

Therapeutic Drug Monitoring of antifungal agents

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Antwerpen 24 October 2014

Yesterday's Medicine

One size (dose) fits all



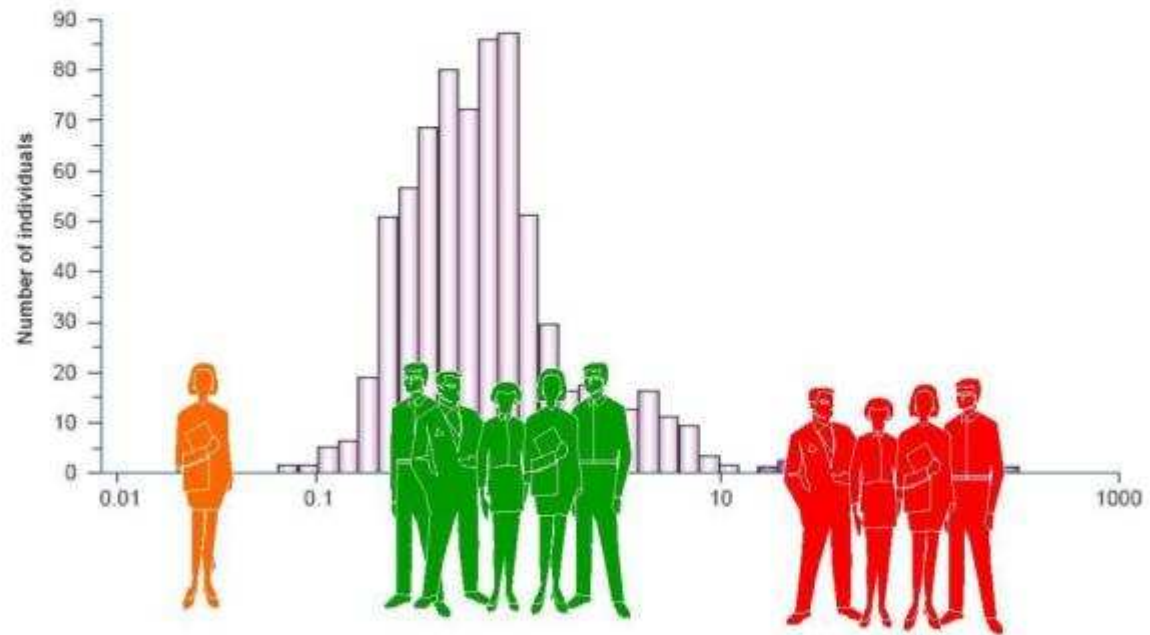
Which Dose Is Right For You?

**Before:
Trial and Error**



100mg

After: PERSONALIZED



500mg

100mg

(10mg)

Therapeutic Drug Monitoring

- Definition of TDM: dose – concentration – response
- TDM must be considered complex process
- Crucial to identify sequential steps in the TDM-process
- Many steps in this process are a source for variation and mistakes
 - ✓ Prevent variation and mistakes
- Interpret TDM results in the light of this process

Clinical Question – When to prompt for TDM?

- Adherence ?
- Lack of therapeutic response due to suboptimal therapy ?
- Side effects due to toxic exposure ?
- Drug interaction ?
- Phenotypic output for genotypic mutations (in the absence of testing facilities ?)
- Effect kidney / liver / other organ-failure on drug concentrations?
- Change from IV to PO and vice versa ?

Interpretation and reporting

- Therapeutic concentrations reflect a chance for efficacy or absence of toxicity (probabilistic concept of the therapeutic range)
- Target concentration: population vs individual patient
 - Individual for sure does not reflect the population
- Therapeutic result may be dependent on the patient, disease, age, etc
- Target concentration: dependent on the “bug”
- What about target concentrations in the setting of combination therapy
- Therapeutic range defined in small population with a wide variety of diseases
 - Validation of range in randomized trial ?
- Drugs with poor dose –response relations
- ‘Treat the patient, not his/her blood level’

Slide 6

2

plaatje toevoegen van verschillende populaties

plaatje toevoegen van verschillende species

plaatje toevoegen van verschillende middelen

Roger Brüggemann, 12/10/2013

Therapeutic Drug Monitoring In the daily clinical care

Therapeutic drug monitoring (TDM) of antifungal agents:
guidelines from the British Society for Medical Mycology.

Ashbee HR¹, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW.

J Antimicrob Chemother. 2014 May;69(5):1162-76.

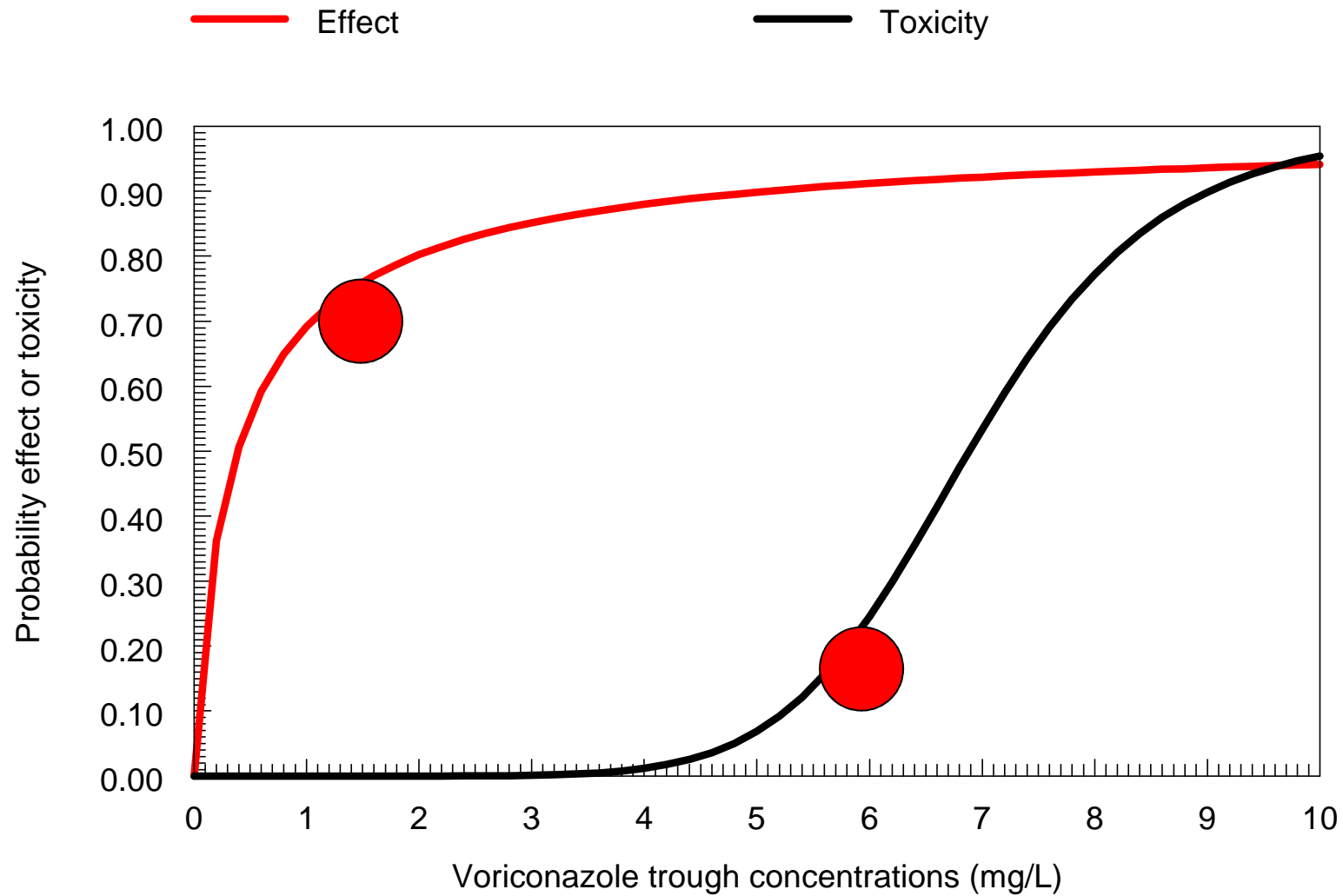
Voriconazole



Voriconazole: evidence for exposure-response relationships

- Despite imperfect datasets, there is a consistent signal that links drug-exposure with outcome, for example:
 - Random levels of < 2.05 mg/L associated with treatment failure¹
 - Trough concentration <1 mg/L associated with decreased survival in children²
 - In adults concentration > 1.7 mg/L show favorable outcome and < 5 mg/L less toxicity³
 - $C_{\text{trough}}/\text{MIC}$ of 2-5. Linkage to susceptibility of the offending organism in relation to exposure⁴

Voriconazole: PK-PD



The Effect of Therapeutic Drug Monitoring on Safety and Efficacy of Voriconazole in Invasive Fungal Infections: A Randomized Controlled Trial

Wan Beom Park,¹ Nak-Hyun Kim,¹ Kye-Hyung Kim,^{1,a} Seung Hwan Lee,² Won-Seok Nam,² Seo Hyun Yoon,² Kyoung-Ho Song,¹ Pyoeng Gyun Choe,¹ Nam Joong Kim,¹ In-Jin Jang,² Myoung-don Oh,¹ and Kyung-Sang Yu²

¹Department of Internal Medicine, and ²Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine, Republic of Korea

Methods

- Randomized, assessor-blinded, controlled, single centre trial.
 - Primary end-point was 3 fold reduction of toxicity
- 110 adult patients were randomly assigned to TDM or non-TDM groups.
- In TDM group: voriconazole dosage was adjusted (target range, 1.0–5.5 mg/L; measured on the fourth day)
- The voriconazole dosage was adjusted 24–48 hours after blood sampling based on the results of TDM.
- The non-TDM group received a fixed, standard dosage.

Results - Adverse Events

- There was no significant difference in the incidence of adverse events between the TDM and non-TDM groups
- Visual disturbance or encephalopathy could be evaluated in 92 (85%) patients who were communicable.
- Discontinuations due to adverse events:
 - 2 (4%) in the TDM group,
 - 9 (17%) in the non-TDM group ($P = .02$).

Results - efficacy

- Overall mortality at 6 weeks after the initiation of therapy
 - 20% (11/55) in the TDM group
 - 34% (18/53) in the non-TDM group (P=not provided)
- Overall mortality at 12 weeks after the initiation of therapy
 - 24% (13/55) in the TDM group
 - 40% (21/53) in the non-TDM group (P = .14).
- Treatment success in probable or proven fungal infections:
 - 86% (25 of 29) in TDM arm treatment success
 - 63% (20 of 32) in the non-TDM group (P = .04),
- Treatment failure was more prevalent in the non- TDM group than in the TDM group (31% vs 10%, respectively; P = .04).

Challenging Recommended Oral and Intravenous Voriconazole Doses for Improved Efficacy and Safety: Population Pharmacokinetics–Based Analysis of Adult Patients With Invasive Fungal Infections

Andres Pascual,^{1,a} Chantal Csajka,^{2,4,a} Thierry Buclin,² Saskia Bolay,¹ Jacques Bille,³ Thierry Calandra,¹ and Oscar Marchetti¹

Table 3. Probability of Achieving Different Voriconazole Trough Plasma Concentrations Targets With 200, 300, and 400 mg Twice-Daily Oral and Intravenous Dosing Regimens

VRC Trough Concentration Target (mg/L)	Probability, by Dosing Regimen and Route of Administration					
	200 mg Twice Daily		300 mg Twice Daily		400 mg Twice Daily	
	Oral (%)	Intravenous (%)	Oral (%)	Intravenous (%)	Oral (%)	Intravenous (%)
1	60	86	78	95	95	97
1.5 ^a	49	<u>70</u>	<u>68</u>	<u>87</u>	<u>78</u>	92
2	35	56	55	77	67	86
4	11	22	22	43	35	56
4.5 ^a	8	<u>18</u>	<u>19</u>	<u>37</u>	<u>29</u>	50
5	4.5	15	16	26	26	44

The percentages represent the probabilities of obtaining trough concentrations above the reported targets. The dosing regimens with the most appropriate predicted probabilities of reaching the therapeutic concentration range (ie maximizing efficacy by minimizing neurotoxicity) are reported in bold and underlined.

Similar probability of treatment outcome can be obtained with the 200 mg 3-times daily oral and intravenous regimens (69% and 86% of patients would reach the 1.5 mg/L lower concentration target and 20% and 37% of patients would have concentrations exceeding the 4.5 mg/L upper target, after oral and intravenous administration, respectively). These results are very close to those reported in the table with the 300 mg twice-daily oral and intravenous dosing regimens.

Abbreviation: VRC, voriconazole.

^a The therapeutic target concentrations for efficacy (ie >85% probability of response) and safety (ie <15% probability of grade 3 neurotoxicity).

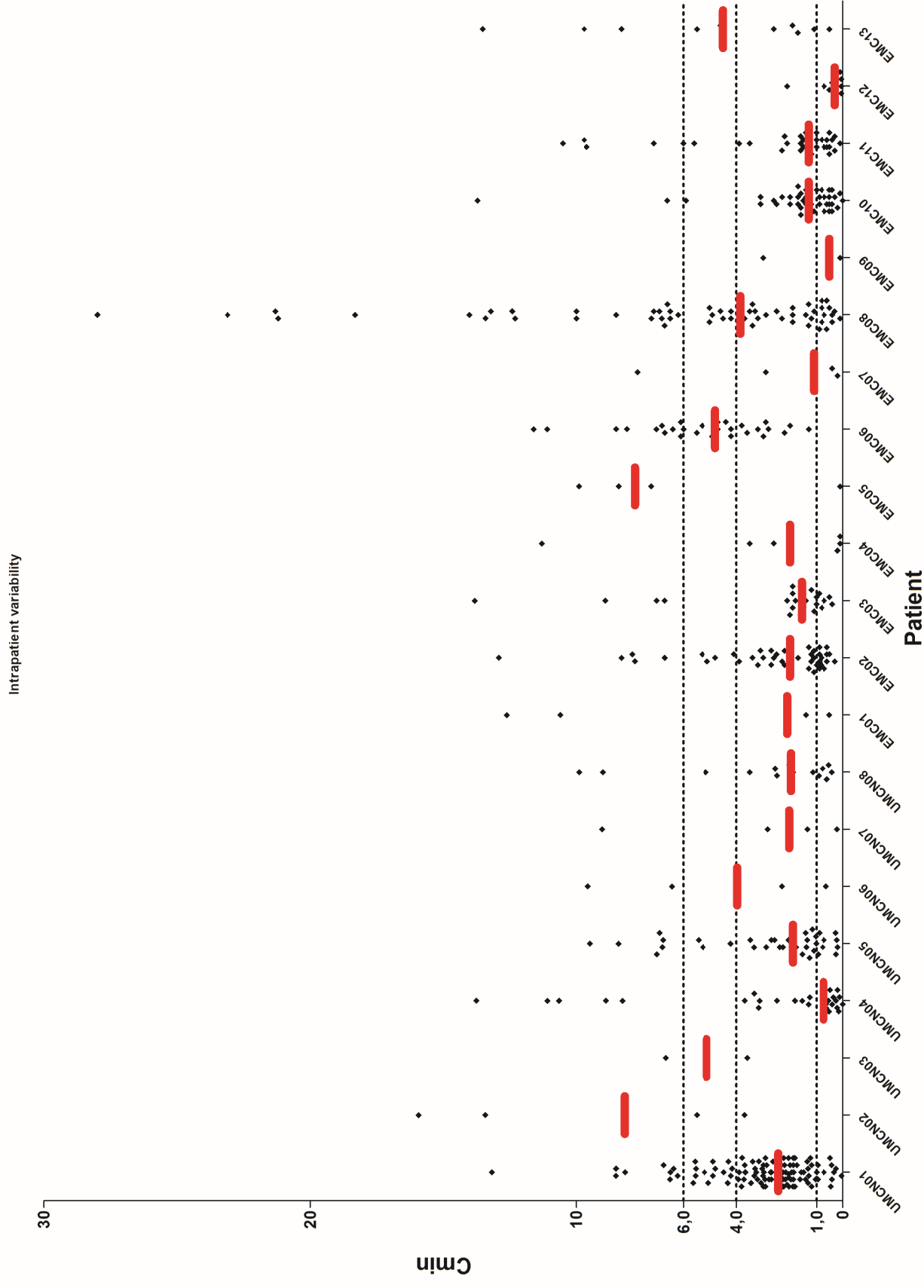
Experience with voriconazole in two academic centres

Voriconazole

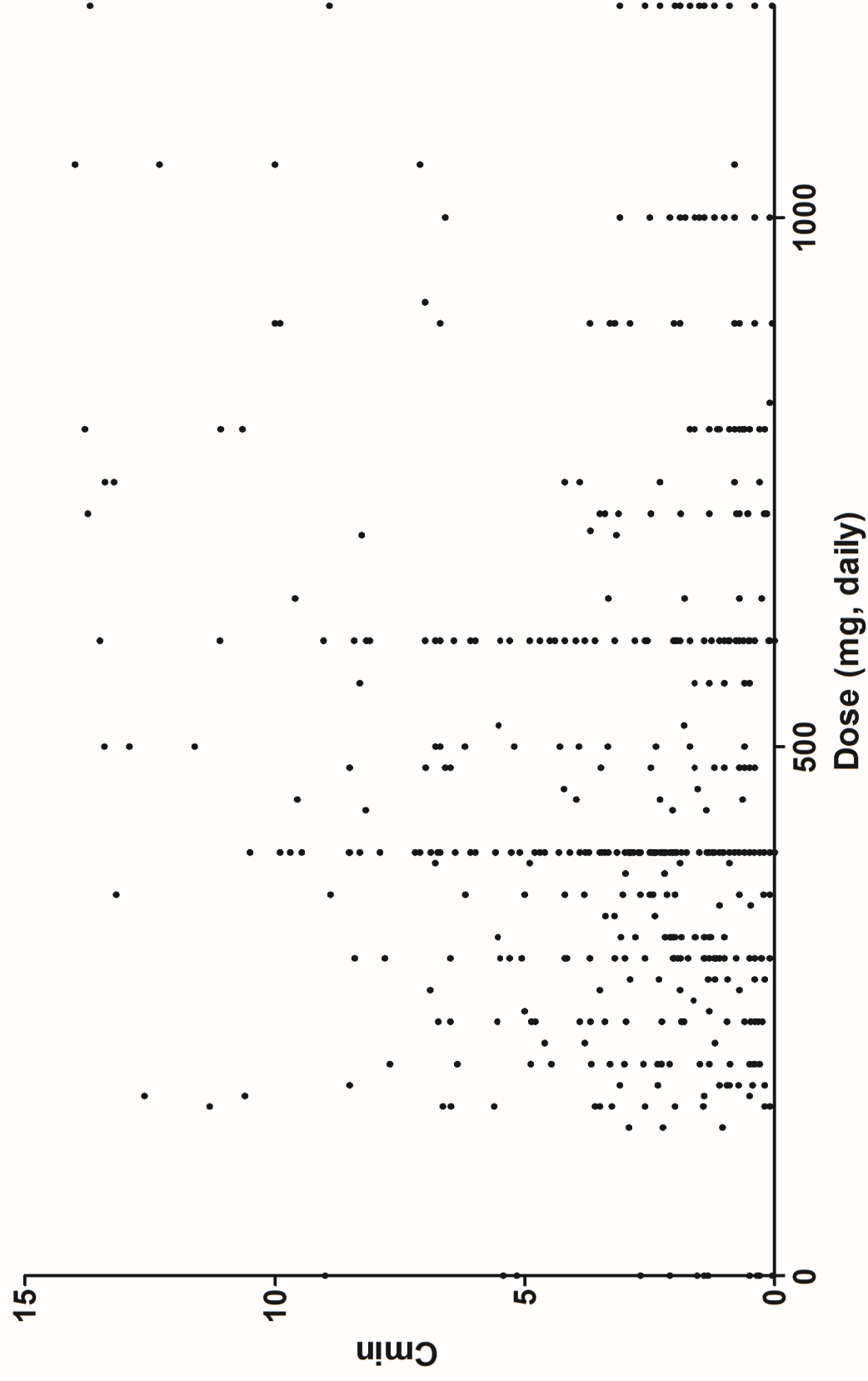
- Retrospective analysis
- Two centres (ErasmusMC, Rotterdam and Radboudumc, Nijmegen)
- Patients selected based on voriconazole Ctrough concentration > 6 mg/L
- Patients aged 0-18 years
- Demographic data collected
- Drug use collected
- 485 samples collected in 21 patients

Baseline characteristics

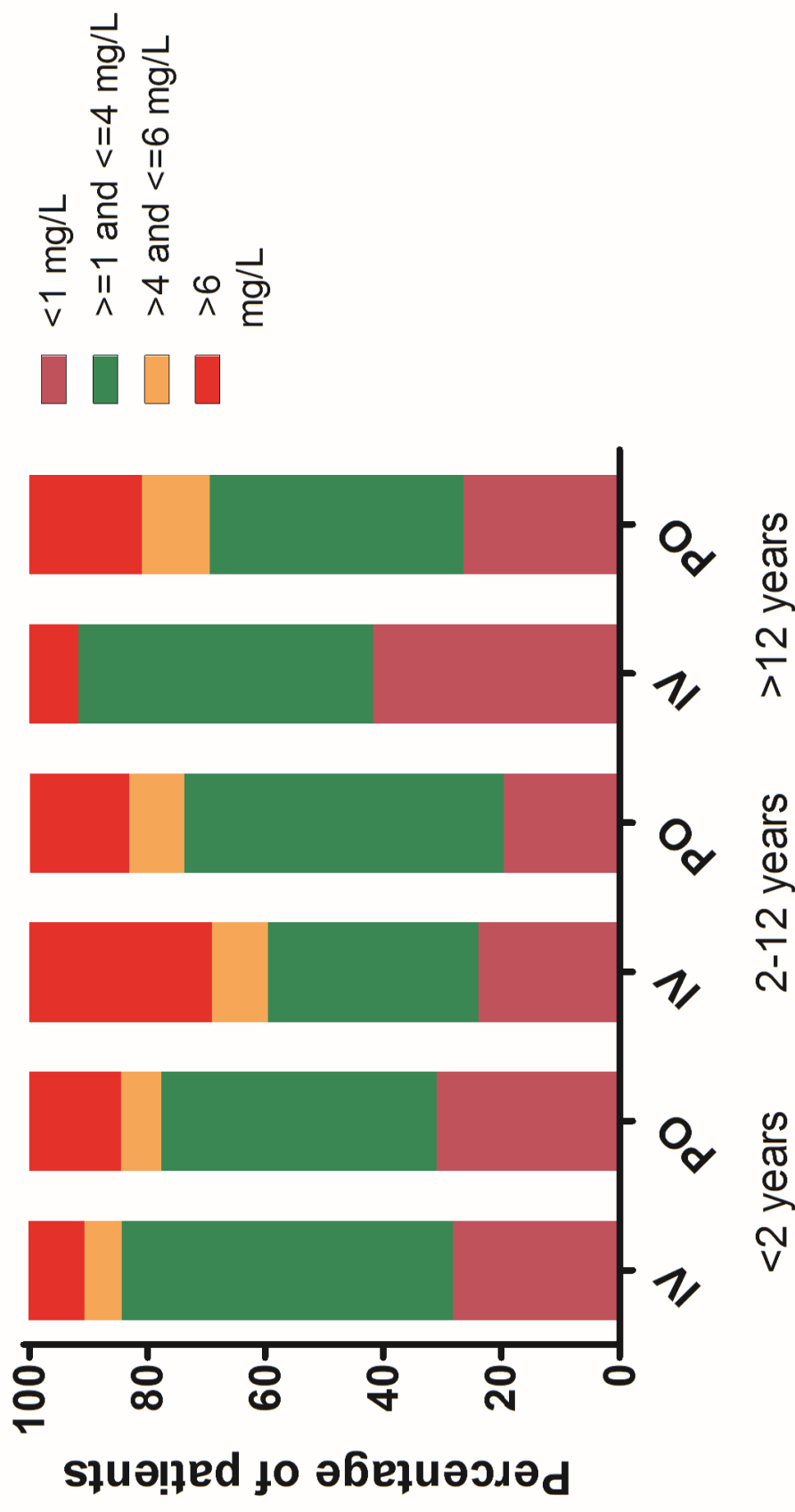
Gender	
Male (n, [%])	8 (38.1)
Female (n, [%])	13 (61.9)
Median age at start (range; yrs)	7.0 (1.2-18.5)
Age class (year)	
0 - 2 (n, [%])	4 (19.0)
3 - 12 (n, [%])	10 (47.6)
13 - 18 (n, [%])	7 (33.3)
Race	
Caucasian (n [%])	100
Median weight (range; kg)	21.9 (8.2 – 65)



Relation dose - concentration



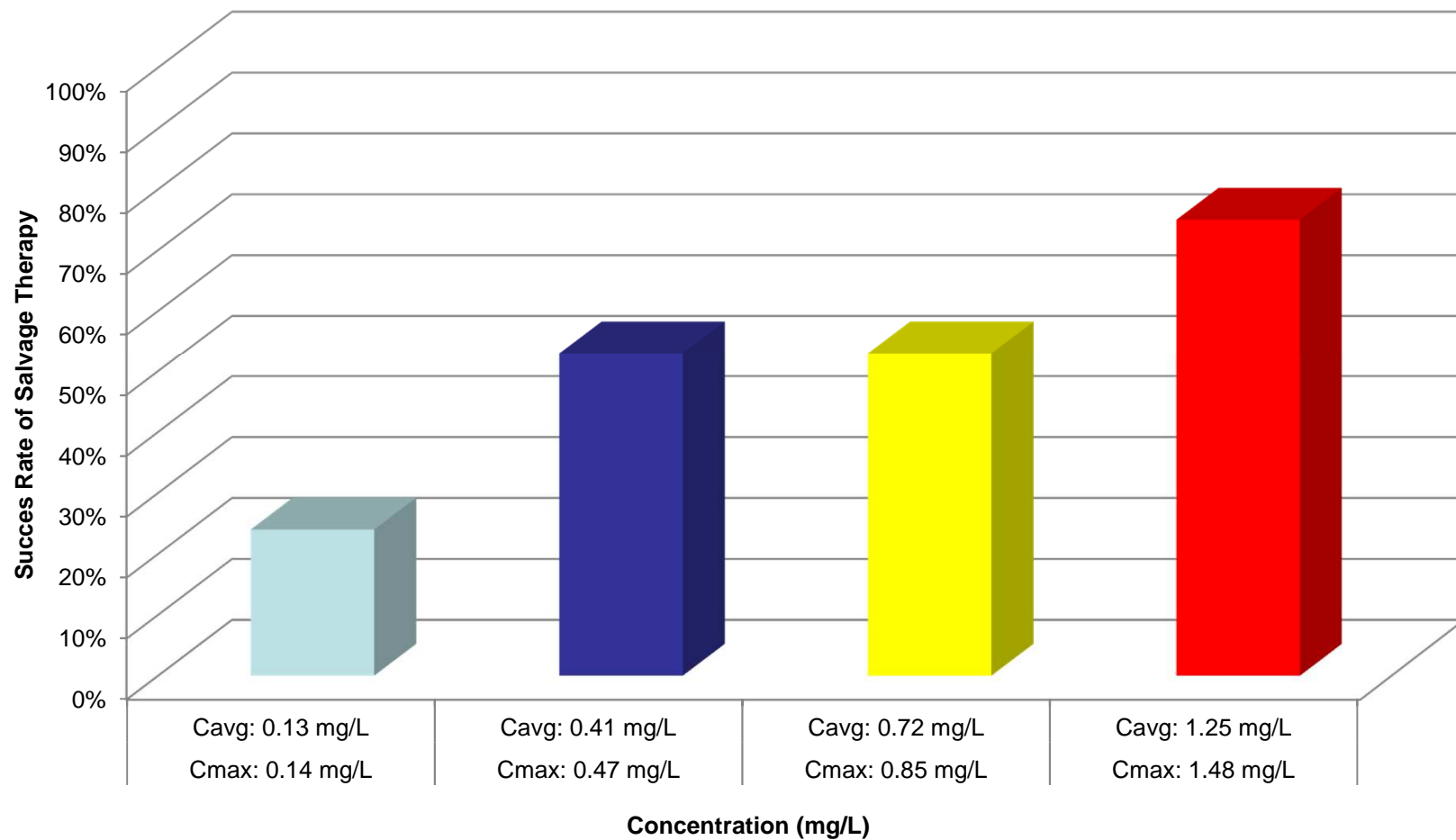
distribution of C_{trough} concentration



Posaconazole



Treatment of Invasive Aspergillosis with Posaconazole in Patients Who Are Refractory to or Intolerant of Conventional Therapy: An Externally Controlled Trial

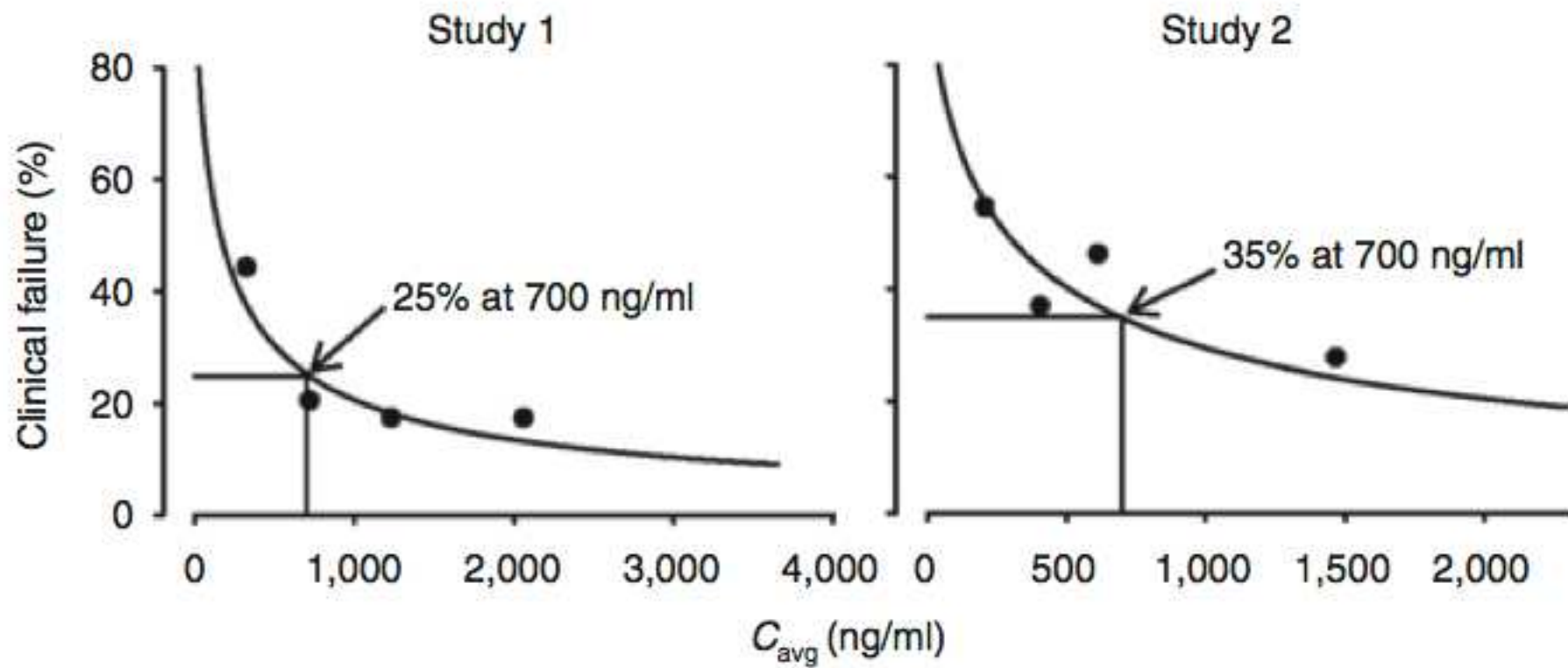


- Posaconazole steady-state average plasma concentrations (C_{avg}) vs. clinical failure rate : Posaconazole 200 mg TID
 - Patients post-HSCT with GvHD (study 1) (Ullmann et al, NEJM 2007)
 - Patients undergoing therapy for AML/MDS (study 2). (Cornelly et al, NEJM

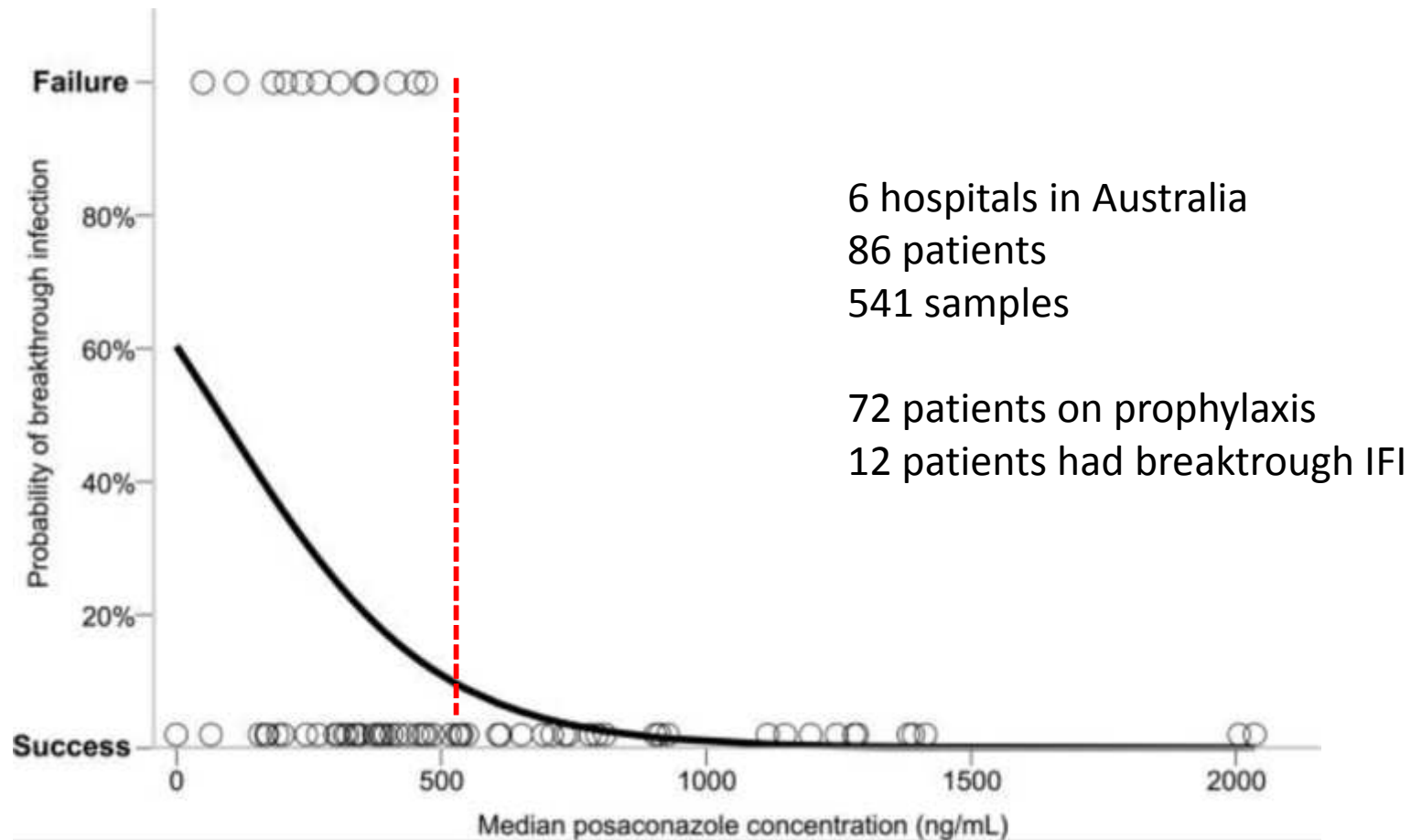
	Study 1 (N=252)^A		Study 2 (N=215)^A	
Quartile	Posaconazole C_{avg} (ng/ml) ^B	Clinical failure rate ^C	Posaconazole C_{avg} (ng/ml) ^B	Clinical failure rate ^C
1st Q	21.5-557 (289)	44% (28/63)	89.65-322 (206)	55% (29/53)
2nd Q	557-915 (736)	21% (13/63)	322-490 (406)	37% (20/54)
3rd Q	915-1563 (1239)	18% (11/63)	490-733.5 (612)	46% (25/54)
4th Q	1563-3650 (2607)	18% (11/63)	733.5-2200 (1467)	28% (15/54)

^A= PK datasets ; ^B= range (midpoint value) ;

^C = number of patients with clinical failure / number of all patients in each quartile



Posaconazole prophylaxis



The iPod experience – One more thing!



Method

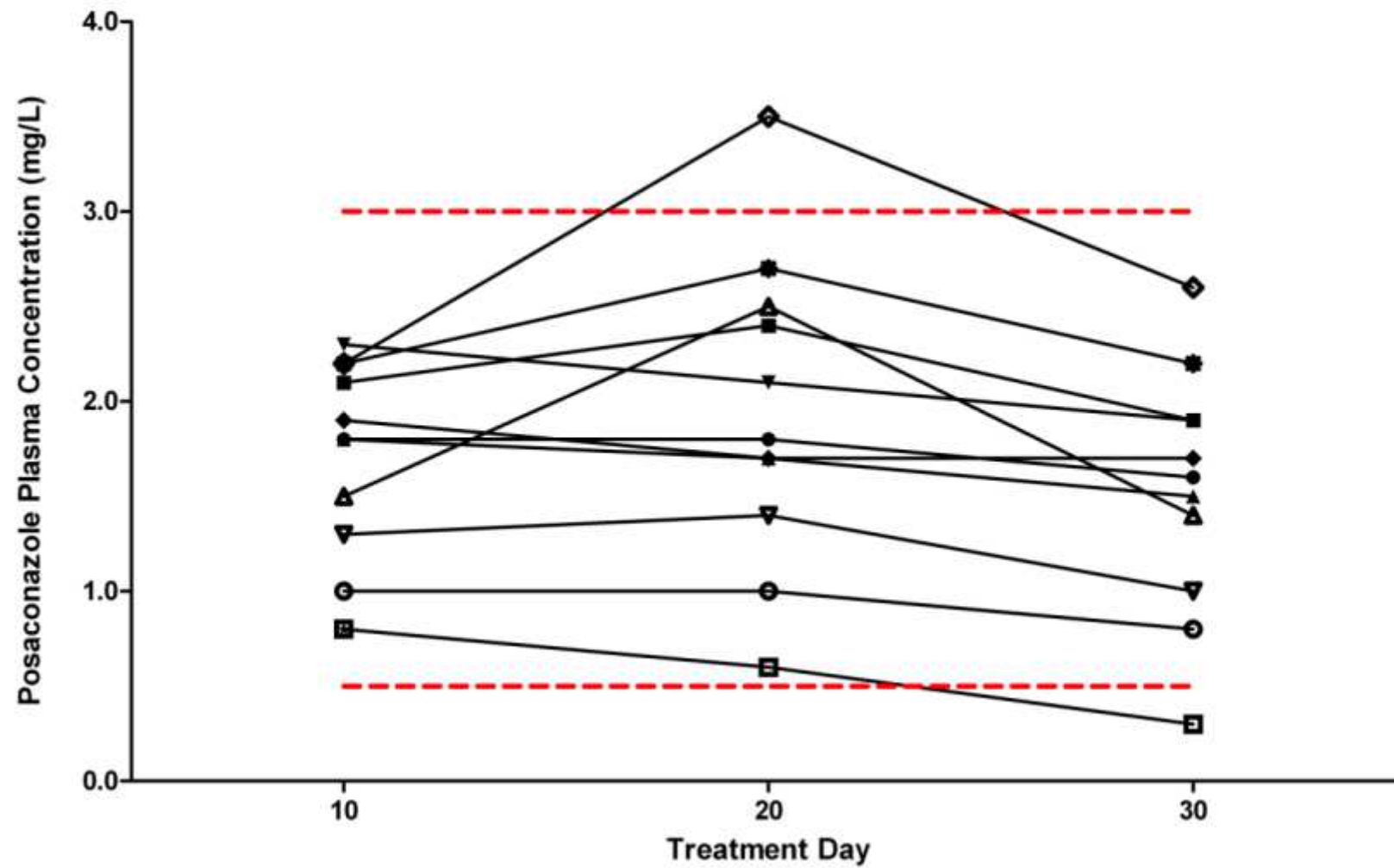
- PSZ oral suspension 40mg/ml based on an allometric dosing regimen
Dose (child) = Dose (adult) x [BW (child) / BW (adult)]^{0.75}
- 2 times daily after breakfast and evening meal

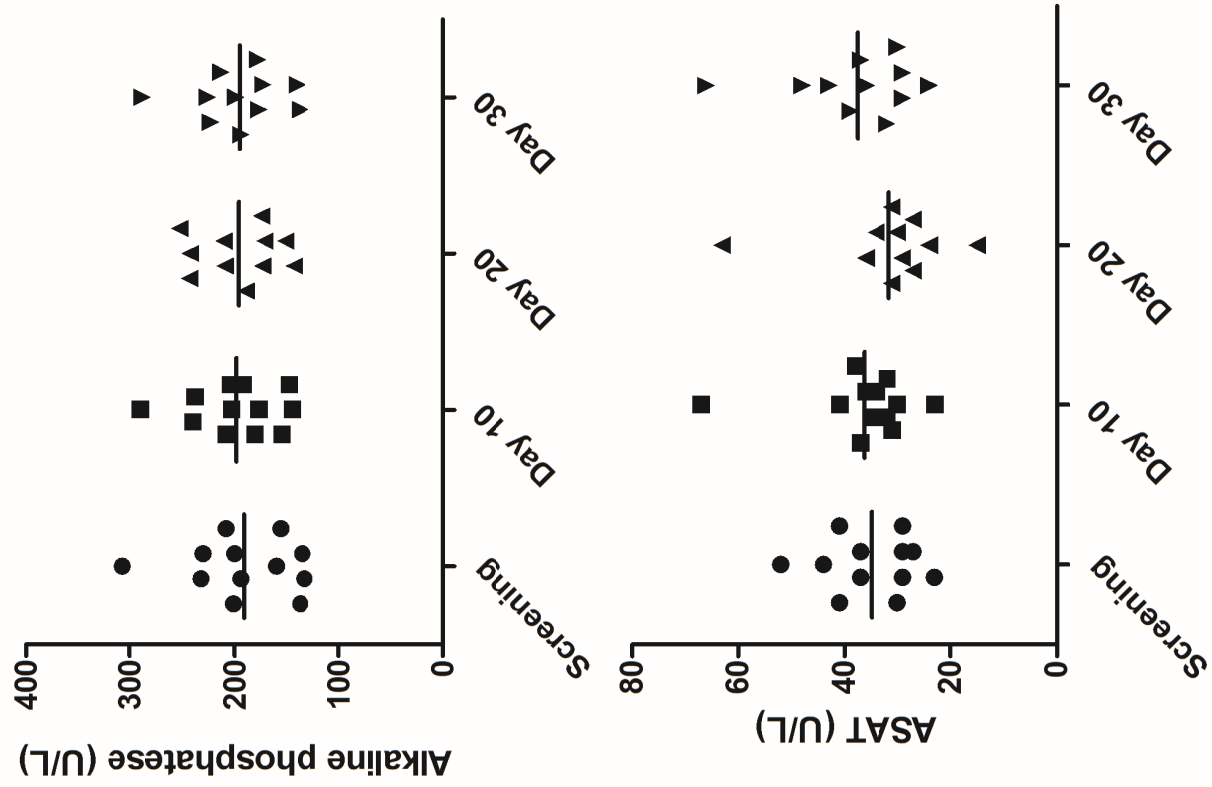
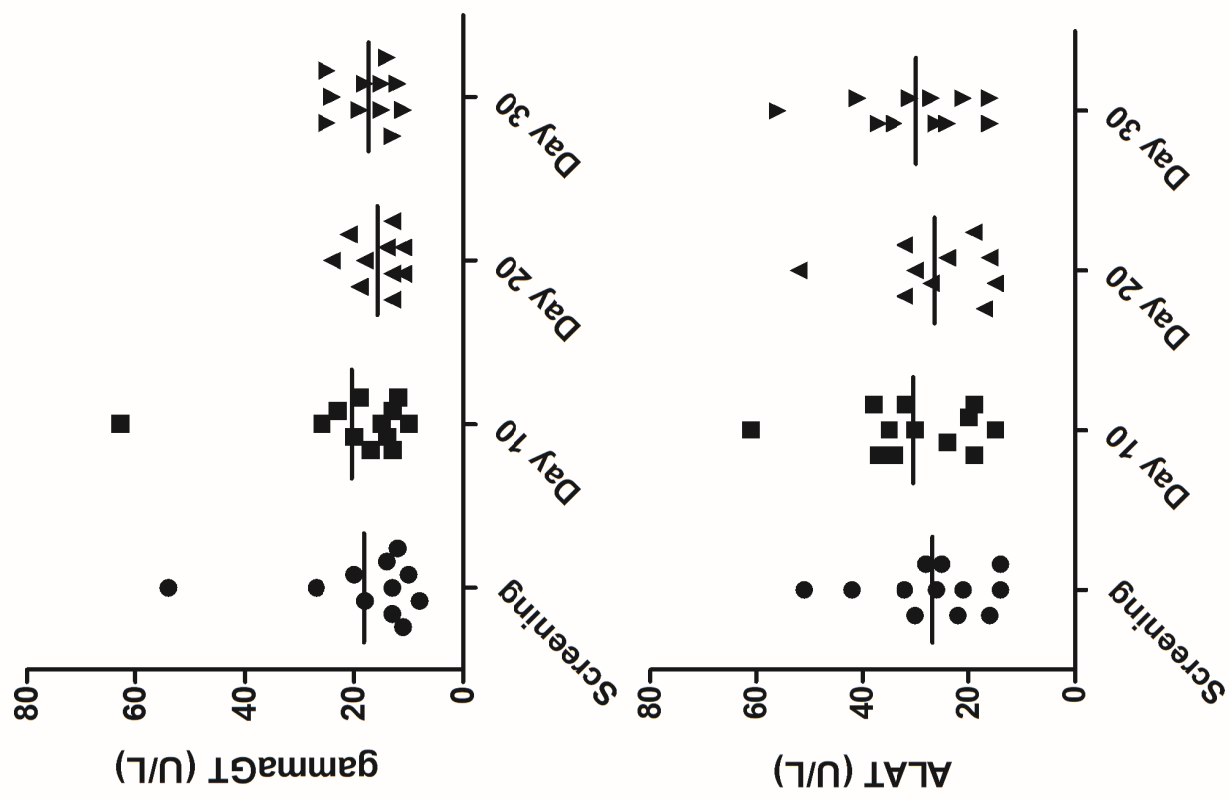
- Prophylaxis
for adults
200mg TID

Body weight (kg)	Dosing (mg) twice daily	Amount (ml) posaconazol suspension 40mg/ml per administration
10 – 14	120	3
15 – 19	160	4
20 – 24	200	5
25 – 29	220	5,5
30 – 34	260	6,5
35 – 39	280	7
≥ 40	300	7,5

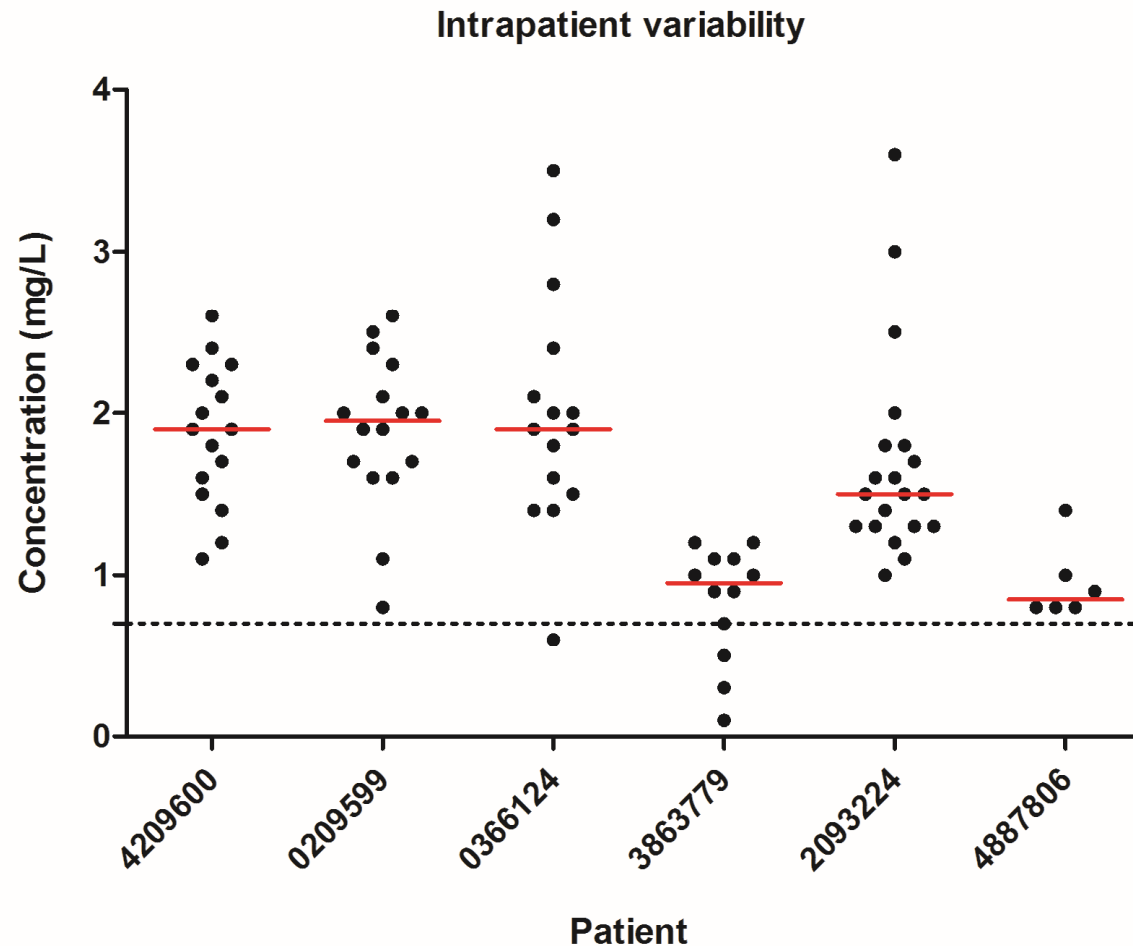


Results





5 – year experience with posaconazole in pediatric CGD patients



In addition: no toxicity ; better taste ;

Can targets easily be attained

What to account for

Understanding Variability in Posaconazole
Exposure Using an Integrated Population
Pharmacokinetic Analysis

Michael J. Dolton, Roger J. M. Brüggemann, David M.
Burger and Andrew J. McLachlan
Antimicrob. Agents Chemother. 2014, 58(11):6879. DOI:
10.1128/AAC.03777-14.
Published Ahead of Print 8 September 2014.

TABLE 1 Posaconazole pharmacokinetic data and participant demographics

Parameter	Study 1 ^a	Study 2 ^b
Study type	Controlled pharmacokinetic study of posaconazole- fosamprenavir interaction	Observational study of posaconazole TDM
Study population	Healthy volunteers	Patients treated with posaconazole
N	20	82
Posaconazole dosing	Day 1, 200 mg; day 2, 200 mg twice a day; days 3–10, 400 mg twice a day	Multiple dosing: 160–1,200 mg total daily dose
No. of samples/dose interval ^c	11	1
Median age (range), in yrs	38 (18–54)	50 (18–79)
Median wt (range), in kg	74 (44–104)	71 (38–122)
Sex [no. (%)]		
Female	9 (45)	35 (43)
Male	11 (55)	47 (57)

^a Based on data reported in reference 21.

^b Based on data reported in reference 6.

^c For subjects in study 2, between 1 to 42 samples were measured per patient across
separate dose intervals.

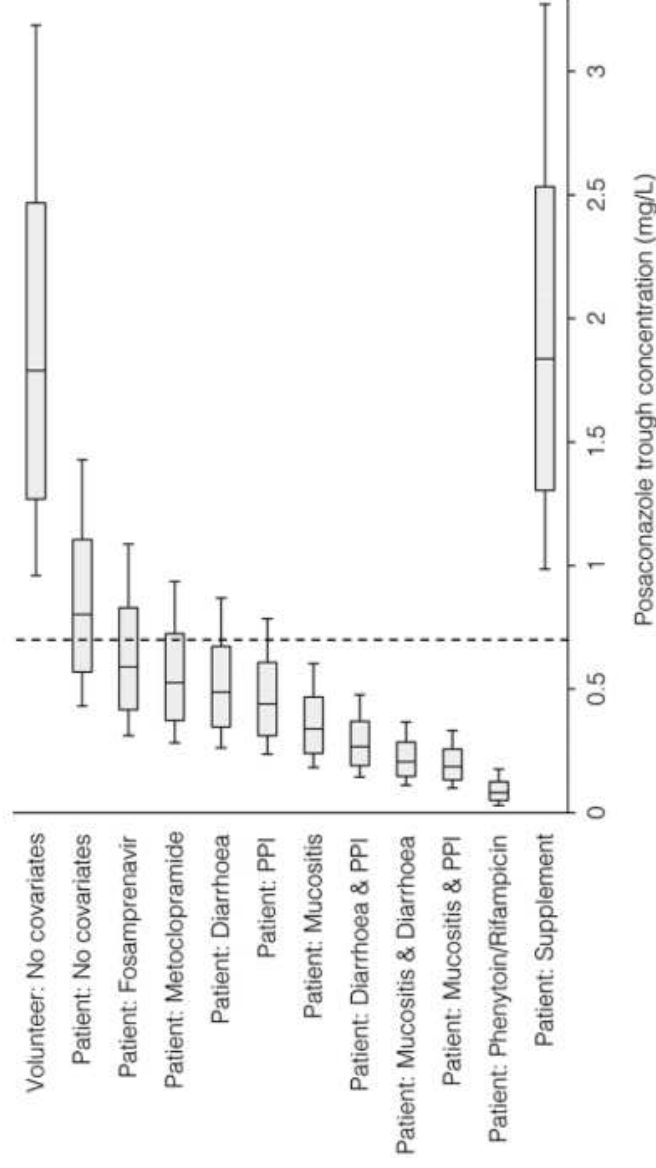


FIG 3 Effects of significant covariates on the predicted posaconazole trough concentration on day 10 of therapy following posaconazole at 200 mg three times daily; data are presented as an adjusted box plot. For each scenario, 1,000 patients or volunteers were simulated with or without the specified covariate(s). The central box line represents the median trough concentration, the lower and upper box ends represent the 25th and 75th percentiles, and the bars extend to the 10th and 90th percentiles. The dashed line represents the proposed minimum cutoff concentration for antifungal prophylaxis with posaconazole (0.7 mg/liter) (9).

Posaconazole Tablet Pharmacokinetics: Lack of Effect of Concomitant Medications Altering Gastric pH and Gastric Motility in Healthy Subjects

Walter K. Kraft, Peter S. Chang, Marlou L. P. S. van Iersel, Hetty Waskin, Gopal Krishna and Wendy M. Kersemaekers
Antimicrob. Agents Chemother. 2014, 58(7):4020. DOI:
10.1128/AAC.02448-13.
Published Ahead of Print 5 May 2014.

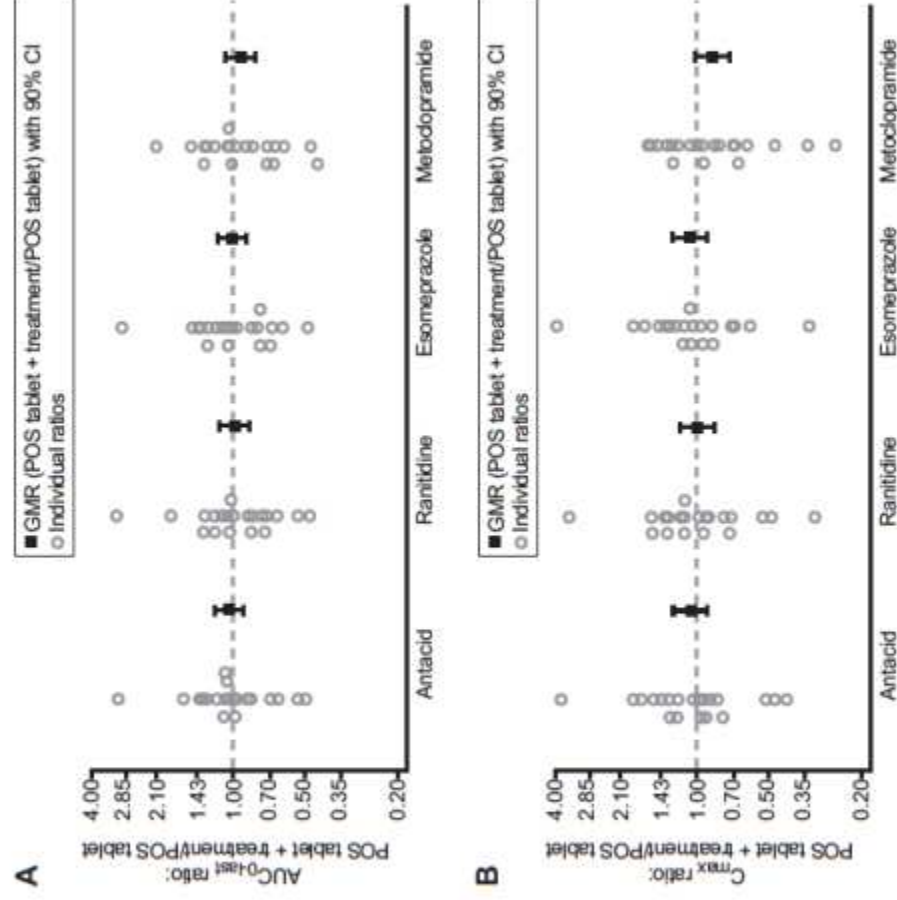


FIG 2 Individual ratios, geometric mean ratios (GMRs) (posaconazole [POS] tablets + treatment/posaconazole tablets), and 90% confidence intervals (CIs) of area under the concentration-time curve from time zero to time of the last quantifiable sample (AUC_{0-12h}) (A) and maximum concentration of drug in serum (C_{max}) (B) for posaconazole tablets (400 mg) alone or with concomitant treatment.

Phase 1B Study of the Pharmacokinetics and Safety of Posaconazole Intravenous Solution in Patients at Risk for Invasive Fungal Disease

Johan Maertens, Oliver A. Cornely, Andrew J. Ullmann,
Werner J. Heinz, Gopal Krishna, Hernando Patino, Maria
Caceres, Nicholas Kartsonis, Hetty Waskin and Michael N.
Robertson

Antimicrob. Agents Chemother. 2014, 58(7):3610. DOI:
10.1128/AAC.02686-13.

Published Ahead of Print 14 April 2014.

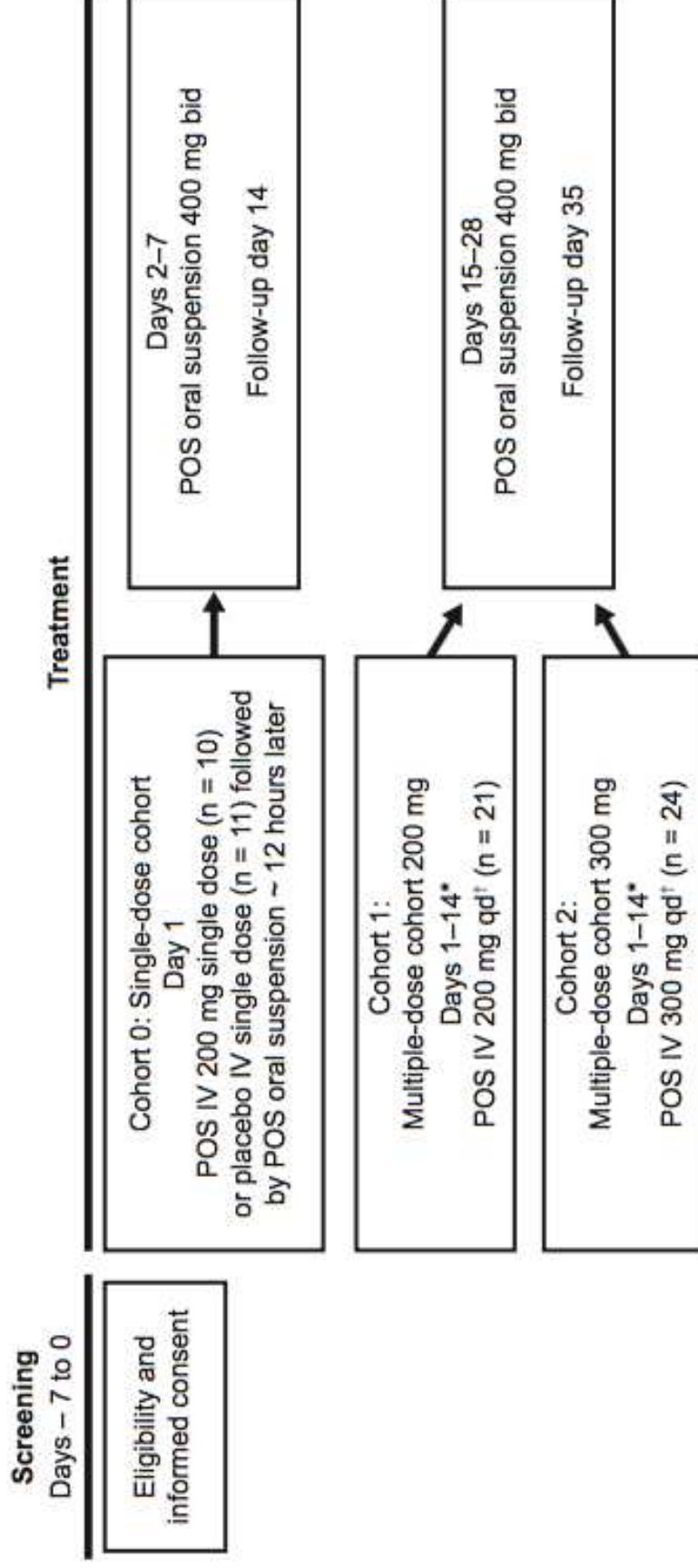


TABLE 2 PK parameter values after twice-daily dosing of POS i.v. (day 1) and multiple doses of POS i.v. (day 14) administered to subjects at high risk for IFD^a

POS day of administration, cohort, and dosage ^b	No. of subjects	C _{max} (mean [CV%] ^c) (ng/ml)	T _{max} (median [range]) (h)	AUC ^d (mean [CV%]) (ng · h/ml)	C _{avg} ^e (mean [CV%]) (ng/ml)	C _{min} (mean [CV%]) (ng/ml)	Accumulation ratio (mean [CV%]) ^f	C _{avg} of ≥500 and ≤2,500 ng/ml (%)
Day 1								
Cohort 1: 200 mg b.i.d.	20	990 (47)	1.48 (1.0–4.0)	5,390 (29)	NA	NA	NA	NA
Cohort 2: 300 mg b.i.d.	22	1,590 (61)	1.54 (1.0–2.0)	8,240 (26)	NA	NA	NA	NA
Day 14								
Cohort 1: 200 mg q.d.	15	1,950 (50)	1.00 (1.0–4.0)	28,200 (51)	1,180 (51)	958 (63)	3.6 (44)	94
Cohort 2: 300 mg q.d.	19	2,610 (39)	1.50 (0.98–4.0)	34,300 (42)	1,430 (42)	1,068 (50)	2.8 (31)	95

^a i.v., intravenous; IFD, invasive fungal disease; POS, posaconazole; PK, pharmacokinetics; NA, not applicable.

^b b.i.d., twice daily; q.d., once daily.

^c CV, coefficient of variation; C_{max}, maximum observed concentration; T_{max}, time to C_{max}; AUC, area under concentration-time curve; C_{avg}, average concentration at steady state;

C_{min}, minimum plasma concentration.

^d AUC from 0 to 12 h (AUC_{0–12 h}) presented for day 1; AUC_{0–24 h} presented for day 14.

^e C_{avg} = AUC_{0–24 h}/dose interval, based on C_{max}.

^f Accumulation ratio based on AUC_{0–24 h}.

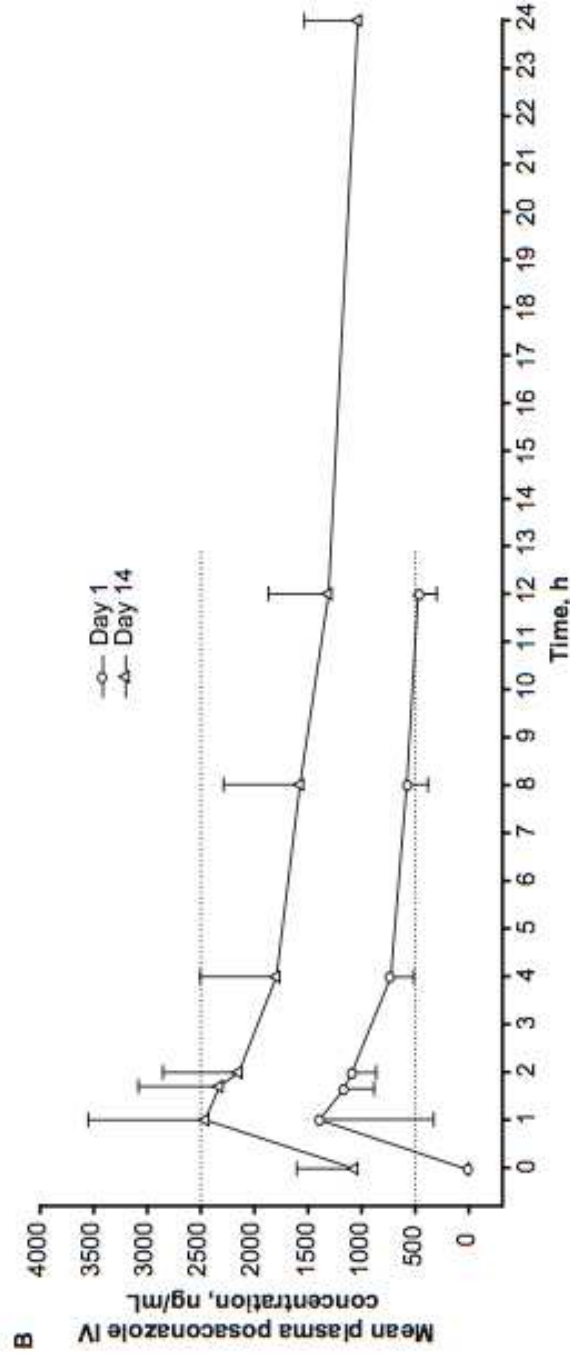
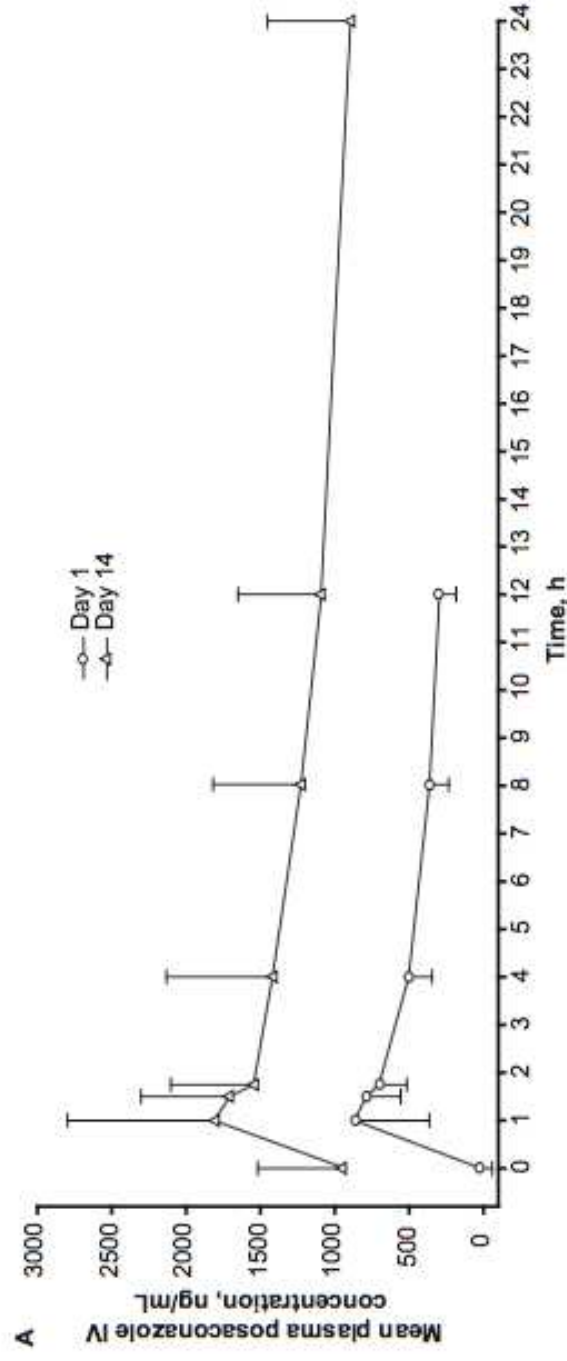


FIG 2 Mean (standard deviation) plasma concentration profiles (days 1 and 14). (A) Cohort 1: intravenous posaconazole 200 mg daily (after 200 mg twice daily on day 1) administered to subjects at high risk for IFD. (B) Cohort 2: intravenous posaconazole 300 mg daily (after 300 mg twice daily on day 1) administered to subjects at high risk for IFD. IV, intravenous.

Phase 1b Study of New Posaconazole
Tablet for Prevention of Invasive Fungal
Infections in High-Risk Patients with
Neutropenia

Rafael F. Duarte, Javier López-Jiménez, Oliver A. Cornely,
Michel Laverdiere, David Helfgott, Shariq Haider,
Pranatharathi Chandrasekar, Amelia Langston, John Perfect,
Lei Ma, Marlou L. P. S. van Iersel, Nancy Connelly, Nicholas
Kartsonis and Hetty Waskin
Antimicrob. Agents Chemother. 2014, 58(10):5758. DOI:
10.1128/AAC.03050-14.
Published Ahead of Print 21 July 2014.

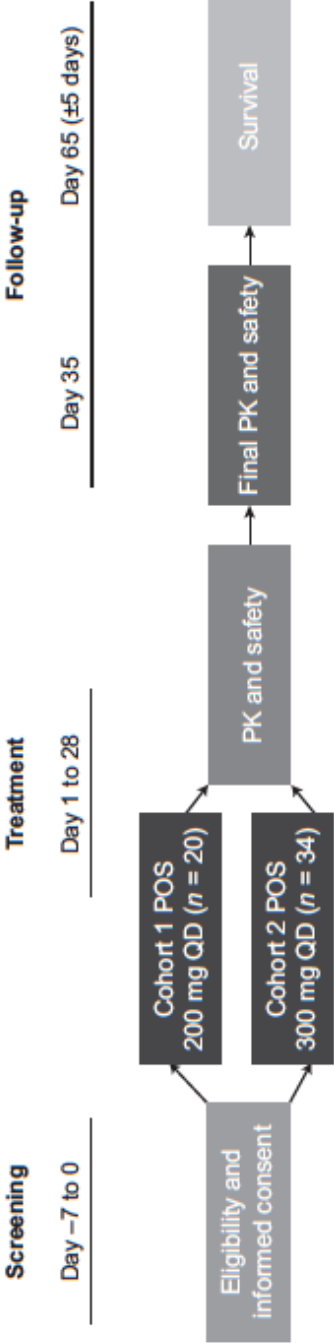


FIG 1 Study design phase 1B. Cohort 1 was completed before cohort 2 patients were administered the study drug. Twice-daily dosing (12 h apart) was given on day 1. For pharmacokinetics and safety, samples were taken on day 1 and day 8 (steady state) at 0 h (predose) and at 2, 4, 6, 8, 12, and 24 h after dose. PK, pharmacokinetics; POS, posaconazole; QD, once daily.

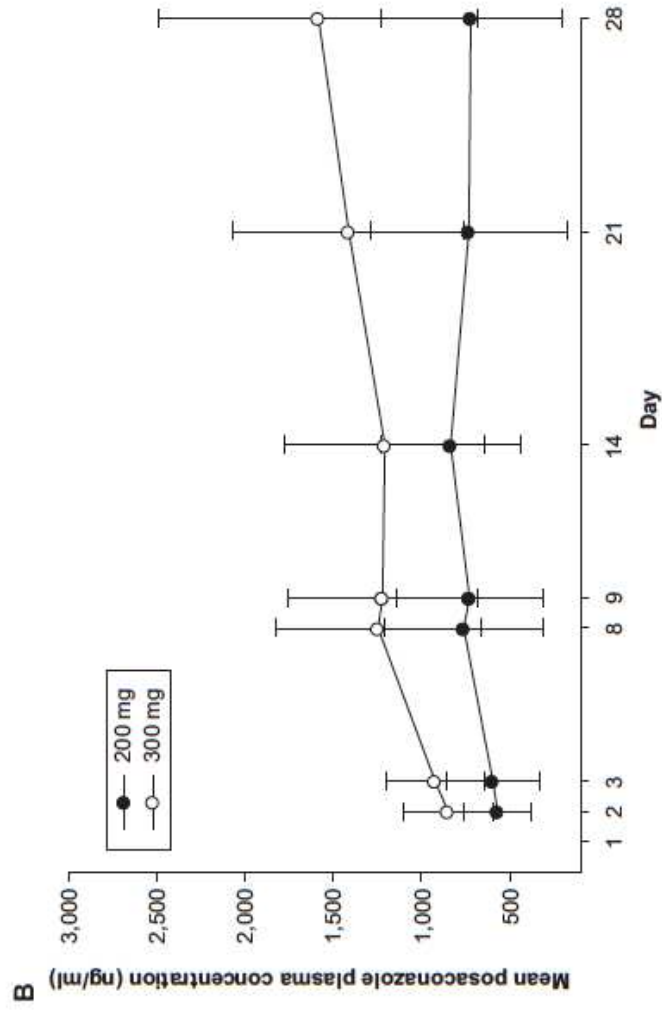
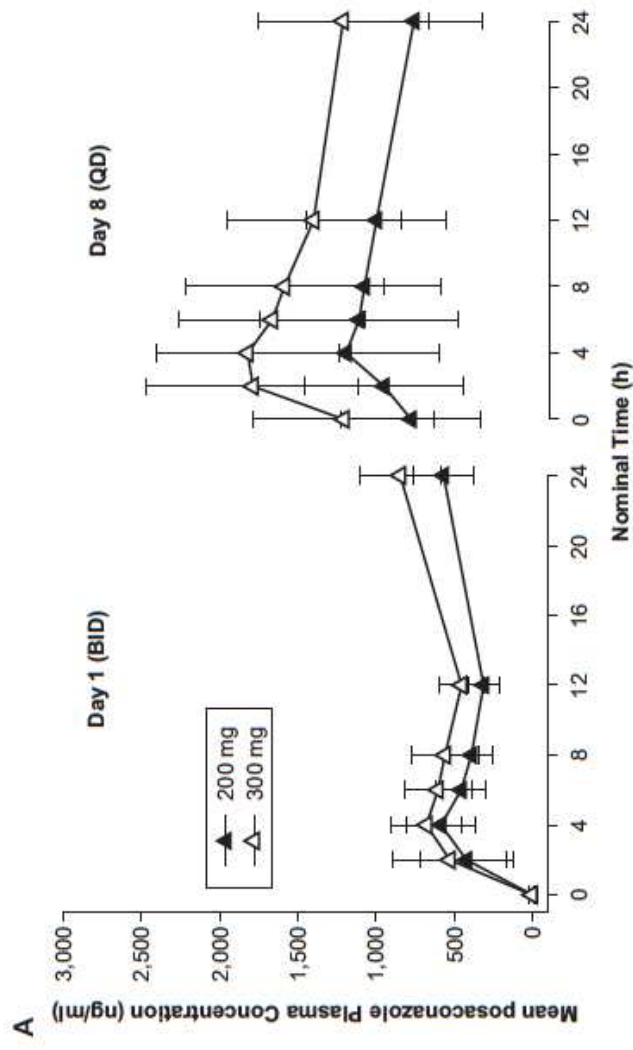


FIG 2 (A) Mean (SD) plasma concentration profiles (days 1 and 8) of posaconazole after multiple-dose oral administration of tablets to patients at high risk for IFI. (B) Mean (SD) trough plasma concentration profiles of posaconazole after multiple-dose oral administration of tablets to patients at high risk for IFI. BID, twice daily; IFI, invasive fungal infection; QD, once daily.

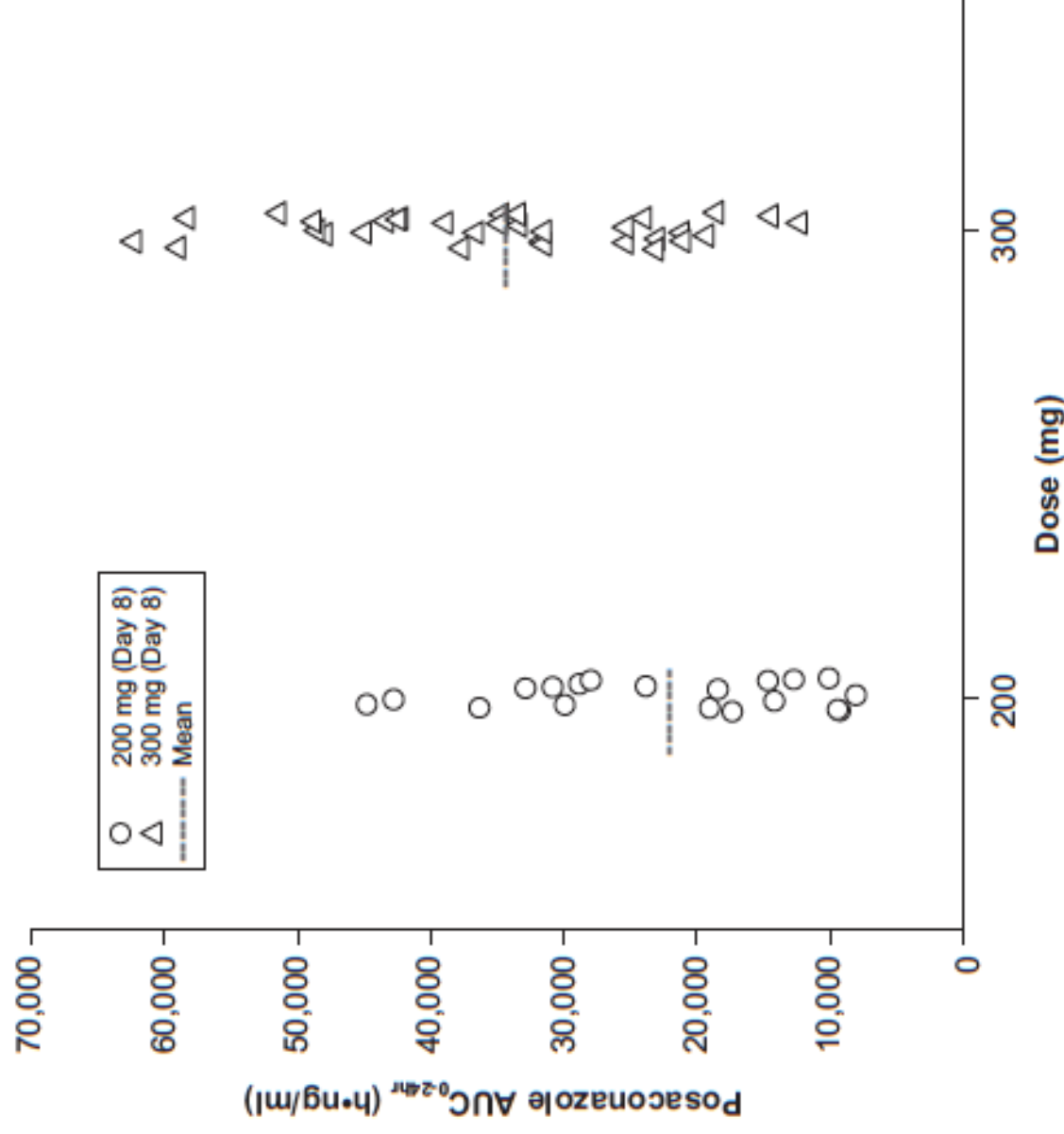


FIG 3 Individual day 8 AUC_{0-24 h} values after multiple doses of posaconazole tablets to patients at high risk for IFI. Dotted lines represent the mean AUC_{0-24 h} steady-state exposure. AUC_{0-24 h}, area under the concentration-time curve from 0 to 24 h; IFI, invasive fungal infection.

Azole resistance

An emerging problem with clinical implications

Resistance mechanisms

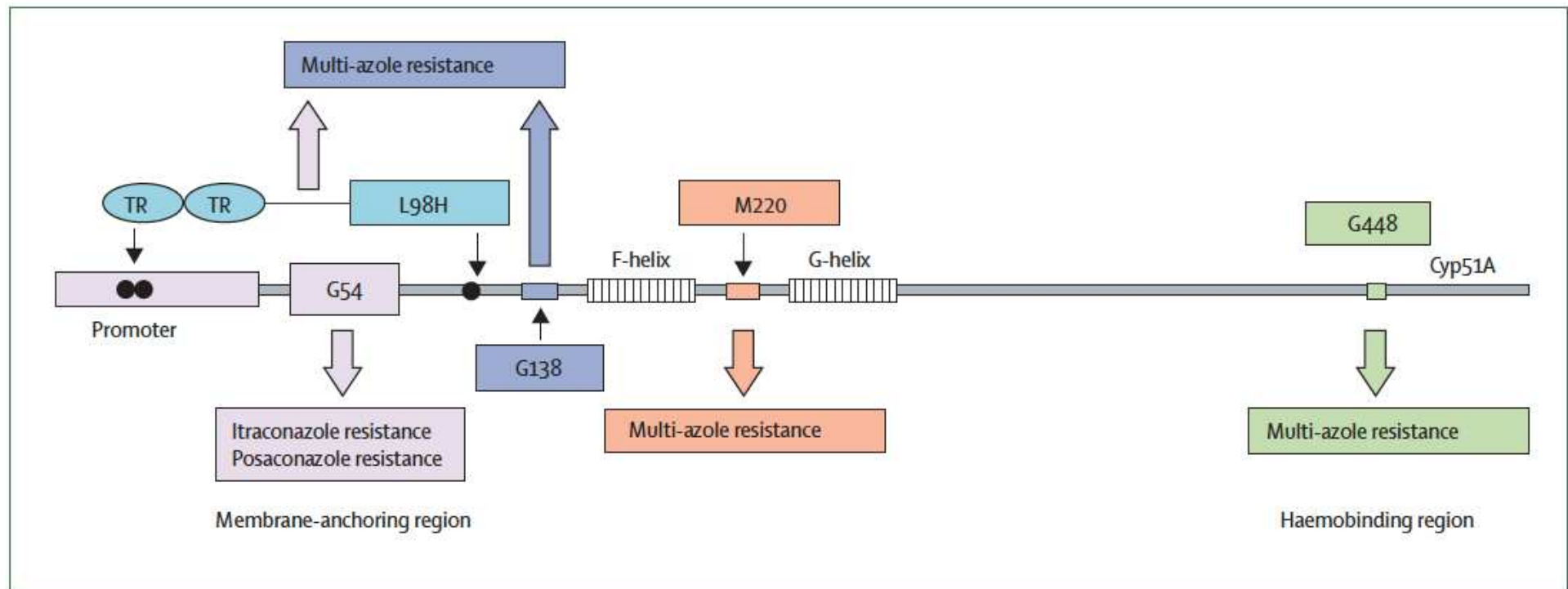


Figure 3: *Aspergillus fumigatus* cyp51A-related resistance mechanisms to azole antifungals

The position of the different mutations are shown with the associated phenotypes. MIC=minimum inhibitory concentration. TR=tandem repeat.

VRC MIC (mg/L)		0.063	0.125	0.25	0.5	1	2	4	8	16
Cyp51A substitution		-	-	-	-	F219I	-	F219I	F219I	-
		-	G54R; -W	G54E; -R; -V; - W	G54E; -V	G54V	-	-	-	-
		-	-	-	-	-	-	G138C	G138C	G138C
		-	-	G432S	G432S	-	-	-	-	-
		-	-	-	-	-	-	G434C	-	-
		-	-	-	-	-	-	G448S	-	G448S
		-	-	-	M220T	M220I; -K; -T; -V	M220K; -R; -V	-	-	-
		-	-	-	-	P216L	-	-	-	-
		-	-	-	-	-	TR ₃₄ /L98H	TR ₃₄ /L98H	TR ₃₄ /L98H	TR ₃₄ /L98H
		-	-	-	-	-	-	-	-	TR ₄₆ /Y121F/T289A
		-	-	-	-	-	-	-	TR ₅₃	TR ₅₃
		-	-	-	-	-	-	Y431C	-	-
Pharmacodynamic target (total AUC/MIC) predicting therapeutic success [adopted from preclinical study of Mavridou 2010, Jeans 2012, Seyedmousavi 2013]						EI ₅₀ : 24.73 – 35.17 (EUCAST)				
Calculated exposure (total AUC) needed to be achieved [calculation made by us]		1.54-2.19	3.09-4.39	6.18-8.79	12.36-17.58	24.73 – 35.17	49.46-70.34	98.92-140.68	197.84-281.36	395.68-562.72
Calculated trough concentration (C _{min}) needed to be achieved [adopted from clinical data of Bruggemann et al. 2010]		< 0.4	< 0.4	< 0.4	< 0.4	0.62-0.98	1.23-1.96	2.90-4.30	> 4.5	> 10
EUCAST breakpoints		S	S	S	S	S	R	R	R	R
Proposed interpretative breakpoints [adopted from Verweij et al. 2009]		S	S	S	S	S	I	R	R	R
Probability of achieving trough concentration (C _{min}) with 200 mg twice daily [adopted from Pascual et al. 2012]	IV	> 86%					56-86%	18-56%	< 15%	< 15%
	Oral	> 60%					35-60%	8-35%	< 4.5%	< 4.5%
Probability of exposure (AUC) attainment following licensed i.v. regimen [adopted from Hope 2012]		99.98 %	99.98 %	99.98 %	99.94 %	92.78%	67.50 %	32.18 %	10.64 %	2.38 %
Probability of reaching the exposure	IV/Oral									

POS MIC (mg/L)			0.031	0.063	0.125	0.25	0.5	1	2	4	8	16
Cyp51A substitution			-	-	-	-	F219I	-	-	-	-	F219I
			-	-	-	G54E	G54E	G54E; -R	-	-	G54W	G54W
			-	-	-	-	-	G138C	G138C	G138C	G138C	G138C
			-	-	-	G432S	-	-	-	-	-	-
			-	-	-	-	-	G434C	-	-	-	-
			-	-	-	-	G448S	G448S	-	-	-	-
			--	-	-	M220T	M220I-T; -V	M220K; -V	M220K; -R	M220K	M220K	M220K
			-	-	-	-	-	P216L	P216L	-	-	-
			-	-	-	-	TR ₃₄ /L98H	TR ₃₄ /L98H	TR ₃₄ /L98H	TR ₃₄ /L98H	TR ₃₄ /L98H	-
			-	-	-	TR ₄₆ /Y121F/T289A	TR ₄₆ /Y121F/T289A	TR ₄₆ /Y121F/T289A	TR ₄₆ /Y121F/T289A	TR ₄₆ /Y121F/T289A	-	-
			-	-	-	TR ₅₃	-	-	-	-	-	-
-	-	-	-	-	Y431C	-	-	-	-			
Pharmacodynamic target (total AUC/MIC) predicting therapeutic success [adopted from preclinical study of Howard 2011, Mavridou 2012, Lepak 2013]												
EI ₅₀ : 167 – 178 (EUCAST)												
Calculated exposure (total AUC) needed to be achieved [calculation made by us]			5.-22-5.5-6	10.43-11.125	20.87-22.5	41.75-44.5	83.5-89	167-178	334-356	668-712	1336-1424	2672-2848
Calculated trough concentration (C _{min}) needed to be achieved [adopted from clinical data of Bruggemann et al. 2010]			<0.4	<0.4	0.72-0.77	1.44-1.54	3.09-3.33	6.18-6.66	>10	>10	>10	>10
EUCAST breakpoints			S	S	S	R	R	R	R	R	R	R
Proposed interpretative breakpoints [adopted from Verweij et al. 2009]			S	S	S	S	I	R	R	R	R	R
Probability of exposure (AUC) attainment with 800 mg a day [adopted from AbuTarif et al. 2012]			96%	68 %	15.3 %	0.6 %	< 0.6 %					
Probability of reaching the exposure [adopted from clinical data]	Oral [Courtney 2004, Krishna 2009]	Fasted										
		Non-fasted (High fat meal)	The AUC increases 400% with a high-fat meal									
	IV [Cornely et al. ICAAC 2013 –A-294]		POS IV 300 mg QD resulted in mean Cavg of 1.5 mg/L									

Raeboud et al.

DBS ZonMW project

Dried Blot Spot for antifungal and immunosuppressive drugs



ZonMw

Spark
H O L L A N D

Radboudumc

Goal

To develop and implement a Dried Blood Spot method for continuous home based monitoring of 5 antifungal drugs



Drugs of interest

Fluconazole

Isavuconazole

Itraconazole + hydroxy-itraconazole

Posaconazole

Voriconazole + voriconazole-n-oxide

Cyclosporine

Everolimus

Mycofenolzuur

Tacrolimus

Sirolimus

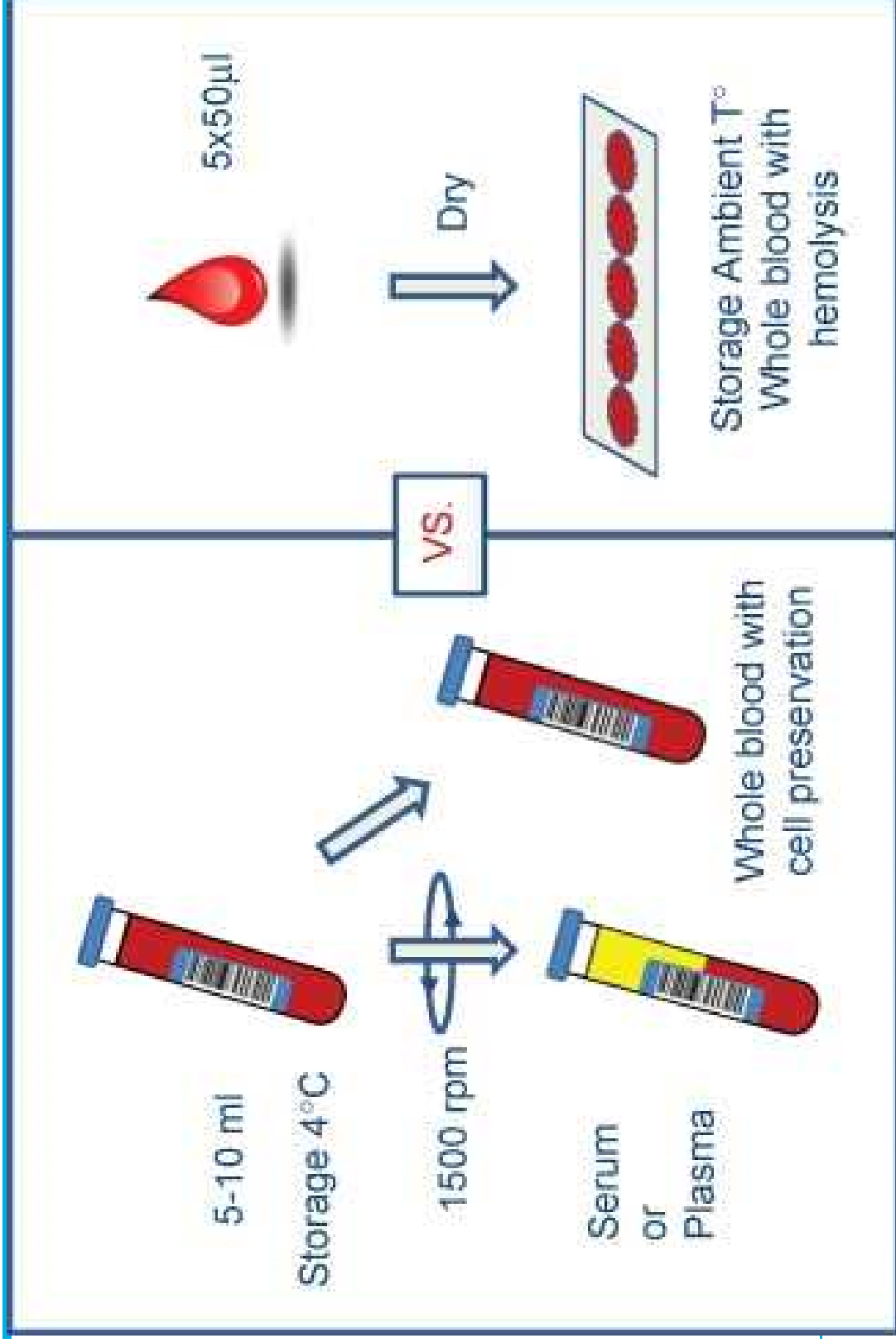
Rationale

Using these drugs requires the frequent determination of plasma concentration monitoring

- Drugs with large intra- and interindividual variability

Challenges of conventional monitoring

1. Sampling must be done in hospital
2. Preferably Ctrough concentration
3. Requires invasive vena punctures
4. Storage and transport conditions can be a challenge
5. Results often available after clinical visit



Fase I

Development of analytical technique for DBS: LC-MS/MS



Collaboration Radboud UMC en Academisch Ziekenhuis Maastricht

Radboudumc

Take home message

We are not there yet – questions that have to be answered:

- Structured and Coordinated efforts to obtain necessary information
 - Preclinical models for targets
 - Population PK data/models in target populations
- Controlled trials TDM vs no-TDM for other agents
- Analytical Challenges: e.g. TAT, Have an adequate (in-house) technique, new sampling techniques
- Incorporation of MIC, disease status, genomics, other covariates
- Practical point of view
 - Take more than one sample
 - Start measuring in the first few days of therapy
 - Difficult to interpret anything that's not a trough
 - Measure again with changed clinical circumstances

www.fungal-druginteractions.org
www.fungalpharmacology.org



Fungal
Pharmacology

Radboudumc

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