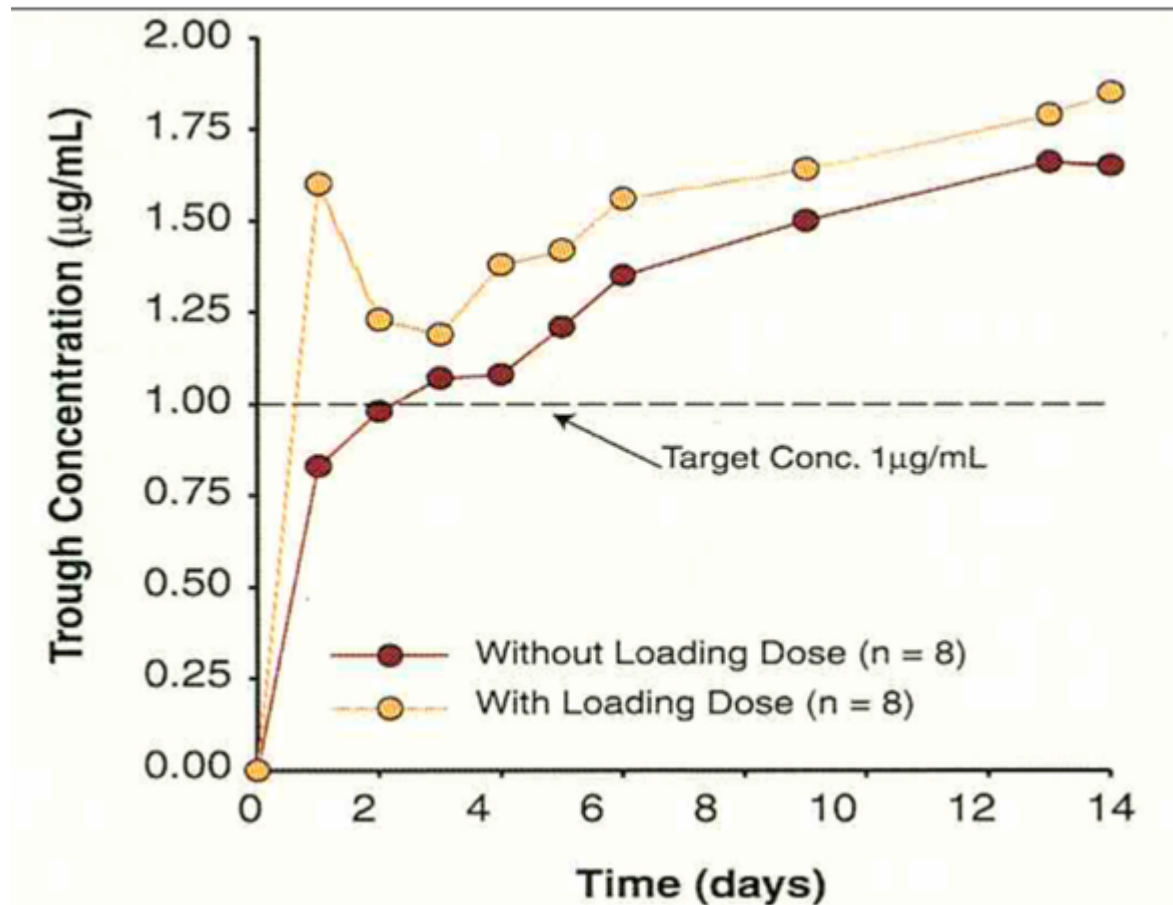
- > Caspofungin
- > Micafungin
- > Anidulafungin

## Nucleic acid synthesis

- > Flucytosine

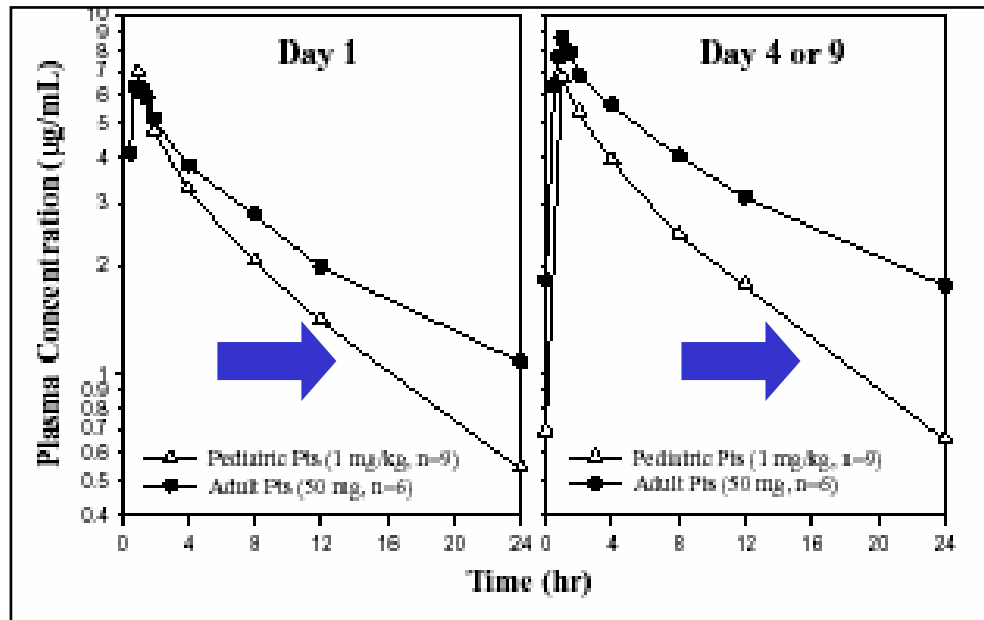
**Caspofungin**

# Caspofungin: Dosing Rationale in Adults

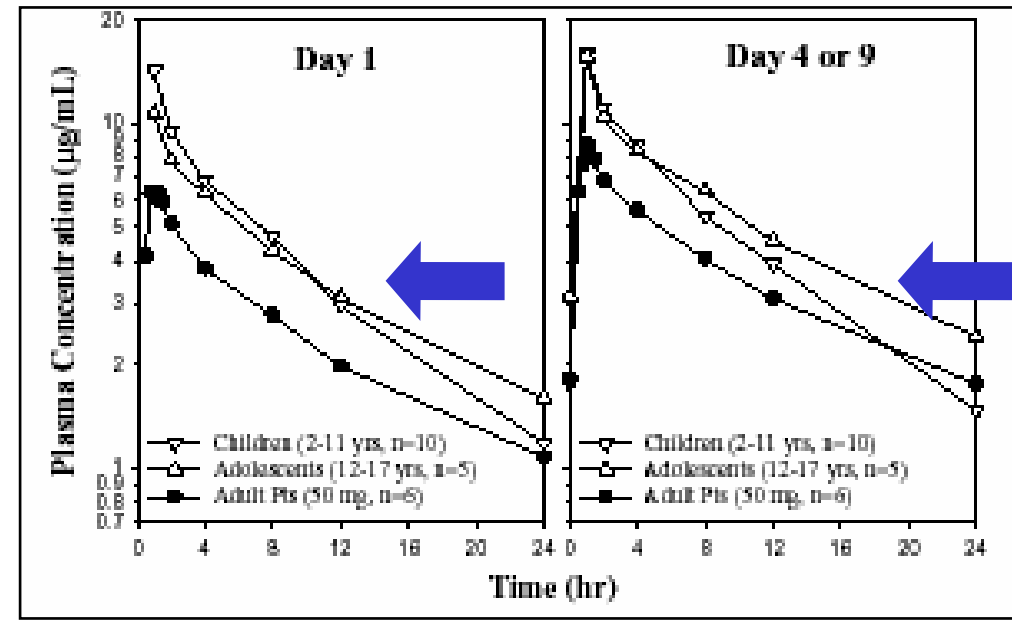


# Protocol 033: Pediatric Dose-Finding

## CAS 1mg/kg




## CAS 50 mg/m<sup>2</sup>



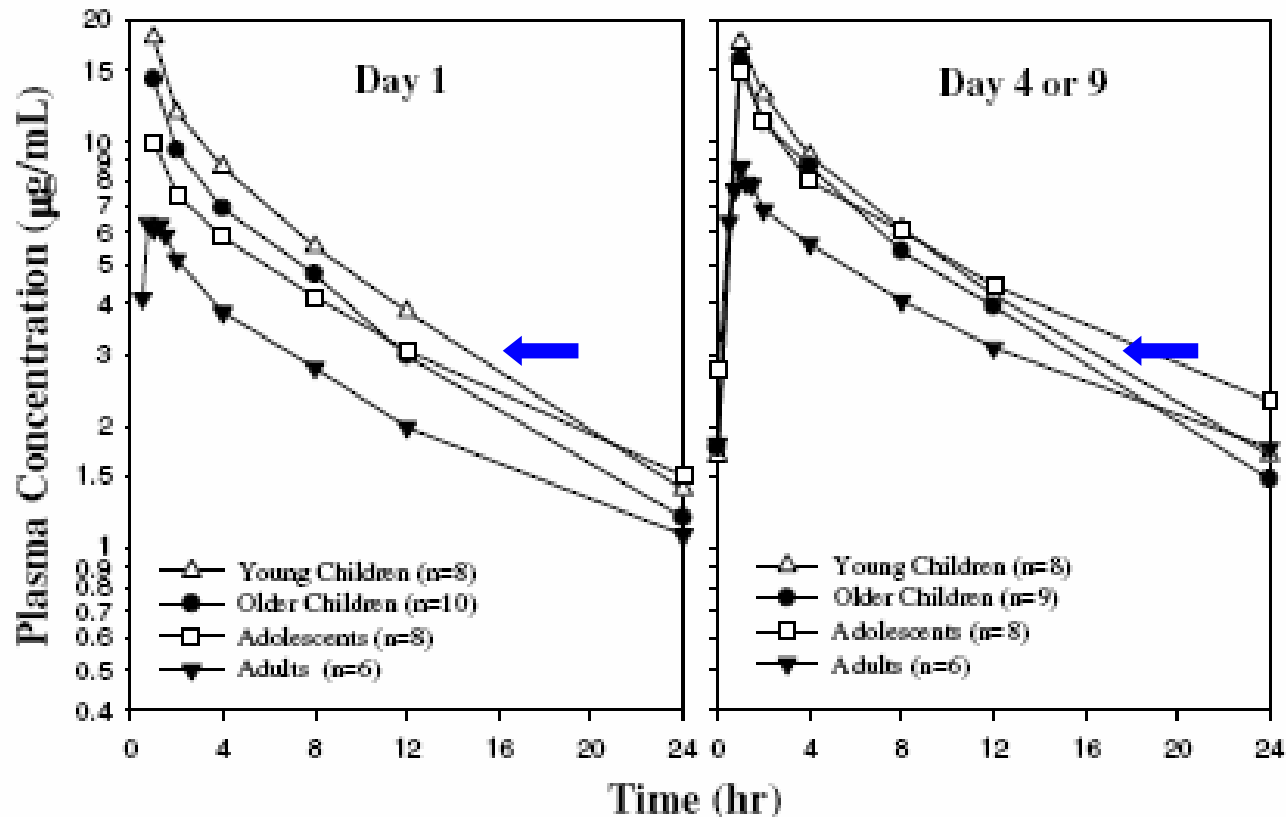
# Caspofungin: Pediatric Dosage

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- ***Children 2 to 11 years have faster clearance in comparison to adults***
  - ***Children and adolescents 12 to 17 years have more similar plasma pharmacokinetics***
-  **Based on PK, pharmacodynamics and safety of higher exposure in adolescents and adults, **50 mg/m<sup>2</sup>** (day 1: 70 mg/m<sup>2</sup>; max. 70 mg/d) *selected for further pediatric development***

# Protocol 042: PK in children 3-24 months

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# Protocol 058: Neonatal PK study

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- **Study Population:** Children ages 0-3 months with documented or highly suspected invasive candidiasis
- **Treatment Regimens:** Caspofungin administered IV as single daily dose (concomitant amphotericin B permitted)
  - 25 mg/m<sup>2</sup> Single dose (Panel A): 6 patients
  - 25 mg/m<sup>2</sup> Multiple dose (Panel B): 12 patients
- **Pharmacokinetics:**
  - Peak/trough PK on Day 1 (both panels) and Day 4 (Panel B)
  - results demonstrate that 25 mg/m<sup>2</sup> results in comparable PK to adults receiving caspofungin 50 mg or children receiving 50 mg/m<sup>2</sup>

**Micafungin**

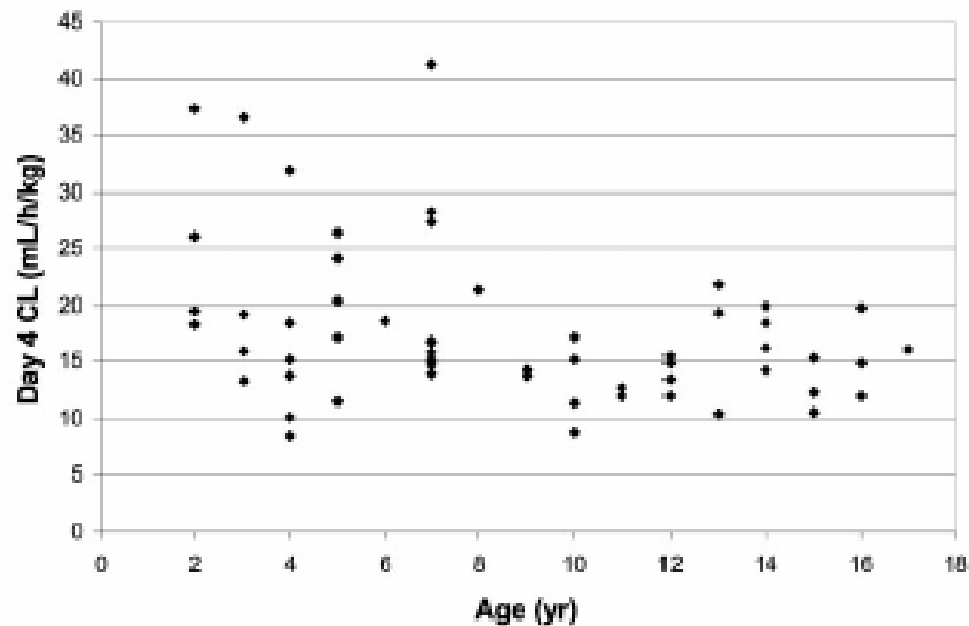
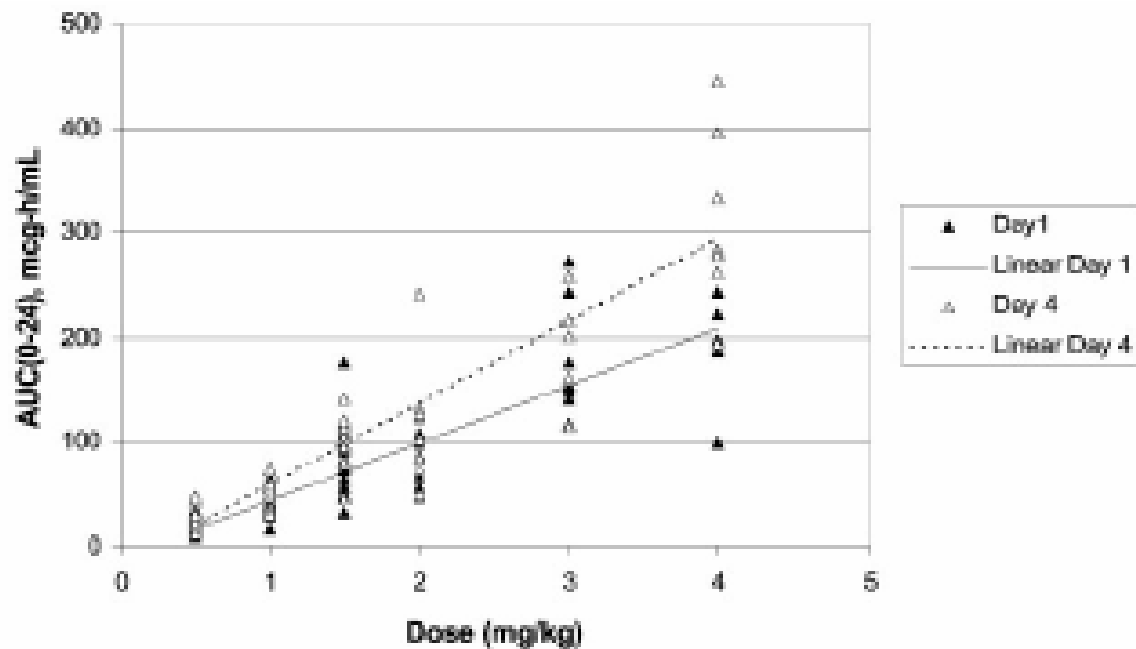
# Micafungin: Pk-Study in in Children 2-17 Years

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- **Open-label, sequential, dose-escalation tolerance study**
  - **Six dose levels of MICA (0.5–4.0 mg/kg); 1-hour infusion once daily**
  - **Two age groups (2–12 and 13–17 years)**
  - **Samples for PK analysis were taken on d 1 and 4**
- **A total of 78 patients with neutropenia (absolute neutrophil count <500 cells/mm<sup>3</sup>) enrolled; 77 received study drug**

# Micafungin: Pk-Study in in Children 2-17 Years

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# Micafungin: PK Study in Children 2-17 Years

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	Pediatric pts (2-17 yr)			Adults	
Dosage	1 mg/kg	2 mg/kg	4 mg/kg	50 mg	100 mg
C <sub>max</sub> (ug/mL)	10.8	15.3	30.3	3.6	7.1
AUC 0-24h (ugxh/mL)	40.3	83.0	191.4	33.9	59.9
T <sub>1/2</sub> beta (h)	12.5	13.2	11.6	12.5	13.0
CL (L/h/kg)	0.021	0.020	0.017	0.017	0.018
VD <sub>ss</sub> [L/kg]	0.33	0.31	0.28	0.31	0.32

# Micafungin: Pk-Study in Premature Infants

Population	$t_{1/2}$ (h)	$K_e$ (1/h)	$Vd_{ss}$ (L/kg)	Cl (mL/h/kg)
Neonates >1000 g (n = 15)				
Mean	8.8	0.088	0.435	38.9
SD	1.8	0.02	0.111	12.1
95% CI	7.4–9.2	0.08–0.1	0.378–0.491	32.8–45.0
Children 2–8 years old (n = 33) <sup>14</sup>				
Mean	11.5	0.064	0.335	22.5
SD	2.9	0.016	0.16	8.6
95% CI	10.5–12.4	0.059–0.069	0.28–0.39	19.6–25.4
Children 9–17 years old (n = 32) <sup>14</sup>				
Mean	13.4	0.056	0.243	15.1
SD	3.8	0.018	0.074	6.3
95% CI	12.1–14.7	0.05–0.062	0.216–0.271	12.87–17.24
Adults (n = 48) <sup>8</sup>				
Mean	13.1	0.055	0.256	14.6
SD	3.0	0.01	0.052	3.4
95% CI	12.2–13.9	0.052–0.058	0.241–0.271	13.6–15.5

$t_{1/2}$  indicates half-life;  $K_e$ , elimination rate constant;  $Vd_{ss}$ , steady-state volume of distribution; Cl, clearance; SD, standard deviation; 95% CI, 95% confidence interval.

# Micafungin: Elevated Dosage in Premature Infants

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- Phase I, repeat-dose, single center, open-label trial
  - neonates >48 hrs of age and < 120 d of life
  - MICA doses 15 mg/kg x 5 days / 60 minutes
  - Sparse sampling day 5 / population PK
- 12 patients; seven <1000 g; median birth weight 775 g, median gestational age 27 weeks
  - Micafungin safe and well tolerated
  - Clt and VD greater than in older children
  - 15 mg/kg dosing corresponded to an exposure of approximately 5 mg/kg in adults

**Voriconazole**

# Voriconazole: Pediatric Dose Finding

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- **Two phase II studies investigating pharmacokinetics of IV VCZ in children 2-12 years at dosages of 2x3 and 2x4 mg/kg**
- **Combined data on 355 plasma samples in 35 patients**
  - ➔ **Linear pharmacokinetics**  
**Faster clearance**
  - ➔ **High interindividual variability (CYP2C19)**

# Voriconazole: Dosage in children 2 to 11 yrs (1)

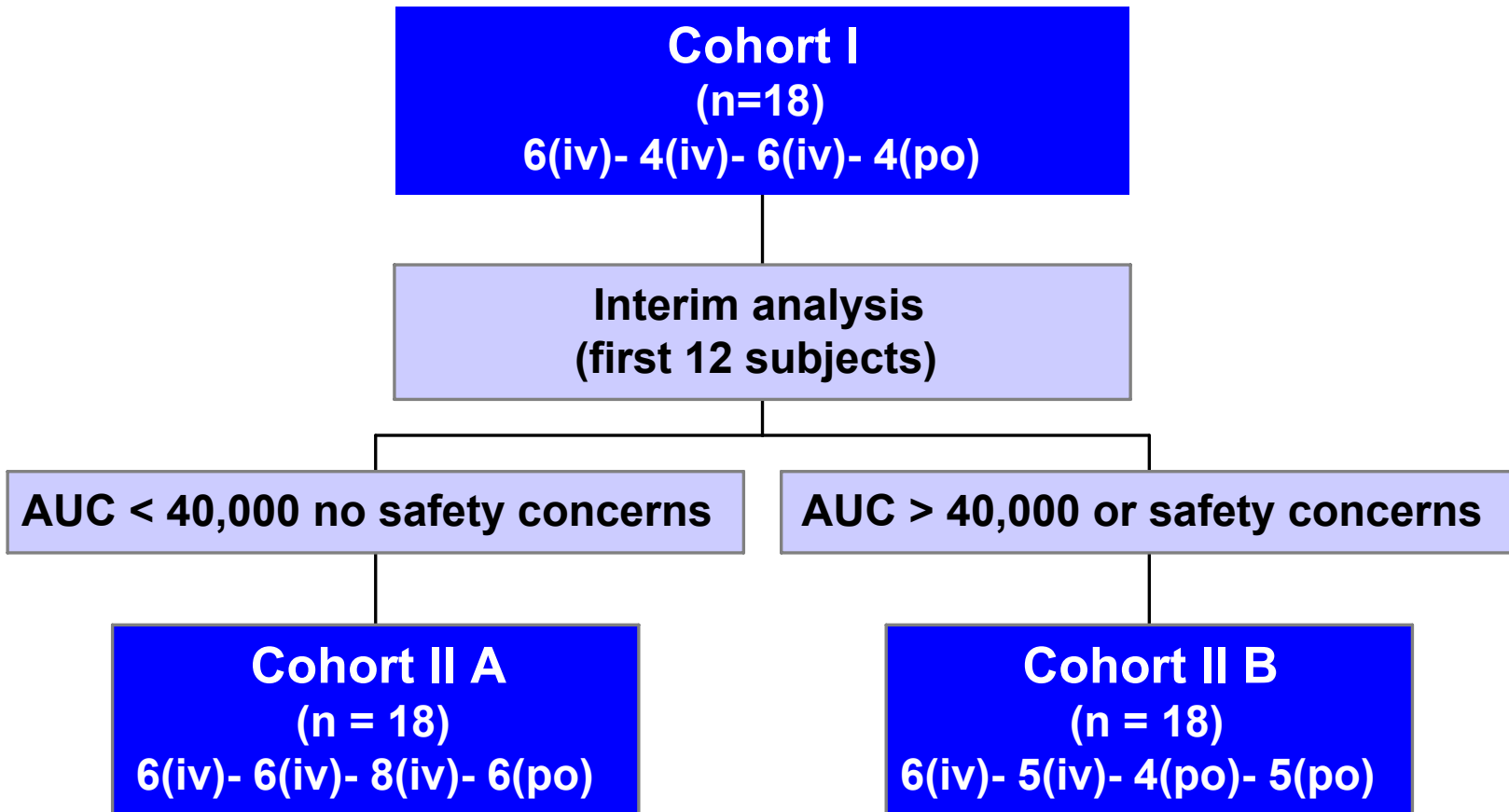
Medians	3mg/kg		4mg/kg	
	*Paed.	**Adults	*Paed.	**Adults
$C_{ave}$ (ng/ml)	889	1155	1186	3217
$AUC_{\tau}$ (ng·h/ml)	10,670	13,855	14,227	38,605

\* 35 subjects from SD and MD PK studies

\*\* 236 healthy volunteers from SD and MD PK studies

# VCZ in children 2-11 yrs: A 1501037

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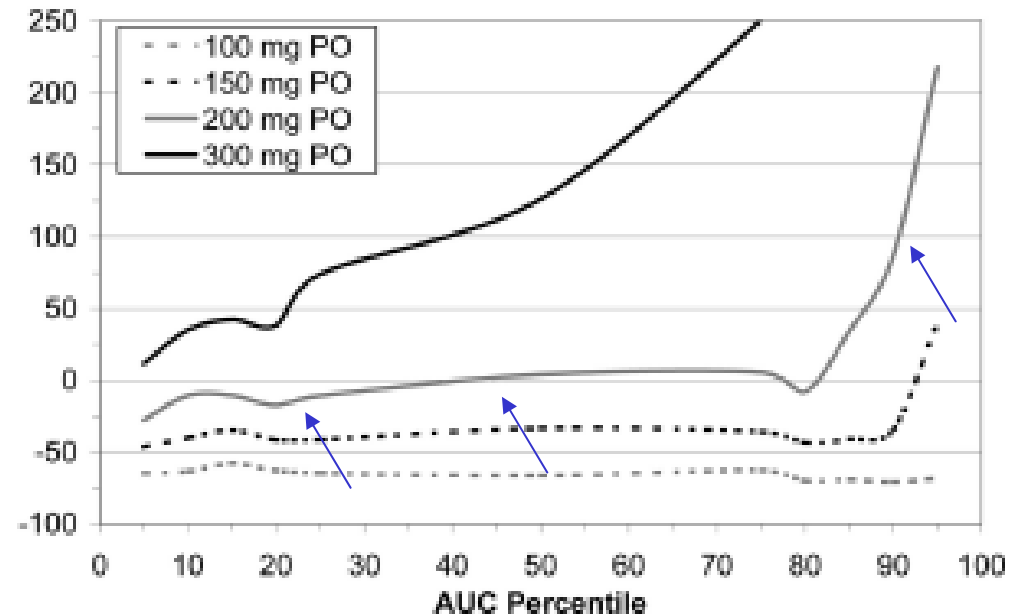
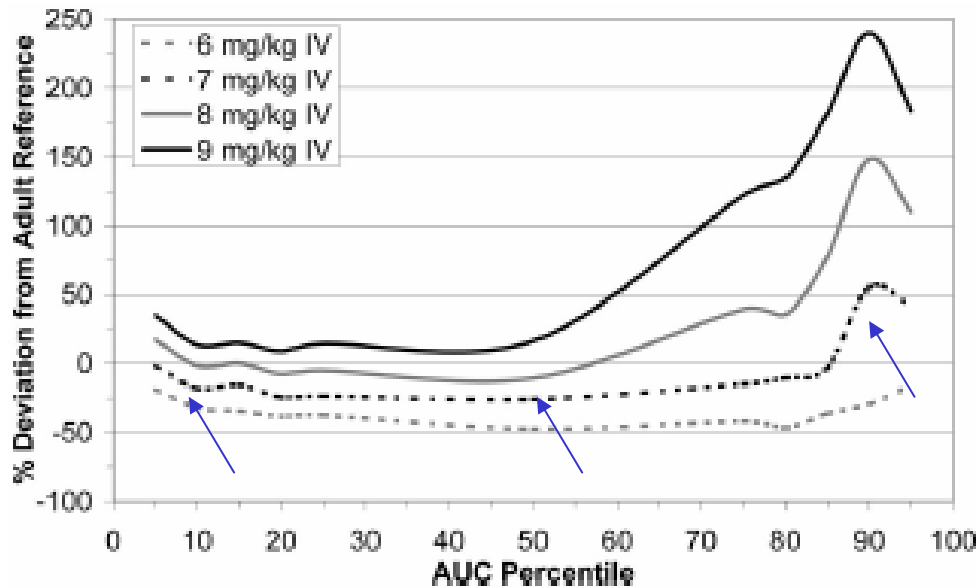
# **VCZ in children 2-11 yrs: A 1501037**

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- **Population PK analysis of plasma data from all 3 PK studies of pediatric patients of 2 to <12 years with a range of SD/MD IV and or PO doses**
- **Final PK model described VCZ *elimination* by a Michaelis-Menten process and *distribution* by a two-compartment model. It also incorporated a statistically significant ( $P < 0.001$ ) *influence of the CYP2C19 genotype and of the alanine aminotransferase level* on clearance**
- **Model was used in a number of deterministic simulations (based on various fixed, mg/kg of body weight, and individually adjusted doses) aimed at finding suitable i.v. and p.o. VCZ dosing regimens for pediatric patients**

# VCZ in children 2-11 yrs: A1501037

Percent deviations from the reference adult population  
AUC distribution (4 mg/kg BID IV; 200 mg BID PO)



# Voriconazole: Pediatric Dose Finding

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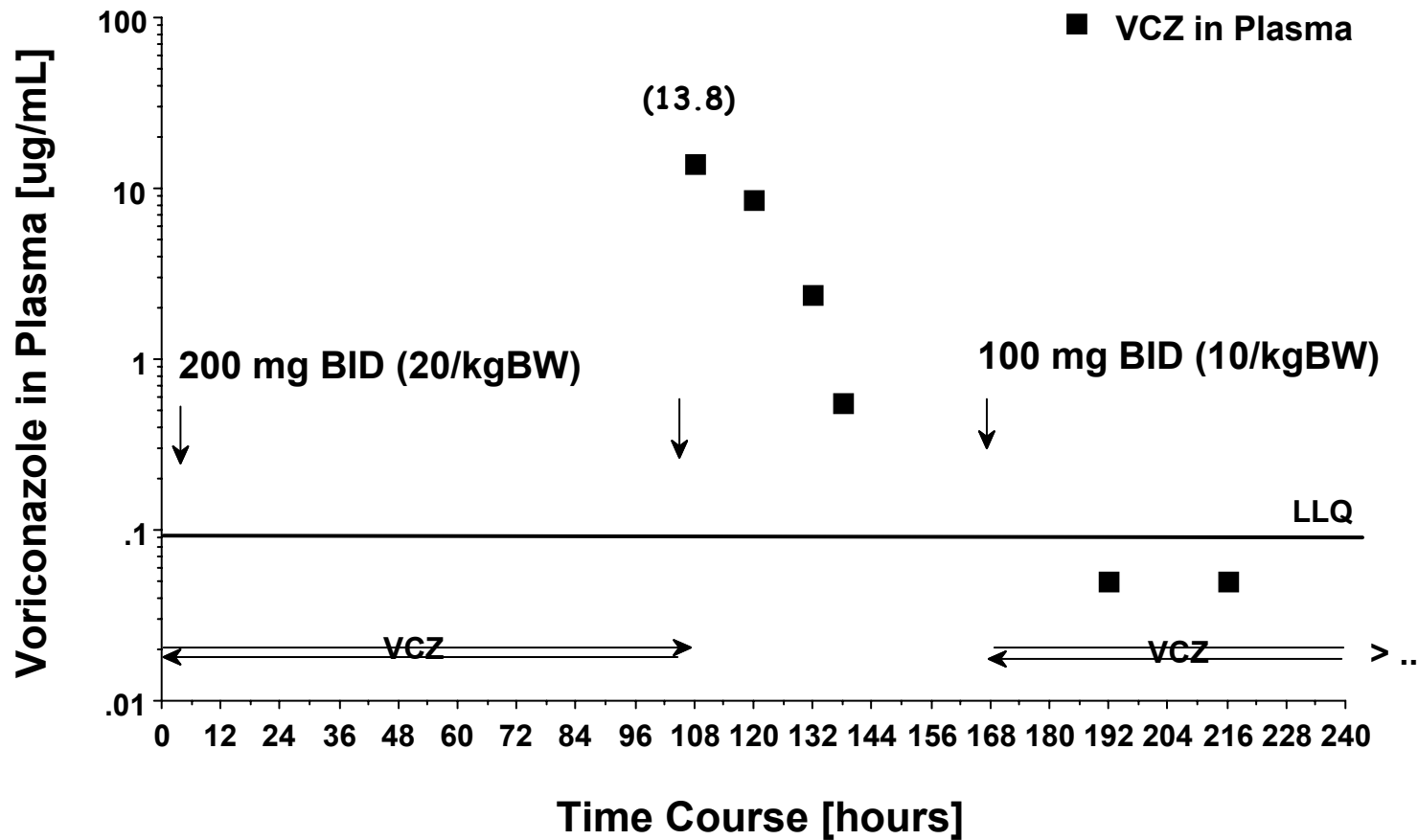
Dosage finding of VCZ for pediatric patients **2 to 11 y** completed

- 2x7 mg/kg IV without loading
- 2x200 mg PO without loading

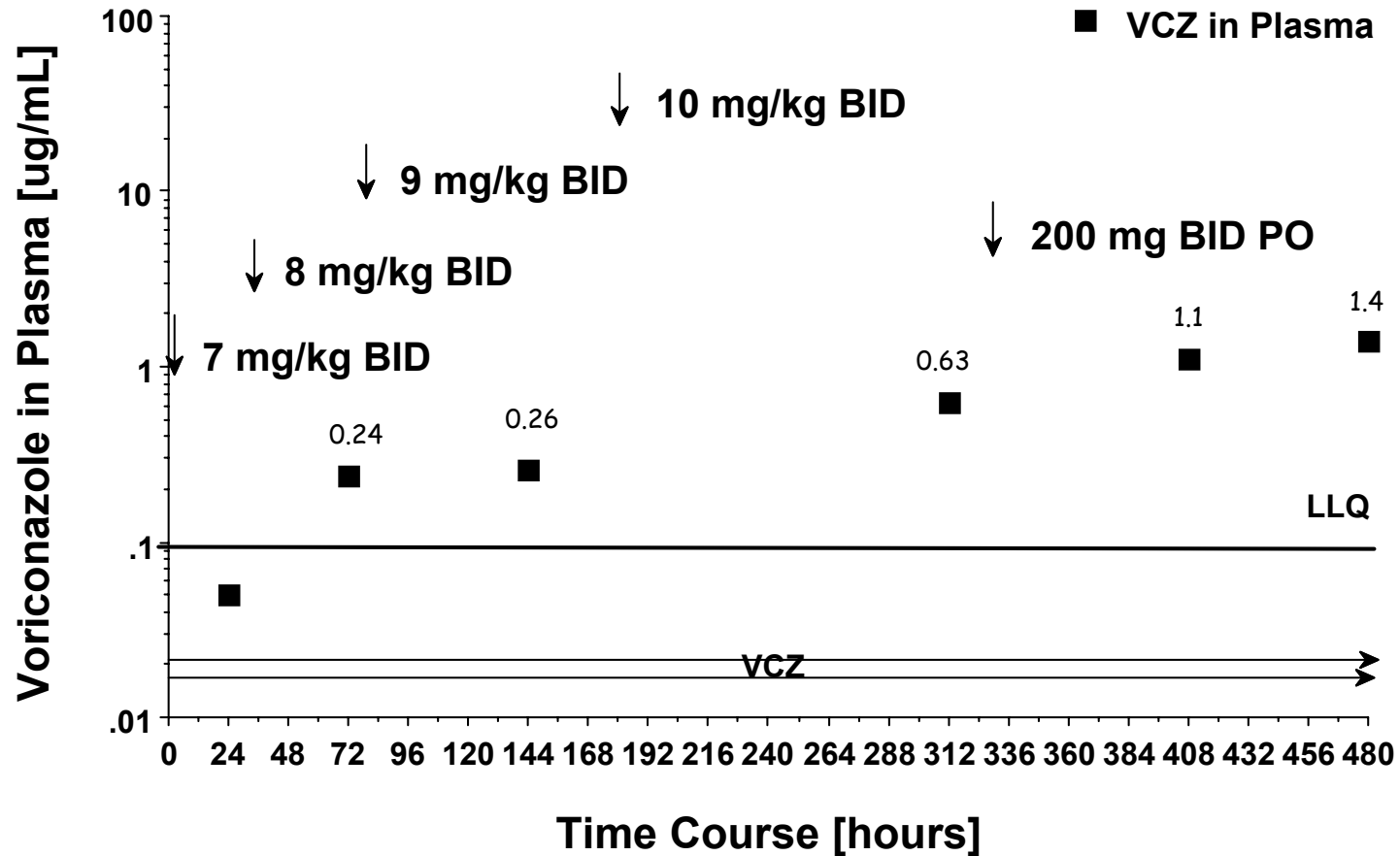
Dosage for adolescents **≥12 years**

- 2x4 mg/kg IV (2x6 mg day 1)
- 2x200 mg PO (2x400 mg day 1)

# VCZ-TDM, case 1:



# VCZ TDM, case 2:



# VCZ TDM - Summary

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- **Two cases illustrate the high interindividual variability in drug exposure following VCZ therapy pts < 12 years**
- **Indicate the need for further validation of the currently recommended dosage in postapproval studies to better understand the exposure-effect relationships**
- **The AUC may be more adequate than trough or random plasma concentrations to study these relationships**