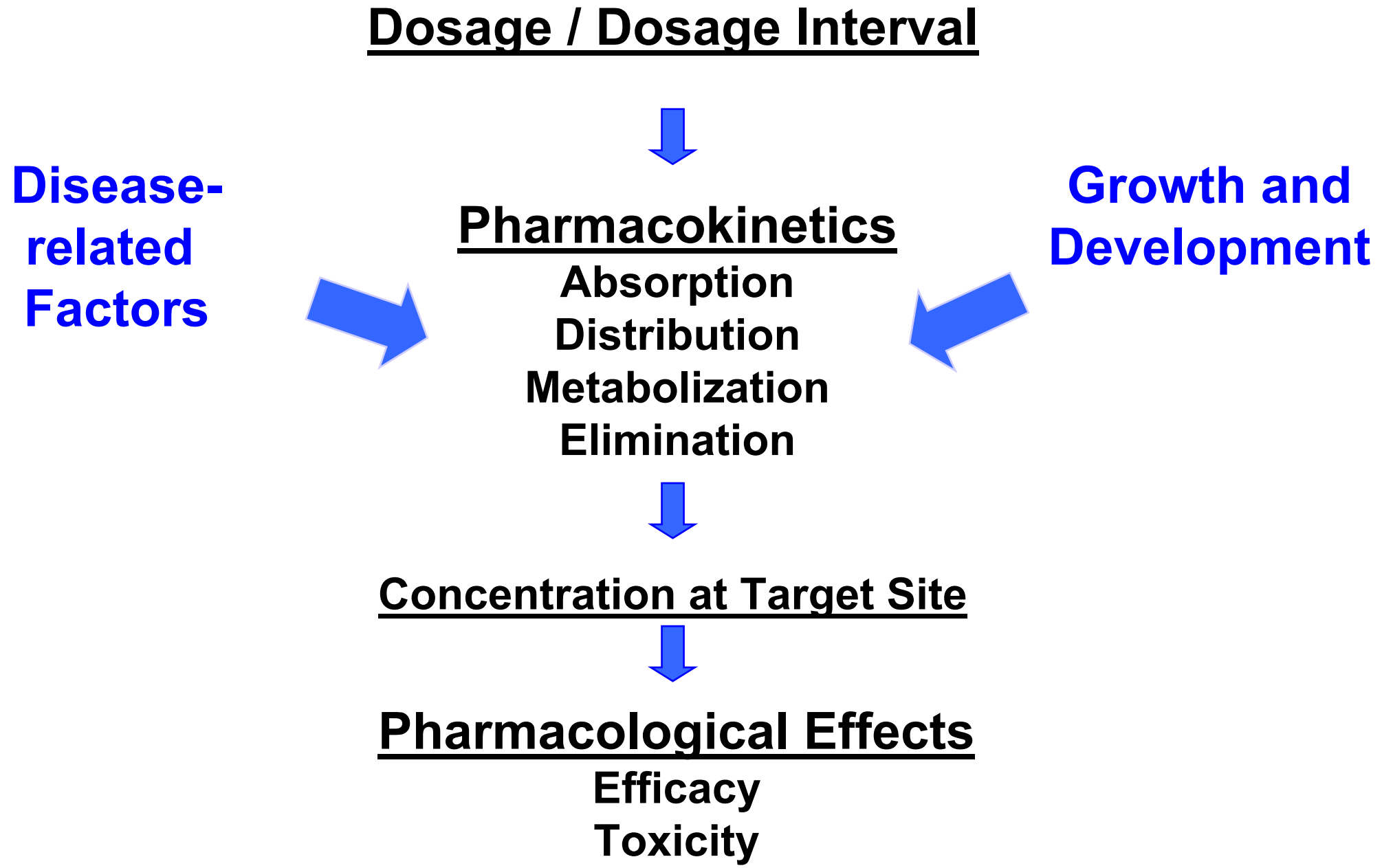
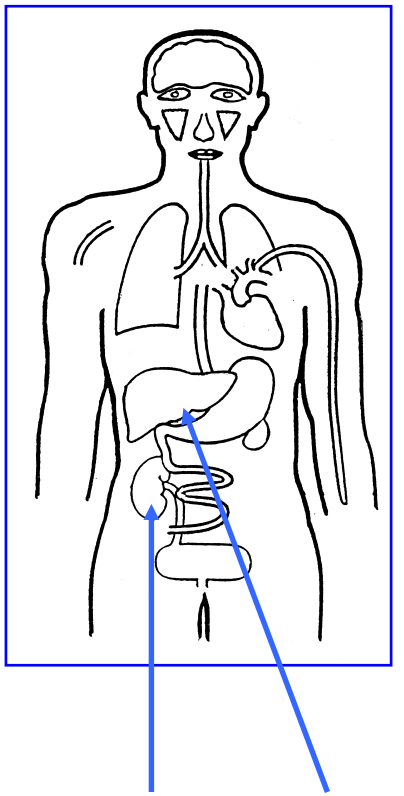
Pharmacokinetics of Antifungal Agents in Pediatric Patients

Andreas H. Groll, M.D.

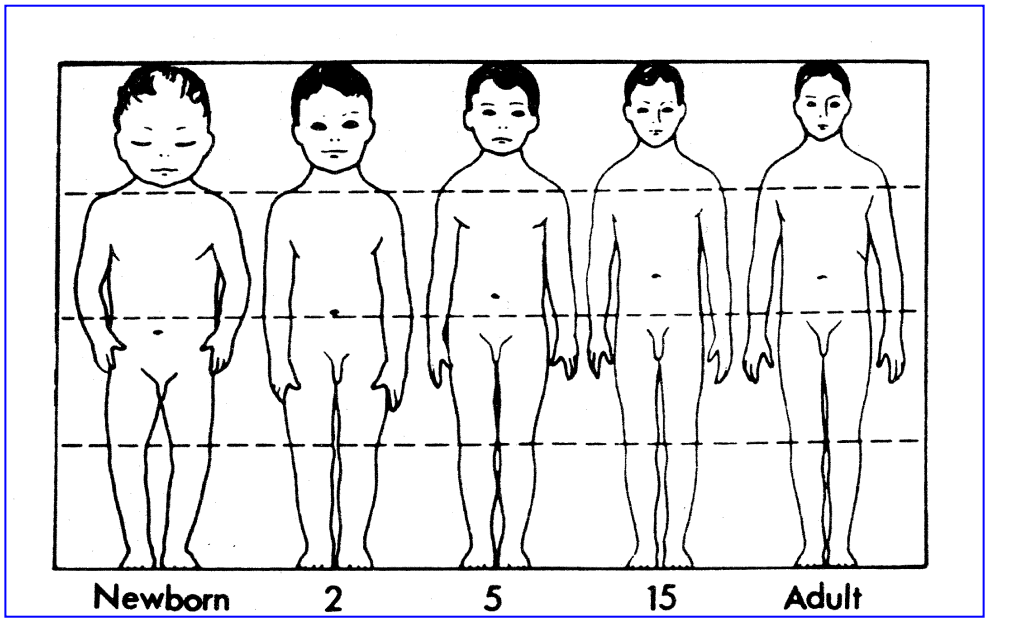
Infectious Disease Research Program
Center for Bone Marrow Transplantation and
Department of Pediatric Hematology/Oncology
University Children's Hospital Muenster
grollan@ukmuenster.de


Dosage / Dosage Interval
Disease-related Factors
Pharmacokinetics
Absorption
Distribution
Metabolization
Elimination
Growth and Development
Concentration at Target Site
Pharmacological Effects
Efficacy
Toxicity



Maturation processes
of excretory organs

Changes in body mass and body composition

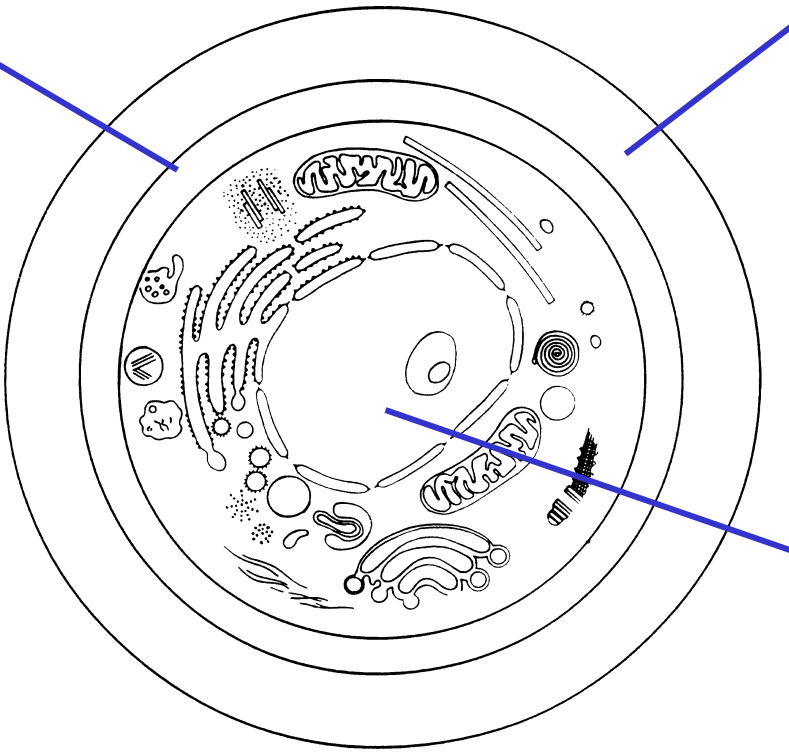


Scaling of dosing regimens based on body weight or body surface area generally inappropriate

Pediatric Antifungal Arsenal

Cell membrane

- Polyenes
  - > D-AmB
  - > L-AmB
  - > ABLC
- Triazoles
  - > Fluconazole
  - > Itraconazole
  - > Voriconazole
  - > Posaconazole



Cell wall

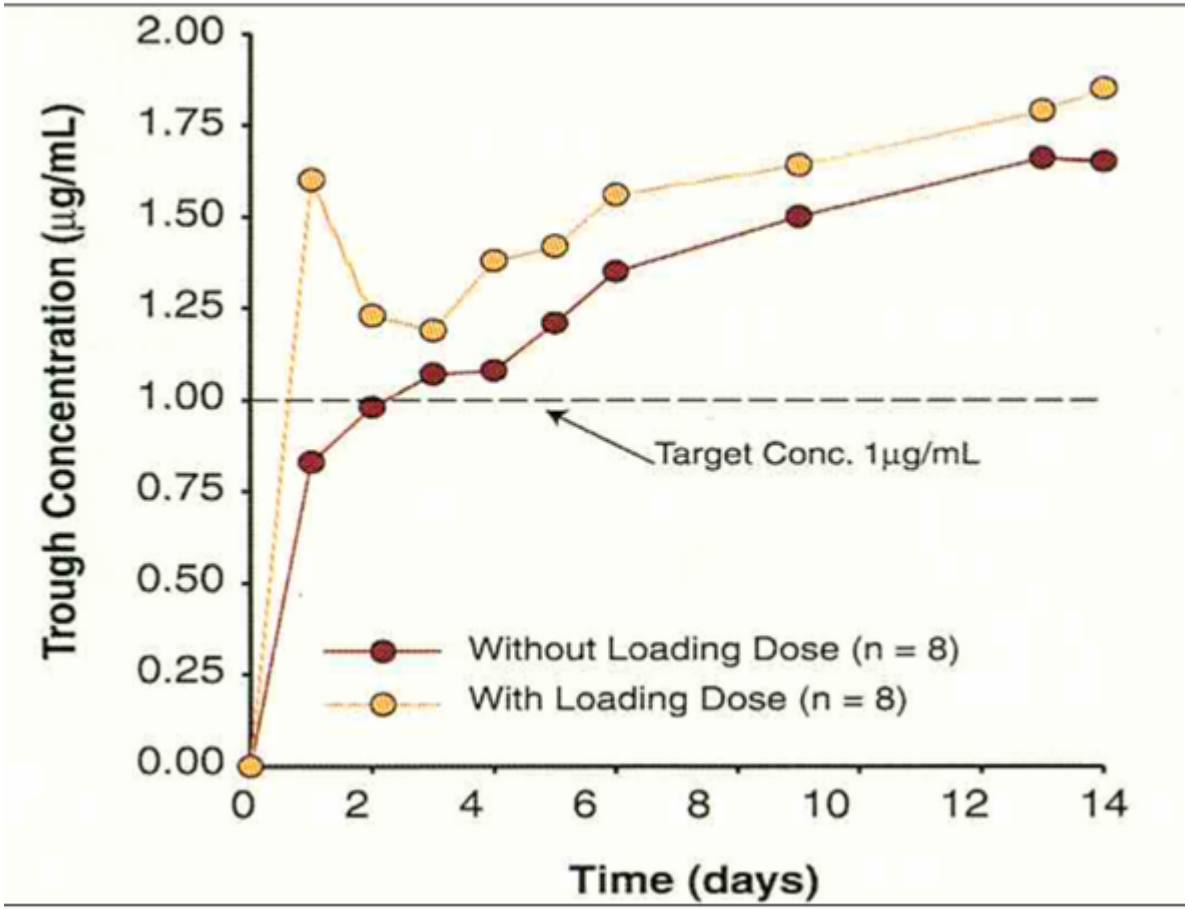
- Echinocandins
  - > Caspofungin
  - > Micafungin
  - > Anidulafungin

Nucleic acid synthesis

- > Flucytosine

Caspofungin

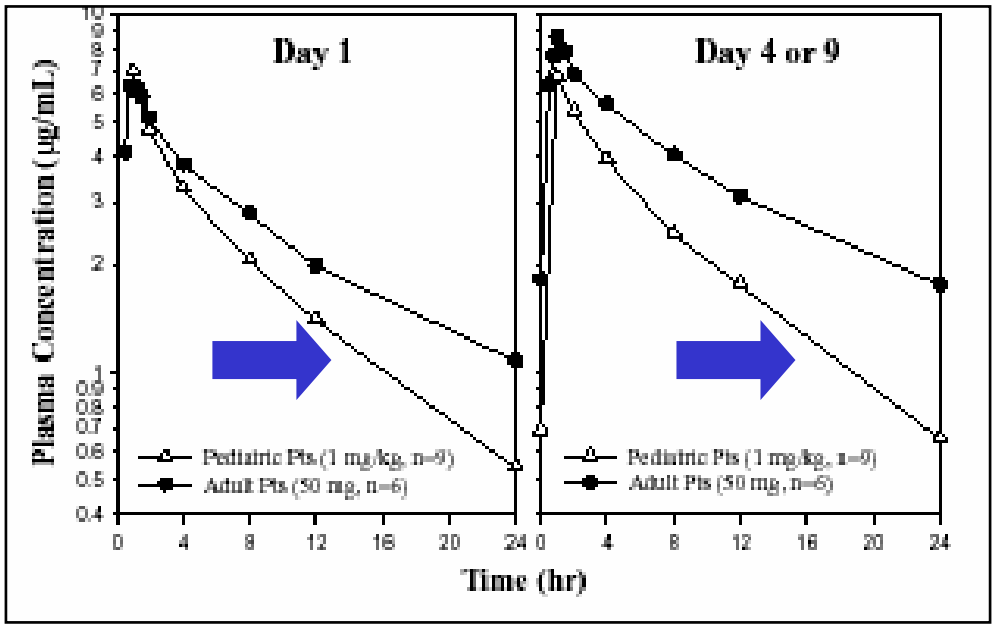
Caspofungin: Dosing Rationale in Adults



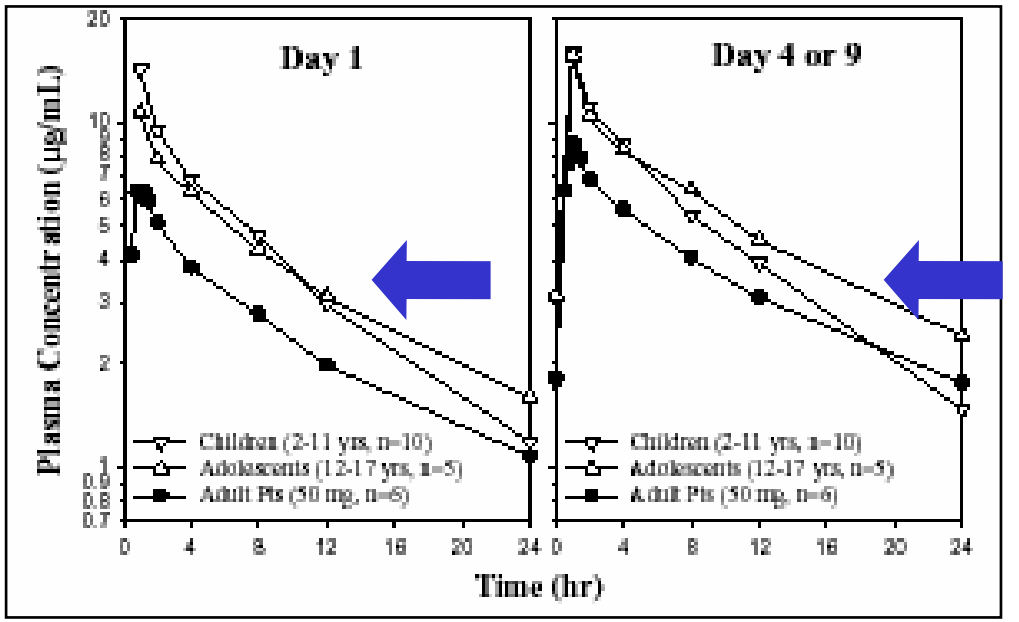
Stone et al. AAC 02

Protocol 033: Pediatric Dose-Finding

CAS 1mg/kg



CAS 50 mg/m2



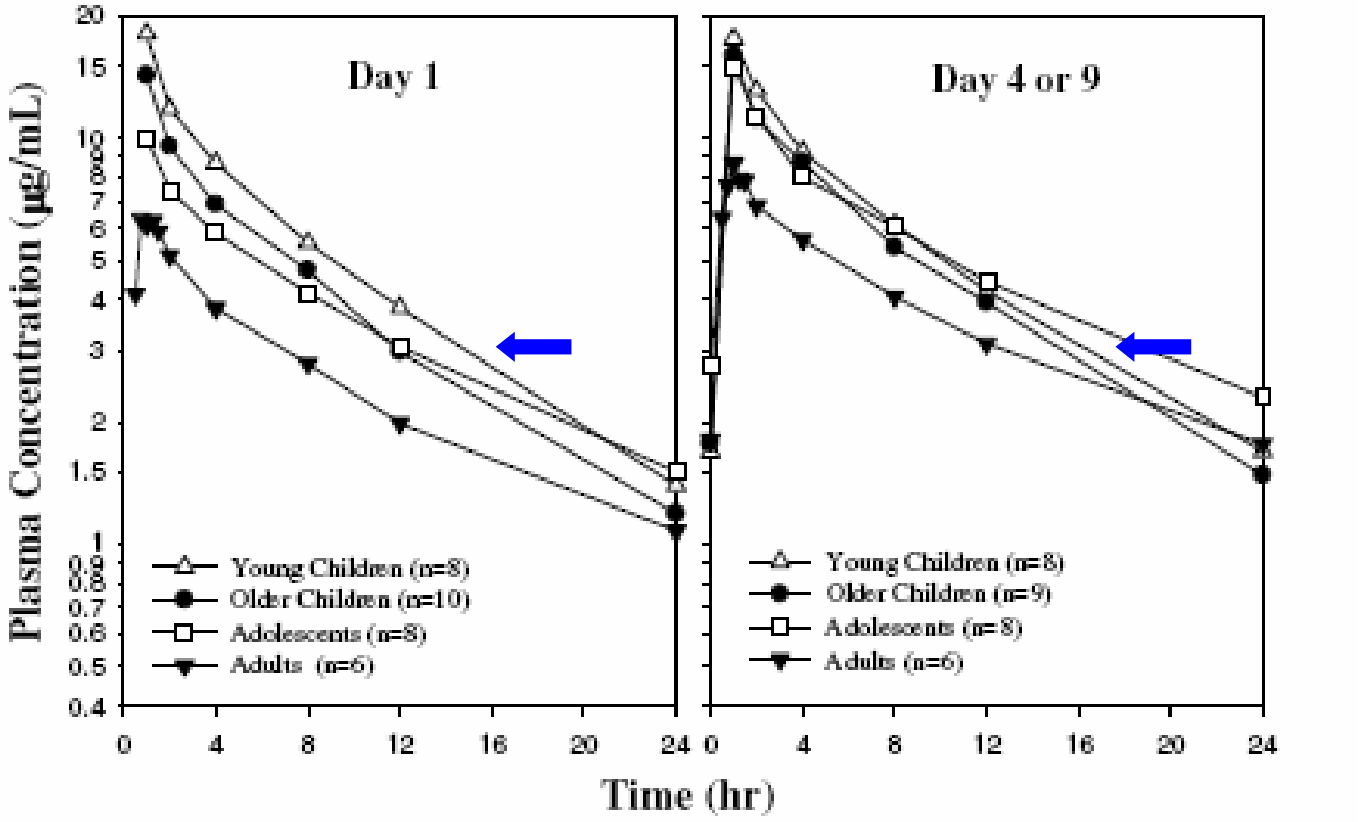
Walsh et al. AAC 05

Caspofungin: Pediatric Dosage

- ***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/m2 (day 1: 70 mg/m2; max. 70 mg/d)** ***selected for further pediatric development***

Protocol 042:
PK in children 3-24 months



Neely et al. AAC 09

Protocol 058: Neonatal PK study

- **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^2 Single dose (Panel A): 6 patients
  - 25 mg/m^2 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^2 results in comparable PK to adults receiving caspofungin 50 mg or children receiving 50 mg/m^2

Saez-Llorens AAC 09

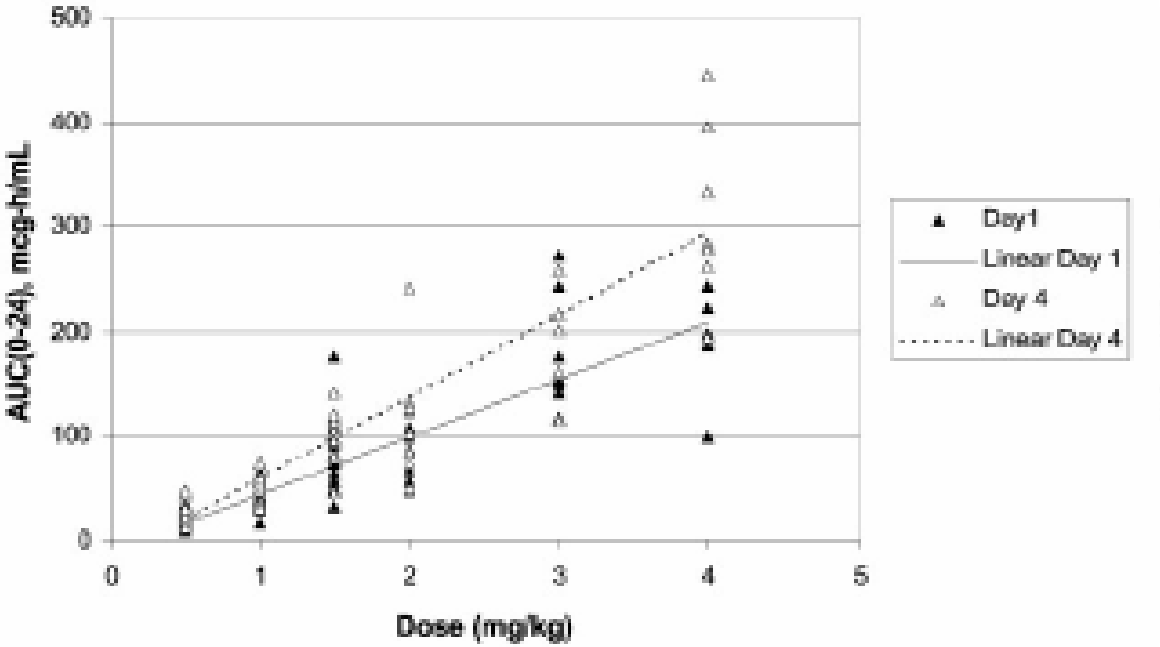
Micafungin

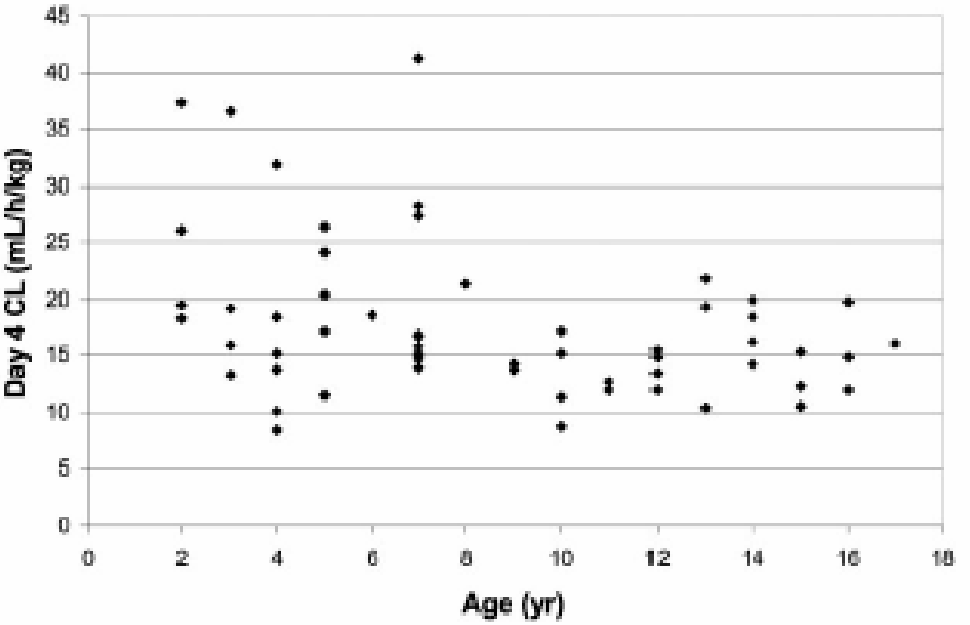
Micafungin: Pk-Study in in Children 2-17 Years

- 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/mm3) enrolled; 77 received study drug

Seibel AAC 05

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





Seibel AAC 05

Micafungin: PK Study in Children 2-17 Years

	Pediatric pts (2-17 yr)			Adults	
Dosage	**1 mg/kg**	**2 mg/kg**	**4 mg/kg**	**50 mg**	**100 mg**
Cmax (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 ½ 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
VDss [L/kg]	0.33	0.31	0.28	0.31	0.32

Seibel AAC 05; Hiemenz AAC 05

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	8.3	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)[14]				
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)[14]				
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)[8]				
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.

Heresi PIDJ 06

Micafungin: Elevated Dosage in Premature Infants

- 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

Smith PIDJ 09

Voriconazole

Voriconazole: Pediatric Dose Finding

- **Two phase II studies investgating 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)**

Walsh et al. 04

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

1.3 -fold dosage

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

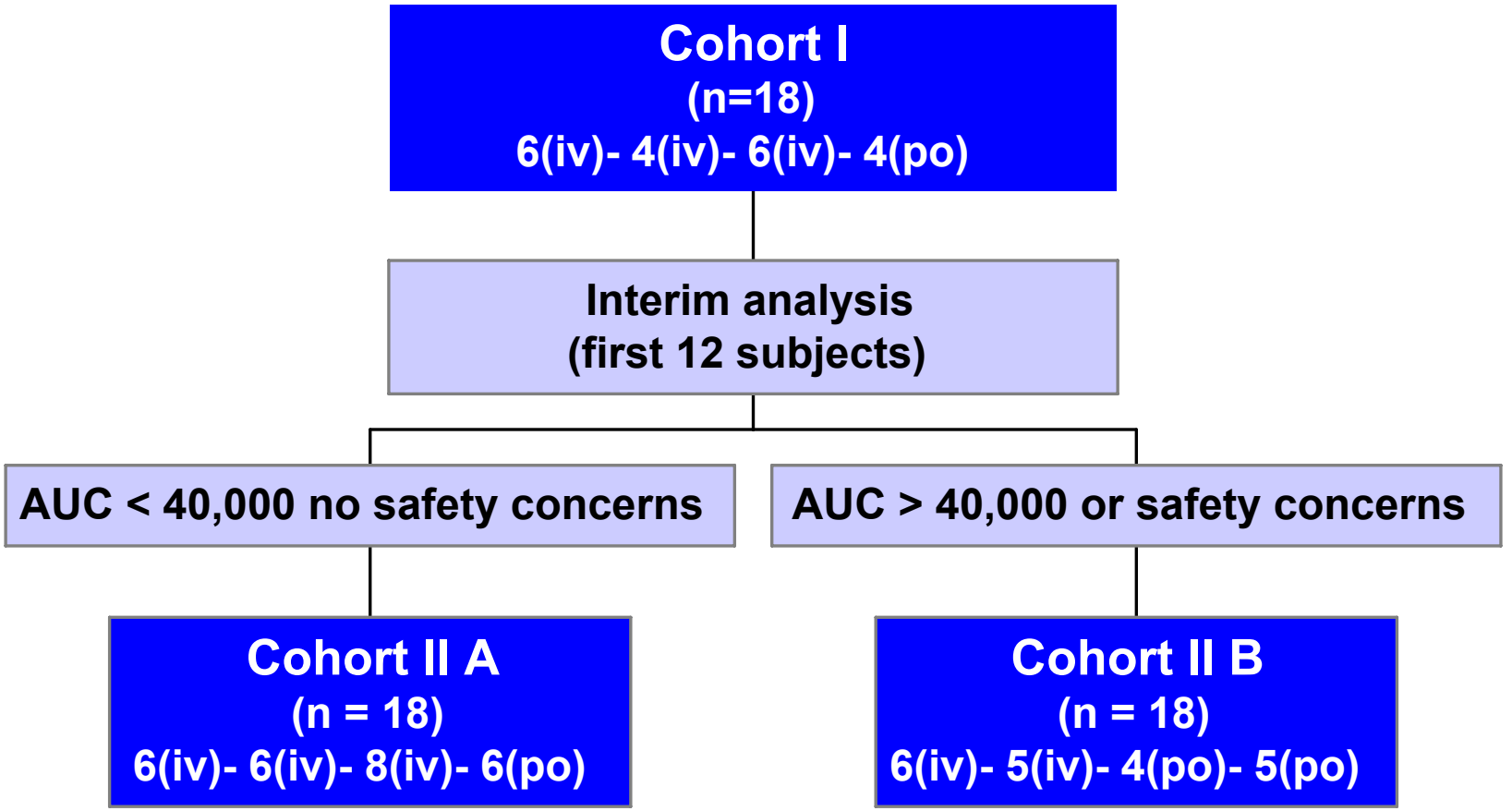
1.3 -fold

2.8 -fold

* 35 subjects from SD and MD PK studies
** 236 healthy volunteers from SD and MD PK studies

Walsh et al. AAC 04

VCZ in children 2-11 yrs: A 1501037



Walsh et al. ICAAC 06

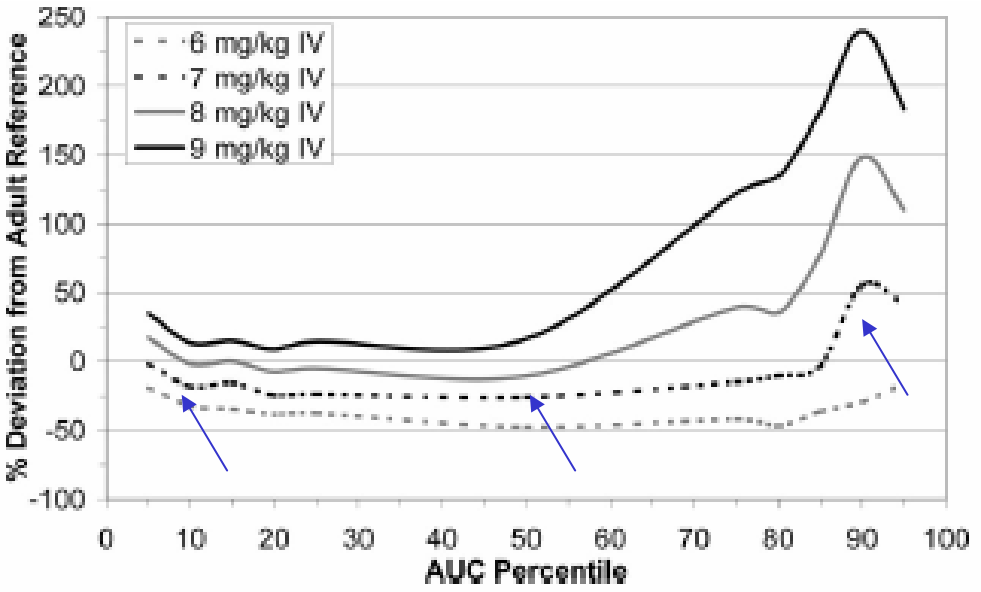
VCZ in children 2-11 yrs: A 1501037

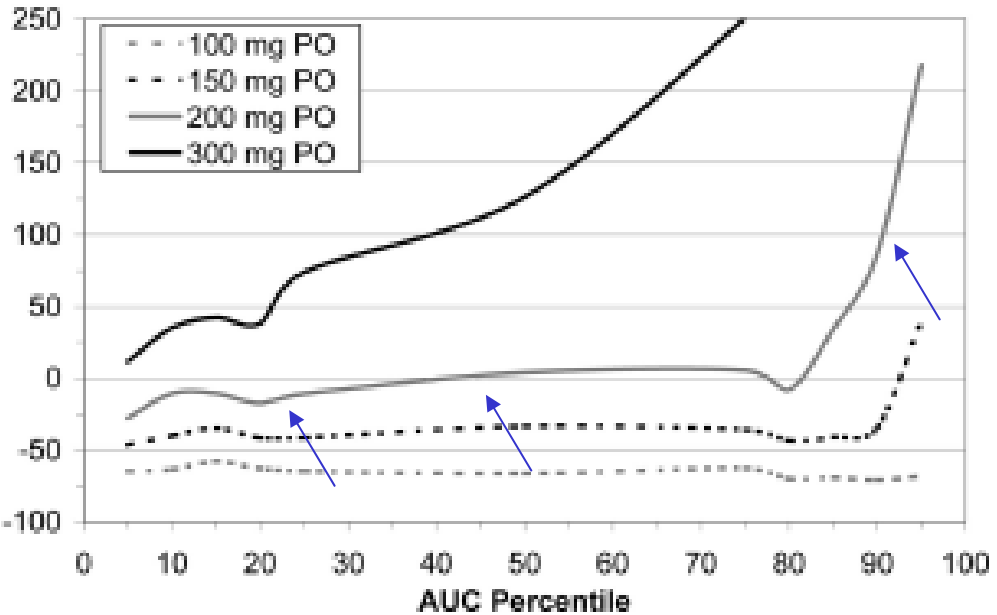
- **Population PK analysis of plasma data from all 3 PK studies of pediatric patients of 2 to <12 years with a range of SD/MD IV and or PO doses**
- **Final PK model described VCZ *elimination* by a Michaelis-Menten process and *distribution* by a two-compartment model. It also incorporated a statistically 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**

Karlsson et al. AAC 2009

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)





Karlsson et al. AAC 09

Voriconazole: Pediatric Dose Finding

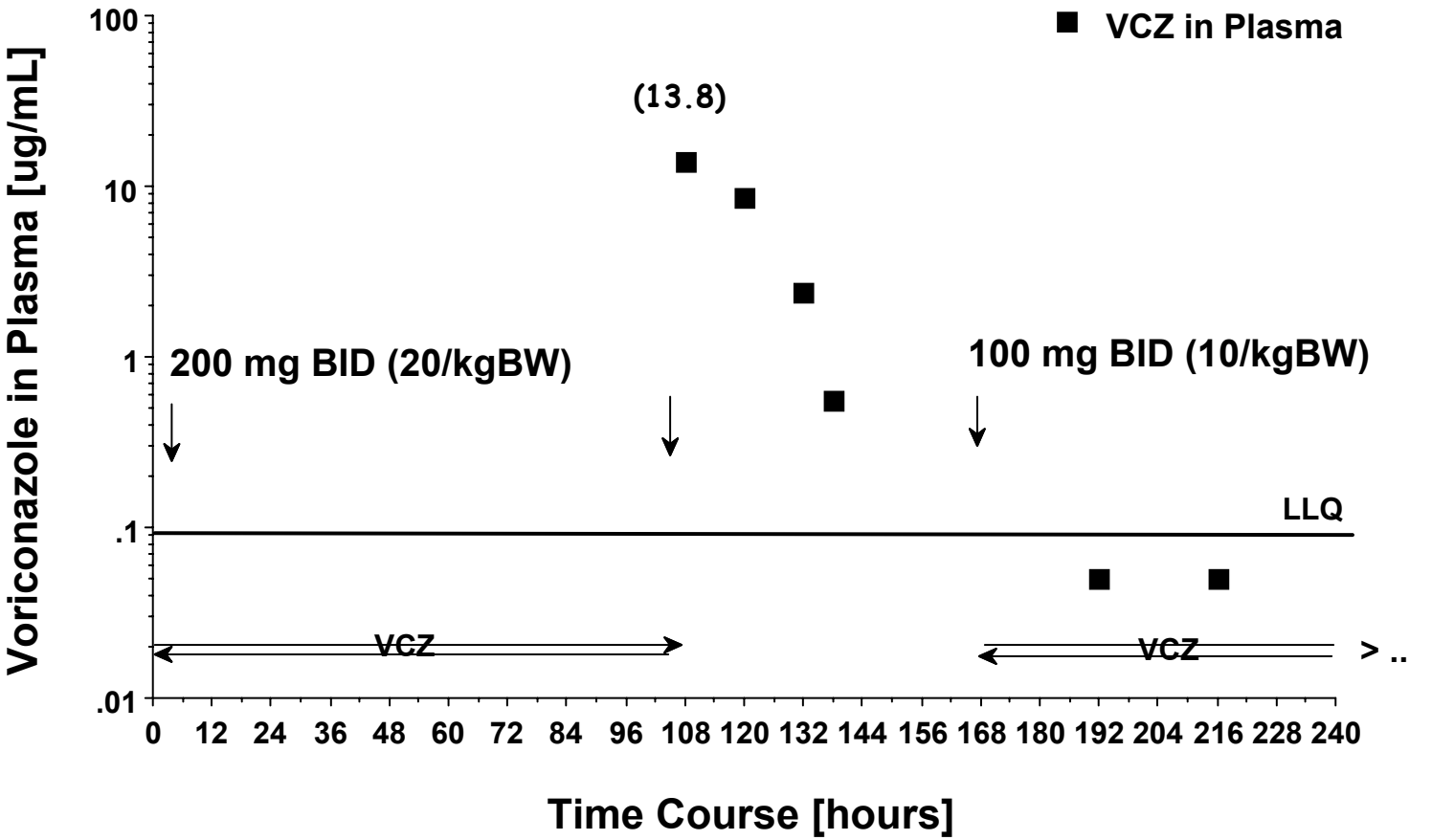
Dosage finding of VCZ for pediatric patients *2 to 11 y* completed

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

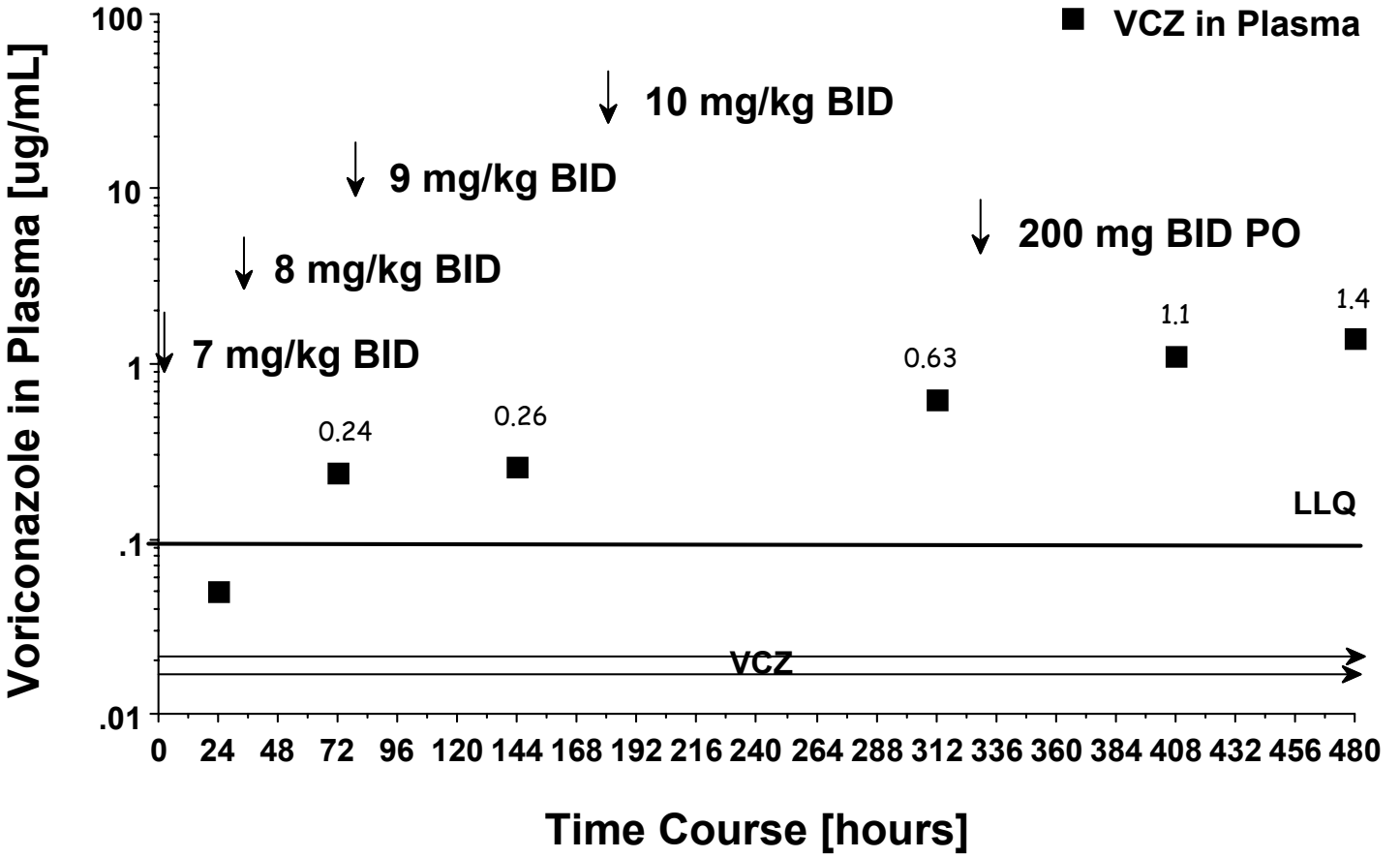
Dosage for adolescents ≥12 years

- **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

- **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**