ISAVUCONAZOLO:

CARATTERISTICHE FARMACOCINETICHE E FARMACODINAMICHE

FEDERICO PEA

ISTITUTO DI FARMACOLOGIA CLINICA

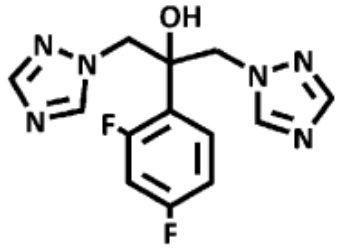
PRESIDIO OSPEDALIERO UNIVERSITARIO SANTA MARIA DELLA MISERICORDIA

AZIENDA SANITARIA UNIVERSITARIA INTEGRATA UDINE

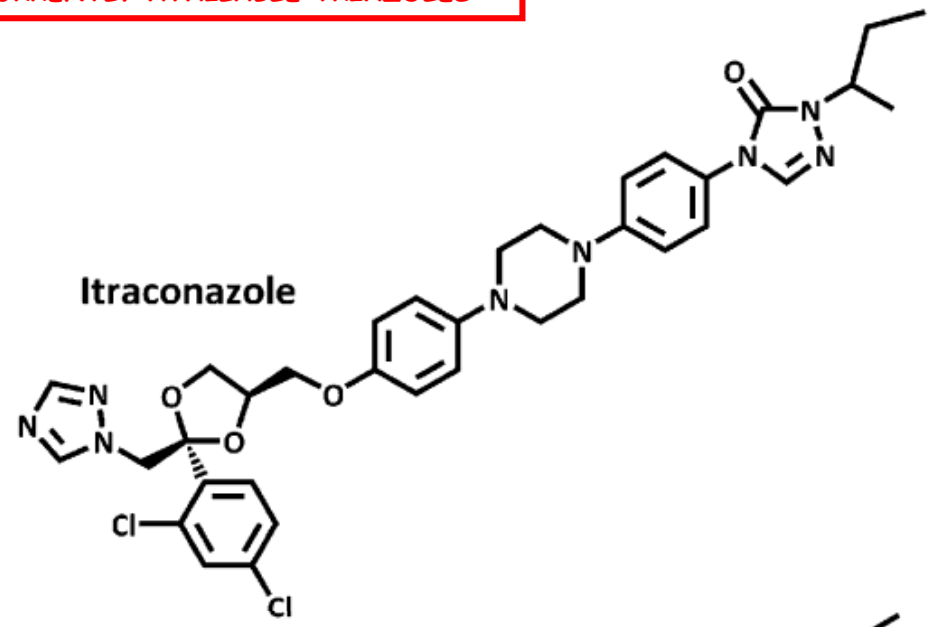
Verona, 14-16 Marzo 2018

CURRENTLY AVAILABLE TRIAZOLES

Fluconazole

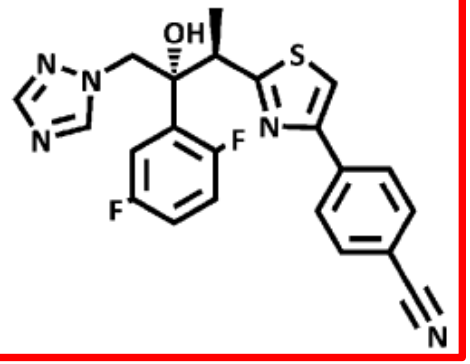


Itraconazole

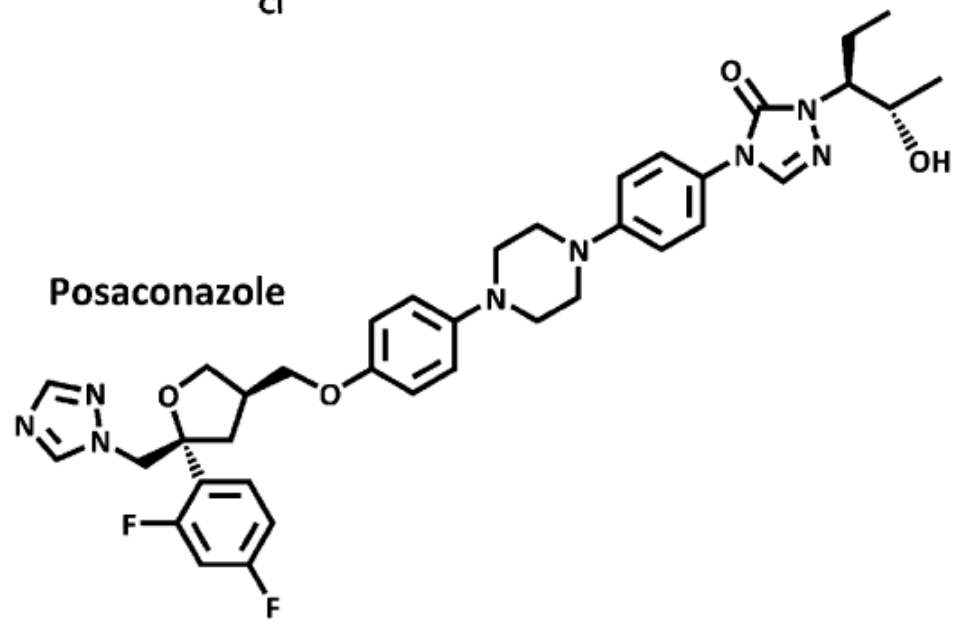


Voriconazole

Isavuconazole



Posaconazole



Rybak JM et al. Pharmacotherapy 2015; 35(11): 1037–1051

ISAVUCONAZONIUM SULFATE: A TRIAZOLE PRODRUG FOR INVASIVE FUNGAL INFECTIONS

Murrell D et al. *Int J Pharm Pract* 2017; 25: 18–30

ADVANTAGES OF ISZ OVER OTHER AVAILABLE TRIAZOLE AGENTS

Characteristic	ISZ[86, 87]	POS[78, 79]	VCZ[80–84]	Itraconazole[85, 86]
Anti-aspergillus and mucorales activity	Aspergillus + mucorales	Aspergillus + mucorales	Aspergillus	Aspergillus

ISAVUCONAZOLE:
A REVIEW IN INVASIVE ASPERGILLOSIS AND MUCORMYCOSIS

Shirley M and Scott LJ *Drugs* 2016; 76: 1647–1657

In vitro ACTIVITY OF ISAVUCONAZOLE AGAINST CLINICALLY IMPORTANT SPECIES

Organism	No. of isolates	MIC range[a] (μg/mL)	MIC_{90} range[a] (μg/mL)	MFC range[a] (μg/mL)
Aspergillus species				
A. flavus	97	0.25–16	1–16	0.5–4
A. fumigatus	939	0.06–4	0.5–2	0.125–4
A. nidulans	70	0.06–2	1	NA
A. niger	84	0.125 to >16	2–4	0.25 to >8
A. terreus	222	0.125 to >16	0.5–4	0.25–2
Mucorales				
Cunninghamella spp.	25	0.12 to >8	>8	2 to >16
Lichtheimia spp.	111	0.03 to >8	1 to >8	4 to >16
Mucor circinelloides	16	2–8	8	NA
Mucor spp.	107	<0.015 to >8	2 to >8	2 to >16
Rhizomucor spp.	38	<0.015 to >8	>8	2 to >8
Rhizopus spp.	189	0.12 to >8	1 to >8	1 to >16
Syncephalastrum spp.	2	0.125–4	NA	1–16

NEW PHARMACOLOGICAL OPPORTUNITIES FOR THE TREATMENT OF INVASIVE MOULD DISEASES

Ledoux MP et al. *J Antimicrob Chemother* 2017; 72 Suppl 1: i48–i58

OVERVIEW OF INTERNATIONAL EXPERT RECOMMENDATIONS FOR CHOICE OF TARGETED TREATMENT OF INVASIVE ASPERGILLOSIS

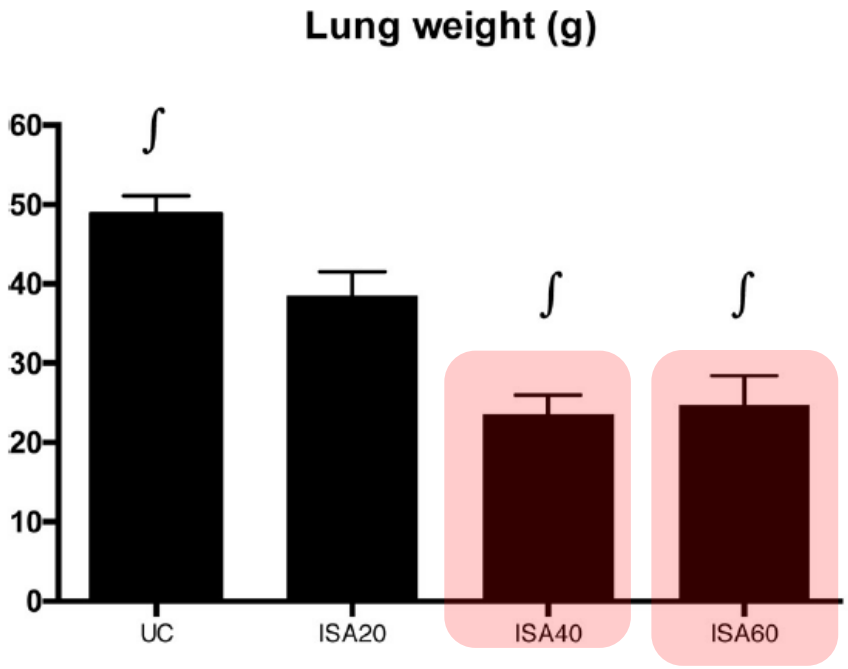
Publication	Location of infection or clinical setting	Agents (grading)
IDSA (2016)[3,4]	General statement	Early initiation of antifungal therapy in patients with strongly suspected invasive pulmonary aspergillosis is warranted while a diagnostic evaluation is conducted (strong recommendation; high-quality evidence)
	Invasive pulmonary aspergillosis	Voriconazole (strong recommendation; high-quality evidence) Isavuconazole (strong recommendation; moderate-quality evidence) LAmB (strong recommendation; moderate-quality evidence)
	Invasive tracheobronchial aspergillosis	Mould-active triazole (strong recommendation; moderate-quality evidence) Intravenous LAmB (strong recommendation; moderate-quality evidence) Adjunctive inhaled AmB in lung transplant recipients (strong recommendation; moderate-quality evidence) Bronchoscopic debridement of airway lesions in selected cases (strong recommendation; low-quality evidence)
	Paranasal sinuses	Surgery and either voriconazole or LAmB (strong recommendation; moderate-quality evidence)
	CNS	Voriconazole (strong recommendation; moderate-quality evidence) LAmB are reserved for those intolerant or refractory to voriconazole (strong recommendation; moderate-quality evidence)
	Endocarditis, osteomyelitis, arthritis, skin (primary lesions following burns, trauma, etc.)	Surgery and antifungal therapy (strong recommendation; moderate-quality evidence)
ECIL-6 (2016/2017)[8]	Patients with haematological malignancy or HSCT: first line	Isavuconazole (A-I) Voriconazole (A-I) LAmB (B-I) ABLC (B-II)
	Patients with haematological malignancy or HSCT: second line	LAmB (B-II) ABLC (B-II) Caspofungin (B-II) Combination (various) (B-II) Posaconazole (B-II) Voriconazole (B-II) if not used in first line

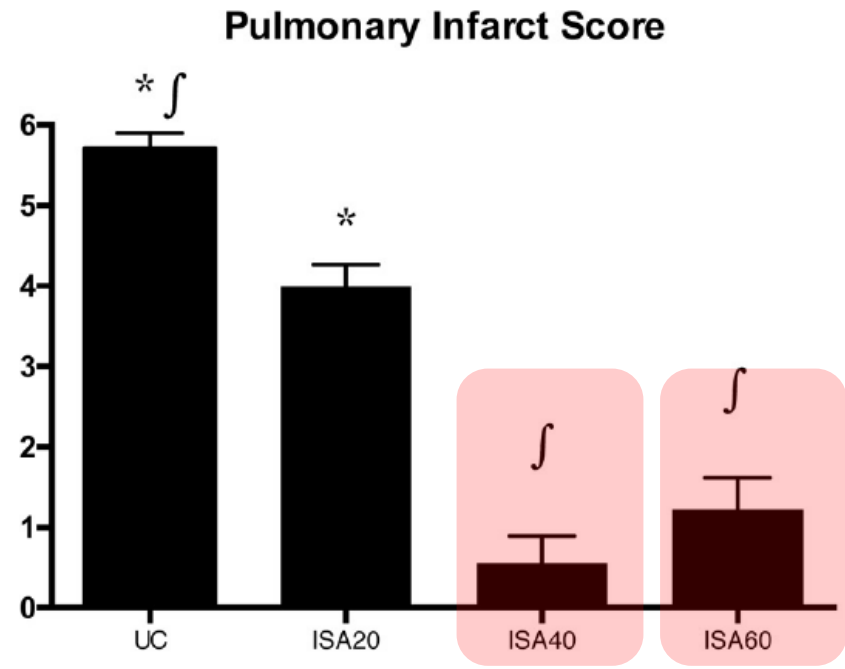
JniUD

PK AND CONCENTRATION-DEPENDENT EFFICACY OF ISAVUCONAZOLE FOR TREATMENT OF EXPERIMENTAL INVASIVE PULMONARY ASPERGILLOSIS

Petraitis V et al. *Antimicrob Agents Chemother* 2016; 60: 27178-2726

RESPONSE OF PRIMARY PULMONARY ASPERGILLOSIS
IN PERSISTENTLY NEUTROPENIC RABBITS TO ANTIFUNGAL THERAPY MEASURED BY:





COMBINATION THERAPY WITH ISAVUCONAZOLE AND MICAFUNGIN FOR TREATMENT OF EXPERIMENTAL INVASIVE PULMONARY ASPERGILLOSIS

Petraitis V et al. *Antimicrob Agents Chemother* 2017 Aug 24; 61 (9). pii:e00305-17

RESPONSE OF PRIMARY PULMONARY ASPERGILLOSIS
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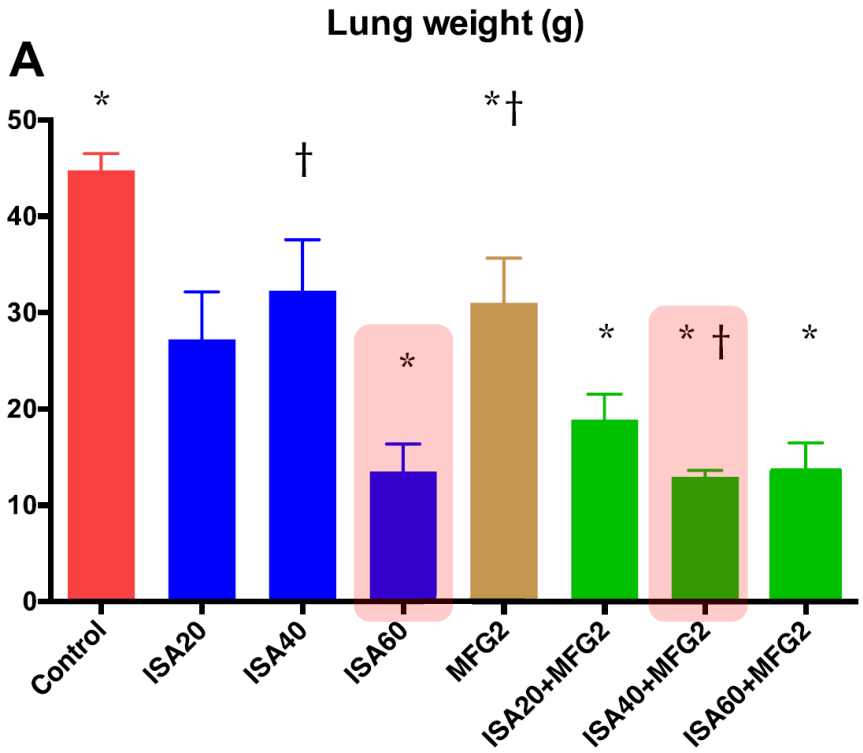

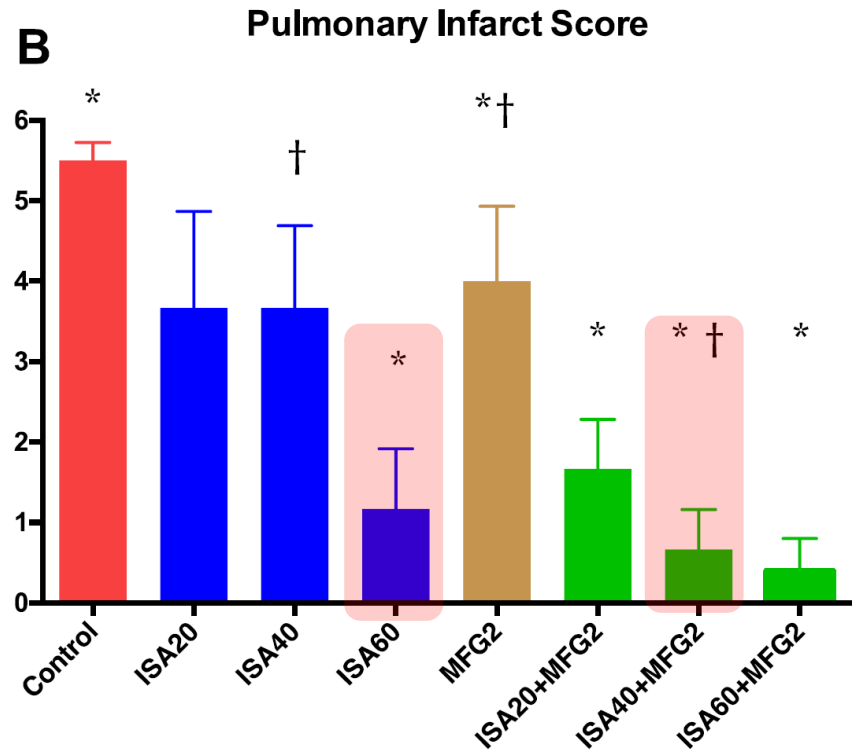

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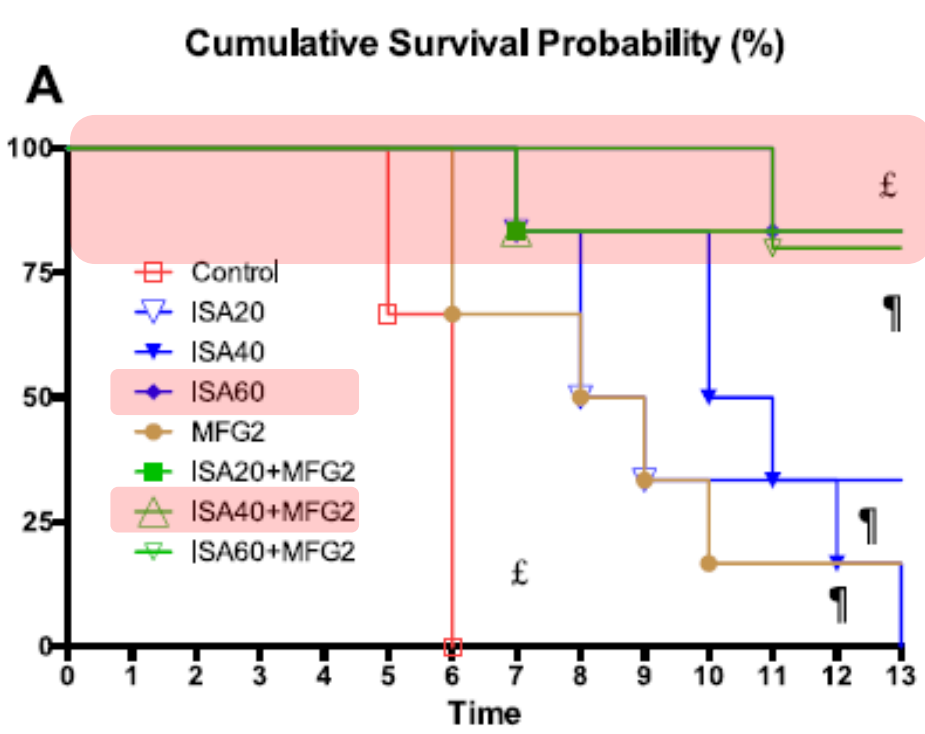

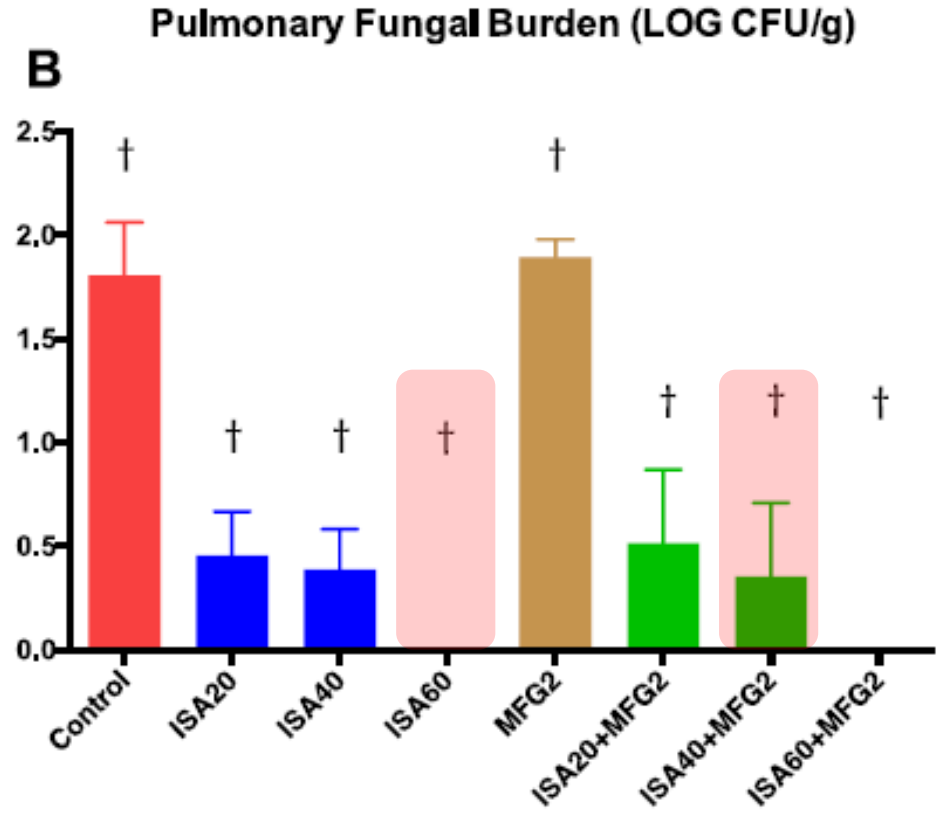

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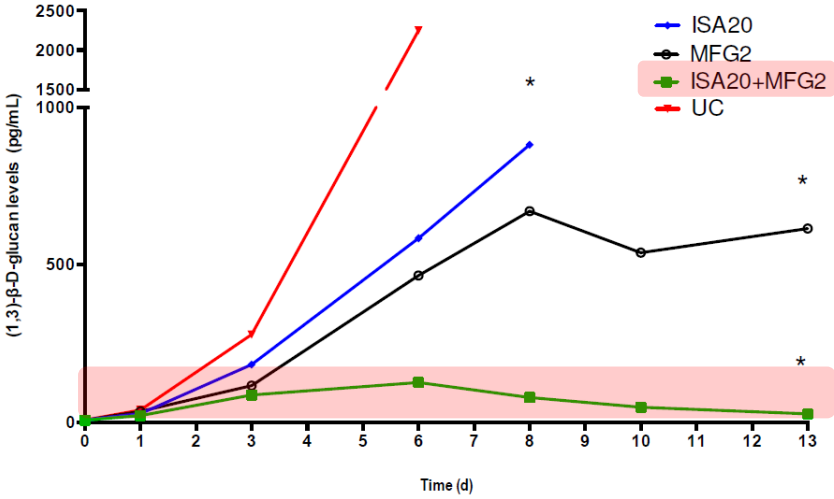
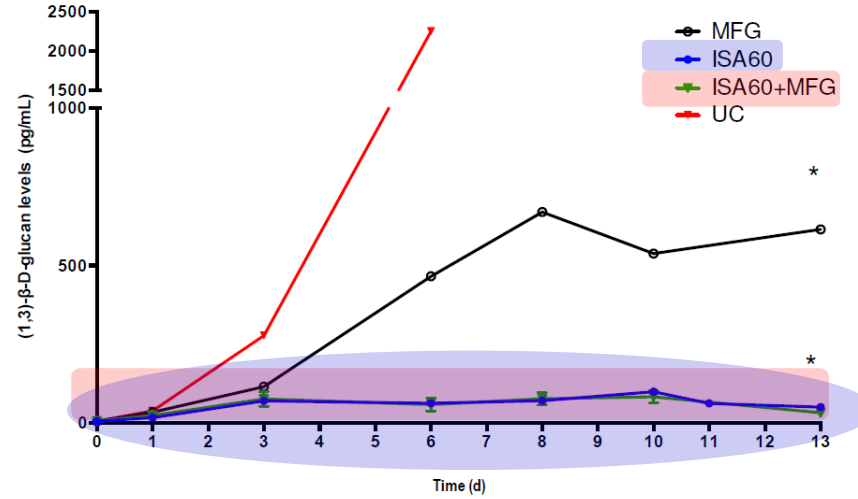
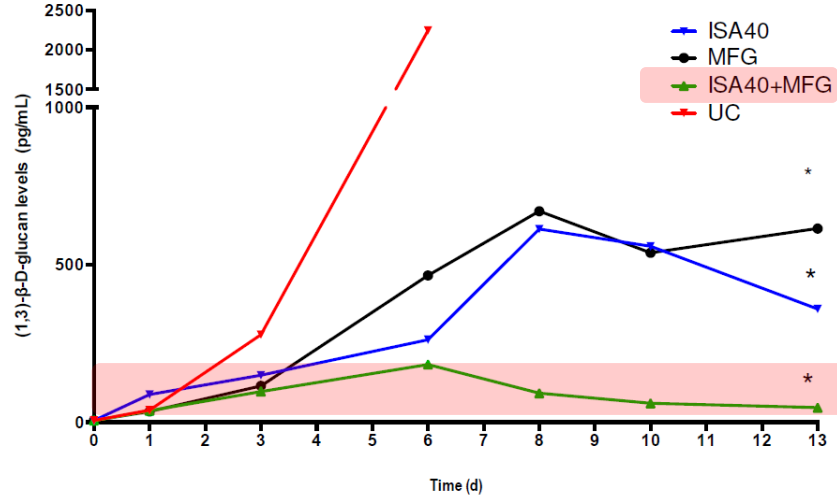
Petraitis V et al. *Antimicrob Agents Chemother* 2017 Aug 24; 61 (9). pii:e00305-17

SERUM (1-3)-Beta-D-GLUCAN LEVELS

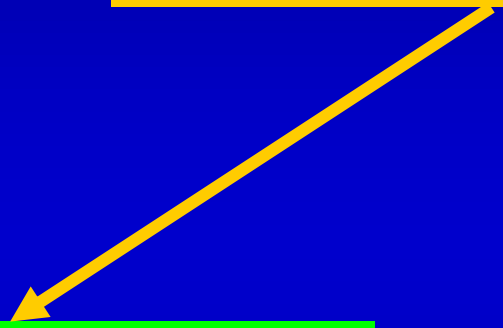






MAJOR CHARACTERISTICS OF TRIAZOLES

HIGH LIPOPHILICITY



HIGH PENETRATION RATE
INTO DEEP-TISSUES
EVEN THROUGH ANATOMICAL
BARRIERS

PHARMACOKINETIC PARAMETERS OF ISAVUCONAZOLE AND VORICONAZOLE

Parameter	Isavuconazole 200 mg/day	Voriconazole 4 mg/kg twice/day
V_d	450 L	1.2 L/kg
C_{max} at SS, mg/L	4	5.4
$t_{1/2}$, hrs	80–130	8
AUC_τ at SS, mg•hr/L	60	30
$fAUC_\tau$ at SS, mg•hr/L	0.6	12.4
Protein binding	> 99%	58%
Metabolism	Hepatic	Hepatic
Elimination	45% feces, 45% urine (as inactive metabolites)	> 80% urine (as inactive metabolites)
Bioavailability	98%	96%

V_d = volume of distribution; C_{max} = maximum serum concentration; SS = steady state; t½ = half- life; $fAUC_\tau$ = area under the free drug concentration–time curve over the dosing interval.

Rybak JM et al. Pharmacotherapy 2015; 35(11): 1037–1051

SUCCESSFUL ISAVUCONAZOLE SALVAGE THERAPY IN A PATIENT WITH INVASIVE MUCORMYCOSIS

Ervens J et al. *Infection* 2014; 42:429–432

POSACONAZOLE:
≥ 200 MG Q6H PER OS WITH HIGH FAT MEAL
+
LIPOSOMAL AMPB: 5 MG/KG/DAY

Day[a]	Posaconazole trough level: plasma (µg/mL)	Posaconazole level: soft-tissue (µg/g)
10	<0.16	
12	<0.19	
13	0.09	
19	0.12	
26	0.10	
29	ND	0.03
32	0.19	

STOP POSACONAZOLE ON DAY 52
LIPOSOMAL AMPB ON DAY 96

ISAVUCONAZOLE:
200 MGQ8H IV ON DAYS 104–105
200 MG QD IV ON DAYS 106–107
200 MG Q24H ORALLY FROM DAY 108 ON

Day[a]	Isavuconazole trough level: plasma (µg/mL)	Isavuconazole level: soft-tissue (µg/g)
112	0.86	1.09–1.38[b]
113	0.76	
117	0.82	
141[c]	1.3	
148	1.65	
155	1.76	
187	2.34	
217	2.83	
250	2.85	
285	3.24	
313	3.02	

TISSUE/PLASMA RATIO = 1.3 – 1.6

MOLD INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

McCarthy M et al. *New Engl J Med* 2014 July 10;371:150-60

THERAPEUTIC OPTIONS FOR MOLD INFECTIONS OF THE CNS

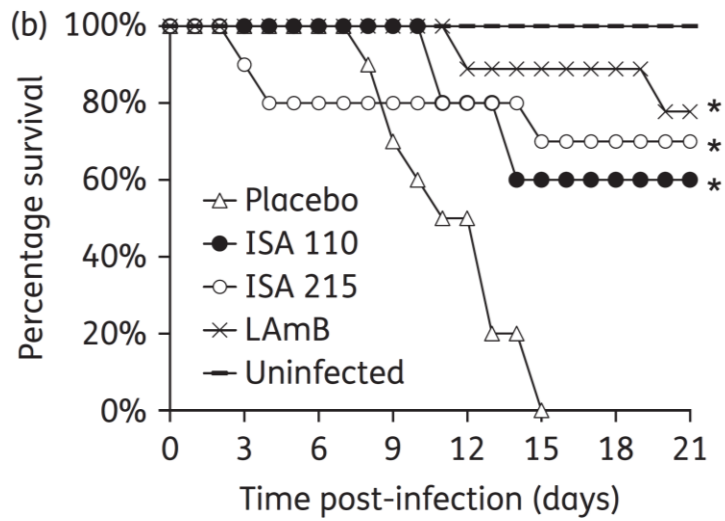
Mold	First-Line Therapy		Second-Line Therapy		Adjunctive Therapy and Comments†
	Adults	Children	Adults	Children	
Aspergillus species	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr‡ Liposomal amphotericin B: 5–7.5 mg/kg/day IV	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr‡ Liposomal amphotericin B: 5–7.5 mg/kg/day IV	Amphotericin B lipid complex: 5 mg/kg/day IV Caspofungin: loading dose, 70 mg/day IV; maintenance dose, 50 mg/day IV Posaconazole: 200 mg 4 times a day initially, then 400 mg PO twice a day§ Itraconazole: dosage depends on formulation	Amphotericin B lipid complex: 5 mg/kg/day IV Caspofungin: loading dose, 70 mg/m²/day IV; maintenance dose, 50 mg/m²/day IV	Reversal of neutropenia, surgical resection, and discontinuation of glucocorticoids should be used as adjunctive therapy Combination therapy with voriconazole plus echinocandin may be more effective than voriconazole alone in pulmonary aspergillosis, but its effectiveness has not been determined for CNS aspergillosis

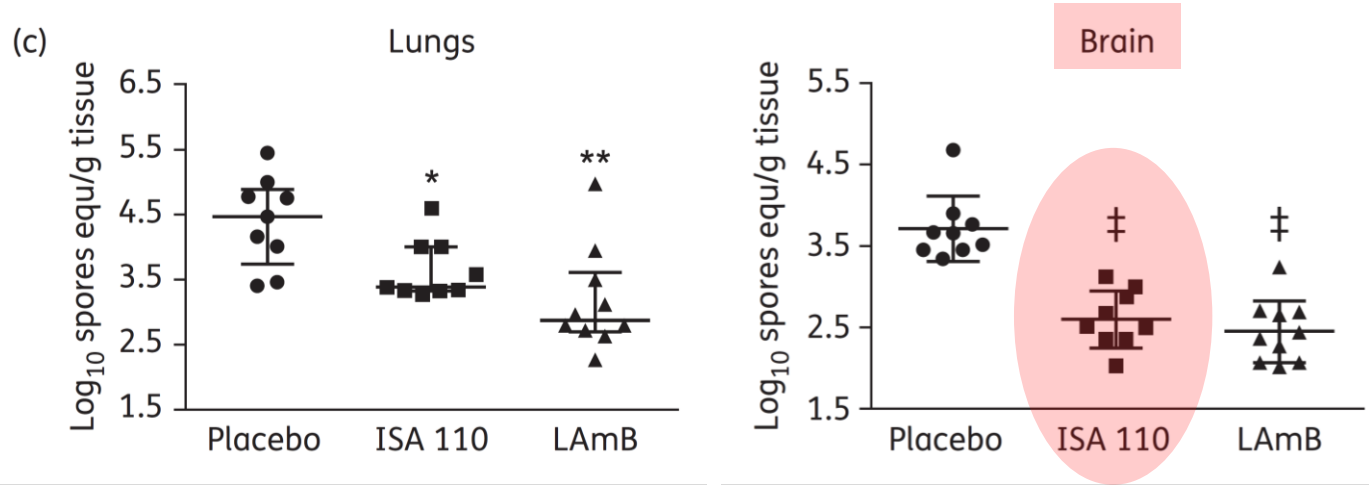
- Voriconazole is the first-line treatment for CNS aspergillosis.
- Although there are no formal guidelines regarding therapeutic drug monitoring in CNS aspergillosis, we recommend maintaining trough concentrations of 2 to 5 mg/L in serum.
- For patients in whom voriconazole as primary therapy might have unacceptable adverse effects, liposomal amphotericin B is an alternative.

MONO OR COMBINATION THERAPY OF ISAVUCONAZOLE AND MICAFUNGIN FOR TREATING MURINE MUCORMYCOSIS

Gebremariam T et al. *J Antimicrob Chemother* 2017; 72: 462–466

COMPARATIVE EFFICACY OF ANTIFUNGALS IN THE TREATRMENT OF INFECTION DUE TO *Mucor circinelloides*





ISAVUCONAZONIUM SULFATE: A TRIAZOLE PRODRUG FOR INVASIVE FUNGAL INFECTIONS

Murrell D et al. *Int J Pharm Pract* 2017; 25: 18–30

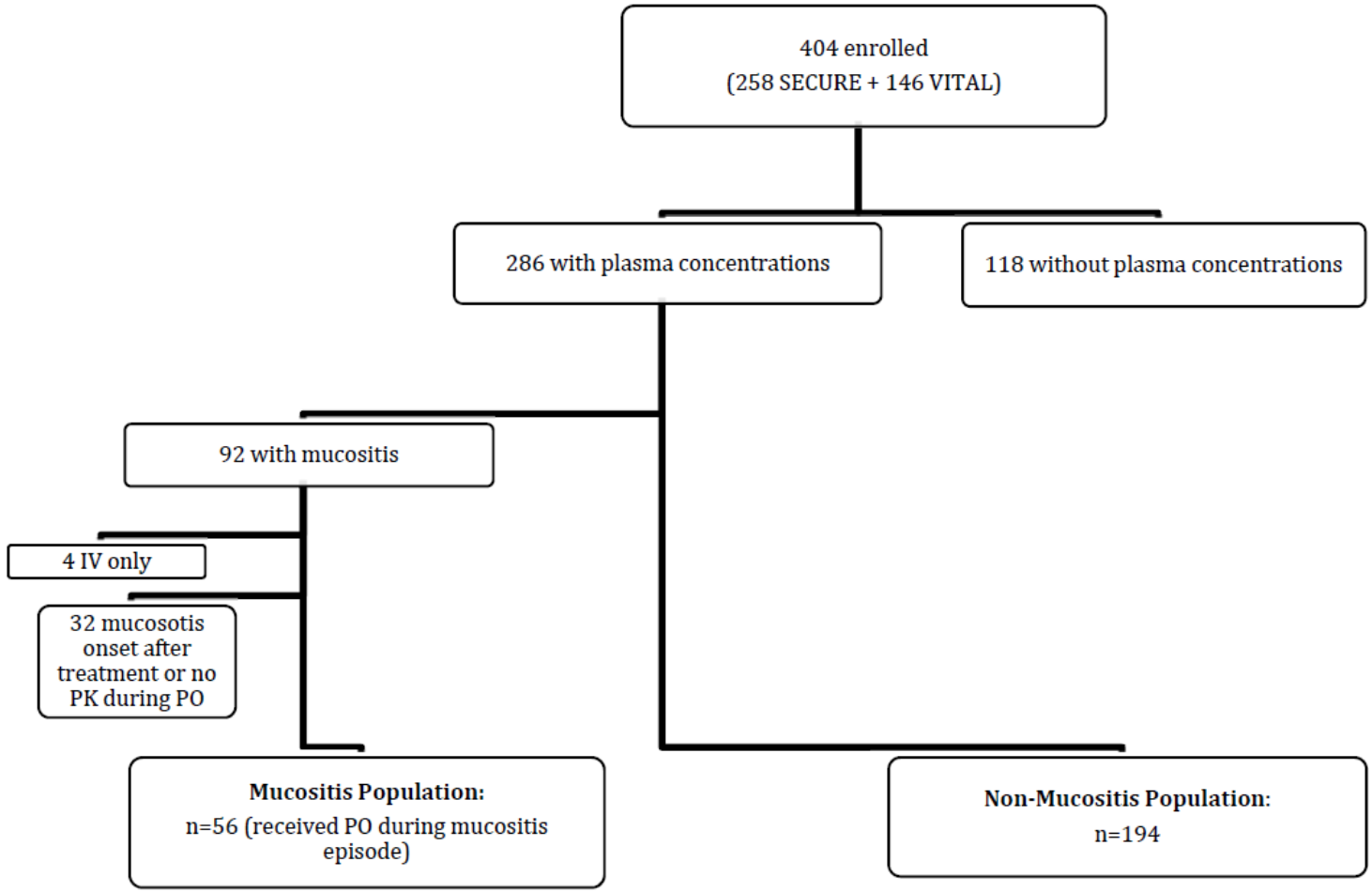
ADVANTAGES OF ISZ OVER OTHER AVAILABLE TRIAZOLE AGENTS

Characteristic	ISZ[86, 87]	POS[78, 79]	VCZ[80–84]	Itraconazole[85, 86]
Anti-aspergillus and mucorales activity	Aspergillus + mucorales	Aspergillus + mucorales	Aspergillus	Aspergillus
Formulation	Oral/IV	Oral/IV	Oral/IV	Oral/IV
Oral bioavailability	Equivalent to intravenous	Depends on dosing frequency and food (range of 8%–47%)	90%–95%	30% tablet 50% solution
Food requirement for absorption	Not required	Increased absorption (with a fatty meal)	Decreased absorption (with a fatty meal)	Increased absorption with acidity

THE IMPACT OF MUCOSITIS ON ABSORPTION AND SYSTEMIC DRUG EXPOSURE OF ISAVUCONAZOLE

Kovanda LL et al. *Antimicrob Agents Chemother* 2017 May 24; 61(6). pii: e00101-17

FLOWCHART ILLUSTRATING FLOW OF ISAVUCONAZOLE-TREATED PATIENTS INTO THE MUCOSITIS AND NON-MUCOSITIS POPULATIONS



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Kovanda LL et al. *Antimicrob Agents Chemother* 2017 May 24; 61(6). pii: e00101-17

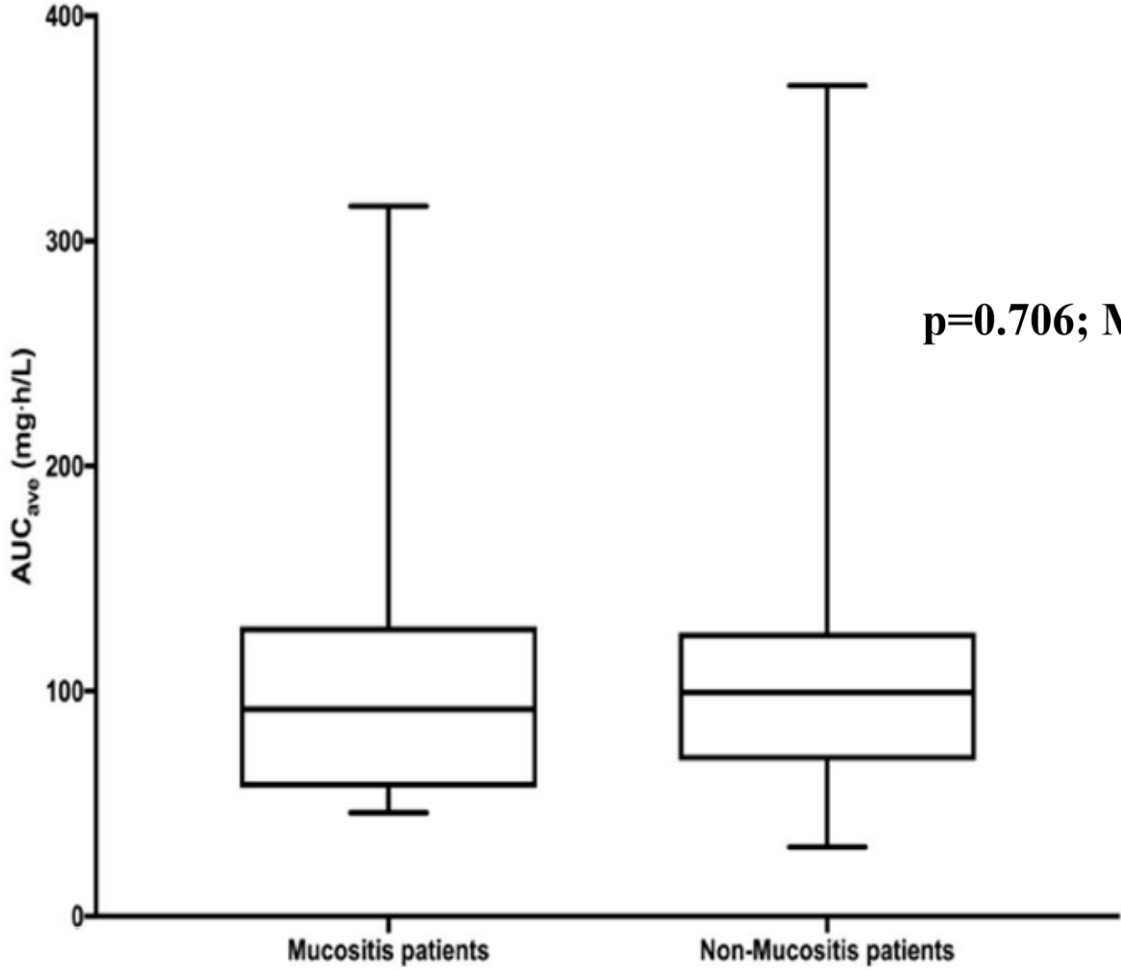
DEMOGRAPHICS, BACKGROUND DISEASE AND DURATION OF THERAPY

Characteristic	Value for: Mucositis patients (n = 56)	Nonmucositis patients (n = 194)	Total (n = 250)
Age (yrs), median (minimum–maximum)	50 (18–79)	52 (19–92)	52 (18–92)
Male sex, no. (%)	32 (57)	123 (63)	155 (62)
Race, no. (%)			
White	48 (86)	149 (77)	197 (79)
Asian	7 (13)	31 (16)	38 (15)
Black	1 (2)	9 (5)	10 (4)
Other	0	5 (3)	5 (2)
Wt (kg), mean ± SD	71.7 ± 18.1	69.5 ± 18.4	70.0 ± 18.3
Underlying disease or condition, no. (%)			
Hematological malignancy	50 (89.3)	101 (52.1)	151 (60.4)
Active malignancy	40 (71.4)	76 (39.2)	116 (46.4)
Allogeneic HSCT	15 (26.8)	33 (17.0)	48 (19.2)
Baseline neutropenia	43 (78.2)	64 (41.8)	107 (51.4)
T-cell immunosuppressants	23 (41.8)	82 (51.9)	105 (49.3)
Use of corticosteroids	8 (14.3)	47 (24.2)	55 (22.0)
Duration of therapy (days), median (range)			
Total duration	75.5 (8–735)	83 (1–882)	82 (1–882)
i.v. formulation	9 (2–45)	7 (0.5–77)	7.5 (0.5–77)
Oral formulation	58 (1–690)	79.8 (0.5–882)	73 (0.5–882)

THE IMPACT OF MUCOSITIS ON ABSORPTION AND SYSTEMIC DRUG EXPOSURE OF ISAVUCONAZOLE

Kovanda LL et al. *Antimicrob Agents Chemother* 2017 May 24; 61(6). pii: e00101-17

COMPARISON OF AVERAGE AUCs CALCULATED FROM THE POP-PK MODEL



p=0.706; Mann Whitney U test

THE IMPACT OF MUCOSITIS ON ABSORPTION AND SYSTEMIC DRUG EXPOSURE OF ISAVUCONAZOLE

Kovanda LL et al. *Antimicrob Agents Chemother* 2017 May 24; 61(6). pii: e00101-17

COMPARISON OF FACTORS IMPACTING ORAL ABSORPTION OF TRIAZOLE ANTIFUNGAL DRUGS

	Datum for drug			
Factor	Isavuconazonium sulfate	Voriconazole	Posaconazole (14)	
Formulation	Capsule	Tablets	Solution	Tablets
Water solubility	Y (prodrug)	N	N	N
Bioavailability (%)				
Healthy subjects	98 (11)	96 (29)	8–48 (fasted)	54 (fasted)
Patients	97 (5)	64 (30)		
GI motility agents	None	No data found	Decreases	None
pH effect	None	None	Decreases in reduced acidity	None
Food effect	None	Decreases concentrations	Increases concentrations (especially high fat, nutritional supplement, or acidic carbonated beverage)	C_{max} and AUC increases 16% and 51% with high-fat foods
Other		*F* significantly lower in CF lung tx (23%) pts vs non-CF lung tx (63%) (23); 2 factors with significant association with *F* in lung tx pts: CF, postoperative time (increased with increasing time) (23)	Divided doses increase absorption	
Substrate of Pgp	N	N	Y	Y

[a]Abbreviations: Y, yes; N, no; GI, gastrointestinal; *F*, bioavailability; CF, cystic fibrosis; Pgp, P-glycoprotein; C_{max}, maximum concentration; tx pts, transplant patients.

RISK FACTORS FOR SUBTHERAPEUTIC LEVELS OF POSACONAZOLE TABLET

Tang LA et al. *J Antimicrob Chemother.* 2017 Oct; 72(10): 2902-2905

PATIENT BASELINE DEMOGRAPHICS

	All patients ($N = 157$)	Posaconazole level <700 ng/mL ($N = 29$)	Posaconazole level ≥700 ng/mL ($N = 128$)	*P*
Demographics				
age (years), median (range)	61 (18–89)	60 (18–70)	62 (18–89)	0.028
female, *n* (%)	62 (39)	11 (18)	51 (82)	0.057
weight (kg), median (range)	81 (42–156)	87 (56–132)	79 (42–156)	0.107
height (m), median (range)	1.73 (1.48–1.95)	1.78 (1.52–1.95)	1.72 (1.48–1.94)	0.007
BMI (kg/m^2), median (range)	26.9 (16.5–55.1)	27.4 (18.1–39.5)	26.6 (16.5–55.1)	0.544
dose (mg/kg), median (range)	3.7 (1.18–8.76)	3.5 (2.27–8.76)	3.8 (1.18–7.23)	0.184
Indications, *n* (%)				
AML	126 (80)	19 (15)	107 (85)	0.038
ALL	5 (3)	0 (0)	5 (100)	0.585
transplant GVHD	18 (11)	7 (39)	11 (61)	0.046
other	8 (5)	3 (37.5)	5 (62.5)	0.166
Treatments, *n* (%)				
other[a]	14 (12)	2 (14)	12 (86)	1.000
3+7[b]	47 (30)	11 (23)	36 (77)	0.369
FLAG	35 (22)	3 (8)	32 (91)	0.136
hypomethylating	17 (11)	1 (6)	16 (94)	0.201
clofarabine	23 (15)	4 (17)	19 (83)	1.000
none[c]	21 (13)	8 (38)	13 (62)	0.029

3+7, idarubicin/daunorubin.

[a]Other chemotherapy regimens included HLH-1994, SGN-CD33A, alemtuzumab + cyclosporine and a combination of cytarabine/daunorubicin/etoposide.

[b]CPX-351 was categorized as 3+7.

[c]Patients with GVHD were classified as none.

RISK FACTORS FOR SUBTHERAPEUTIC LEVELS OF POSACONAZOLE TABLET

Tang LA et al. *J Antimicrob Chemother.* 2017 Oct; 72(10): 2902-2905

PATIENT BASELINE DEMOGRAPHICS

Risk factor	All patients (*N* = 157)	Posaconazole level <700 ng/mL (*N* = 29)	Posaconazole level ≥700 ng/mL (*N* = 128)	*P*	Multivariable logistic regression	
					OR (95% CI)	*P*
PPI, *n* (%)	119 (76)	27 (93)	92 (72)	0.016	0.109 (0.018–0.647)	0.015
Receipt of a loading dose, *n* (%)	120 (76)	23 (79)	97 (76)	0.811		
Diarrhoea, *n* (%)	73 (46)	24 (83)	49 (38)	<0.001	0.073 (0.021–0.247)	<0.001
Active GI GVHD, *n* (%)	3 (2)	2 (7)	1 (1)	0.088		
>90 kg, *n* (%)	50 (32)	14 (48)	36 (28)	0.047		
Baseline albumin (g/dL), median (range)	3.3 (2.5–4.3)	3.1 (2.6–3.7)	3.3 (2.5–4.3)	0.080	0.188 (0.052–0.679)	0.011
Age (years), median (range)	61 (18–89)	60 (18–70)	62 (18–89)	0.028	0.968 (0.934–1.003)	0.073
Height (m), median (range)	1.73 (1.48–1.95)	1.78 (1.52–1.95)	1.72 (1.48–1.94)	0.007		
Female, *n* (%)	62 (39)	11 (18)	51 (82)	0.057	5.918 (1.635–21.423)	0.007
AML, *n* (%)	126 (80)	19 (15)	107 (85)	0.038	5.042 (1.394–18.236)	0.014

[b]CPX-351 was categorized as 3+7.
[c]Patients with GVHD were classified as none.

ISAVUCONAZONIUM SULFATE: A TRIAZOLE PRODRUG FOR INVASIVE FUNGAL INFECTIONS

Murrell D et al. *Int J Pharm Pract* 2017; 25: 18–30

ADVANTAGES OF ISZ OVER OTHER AVAILABLE TRIAZOLE AGENTS

Characteristic	ISZ[86, 87]	POS[78, 79]	VCZ[80–84]	Itraconazole[85, 86]
Anti-aspergillus and mucorales activity	Aspergillus + mucorales	Aspergillus + mucorales	Aspergillus	Aspergillus
Formulation	Oral/IV	Oral/IV	Oral/IV	Oral/IV
Oral bioavailability	Equivalent to intravenous	Depends on dosing frequency and food (range of 8%–47%)	90%–95%	30% tablet 50% solution
Food requirement for absorption	Not required	Increased absorption (with a fatty meal)	Decreased absorption (with a fatty meal)	Increased absorption with acidity
Kinetics	Linear and predictable	Nonlinear	Nonlinear	Nonlinear
Interpatient variability	Minimal	Significant	Significant	Significant

ISAVUCONAZOLE:
A NEW BROAD-SPECTRUM TRIAZOLE ANTIFUNGAL AGENT

Miceli MH and Kauffman CA. *Clin Infect Dis* 2015 Nov 15; 61(10): 1558-65

PHARMACOLOGY

- Isavuconazole has a large volume of distribution, is >99% protein bound, and has a long terminal half-life of 100–130 hours
- Metabolism of isavuconazole takes place in the liver via the CYP enzyme family, specifically CYP3A4 and CYP3A5 isoenzymes.

POPULATION PHARMACOKINETICS OF ISAVUCONAZOLE IN SUBJECTS WITH MILD AND MODERATE HEPATIC IMPAIRMENT

Desai A et al. *Antimicrob Agents Chemother* 2016 Apr 22; 60(5): 3025-31

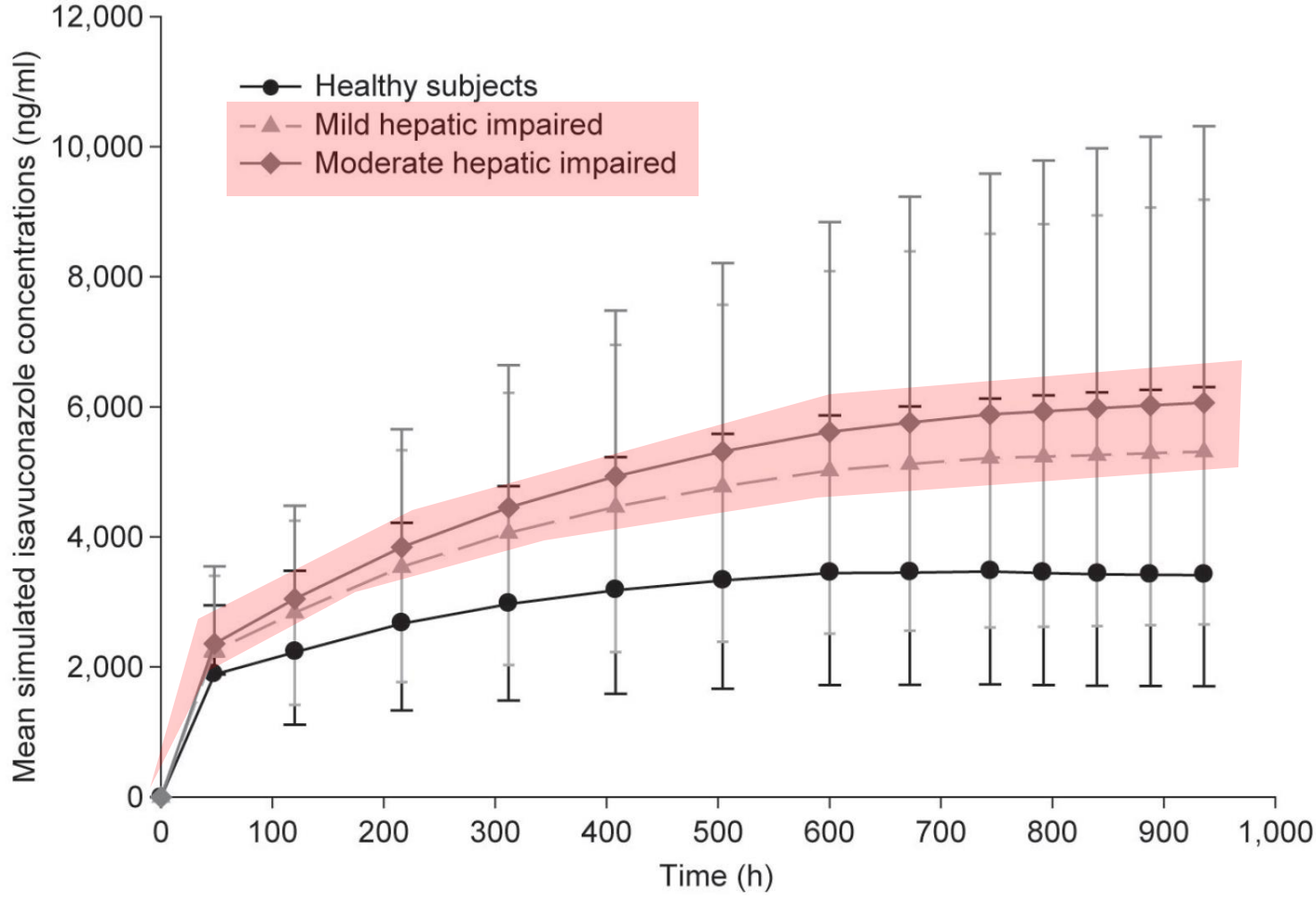
DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics	Healthy (N = 32) *n* (%)	Mild hepatic impairment (N = 32) *n* (%)	Moderate hepatic impairment (N = 32) *n* (%)
Sex			
Male	21 (66)	21 (66)	21 (66)
Female	11 (34)	11 (34)	11 (34)
Smoking status			
Smokers	19 (59)	24 (75)	24 (75)
Non-smokers	13 (41)	8 (25)	8 (25)
Median age (range), years	50 (40–64)	54 (37–64)	54 (42–64)
Median ht (range), cm	171 (148–185)	168 (147–180)	171 (155–180)
Median wt (range), kg	78 (53–107)	76 (56–105)	76 (58–103)
Median body mass index (range), kg/m^2	27 (22–33)	28 (21–34)	26 (22–34)

POPULATION PHARMACOKINETICS OF ISAVUCONAZOLE IN SUBJECTS WITH MILD AND MODERATE HEPATIC IMPAIRMENT

Desai A et al. *Antimicrob Agents Chemother* 2016 Apr 22; 60(5): 3025-31

MEAN SIMULATED ISAVUCONAZOLE CONCENTRATIONS



POPULATION PHARMACOKINETICS OF ISAVUCONAZOLE IN SUBJECTS WITH MILD AND MODERATE HEPATIC IMPAIRMENT

Desai A et al. *Antimicrob Agents Chemother* 2016 Apr 22; 60(5): 3025-31

CONCLUSIONS

- Due to the observation that there was less than a two-fold increase in total isavuconazole concentrations for subjects with mild-to-moderate hepatic impairment and no clinically relevant effect on vital signs or physical examination findings
- there appears to be no need for a dose adjustment of isavuconazonium sulfate in patients that present with invasive aspergillosis and or mucormycosis that also have mild-to-moderate liver impairment

TDM FOR INVASIVE MOULD INFECTIONS AND DISEASE: PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

Scott KE and Hope WW. *J Antimicrob Chemother* 2017; 72 Suppl 1: i12–i18

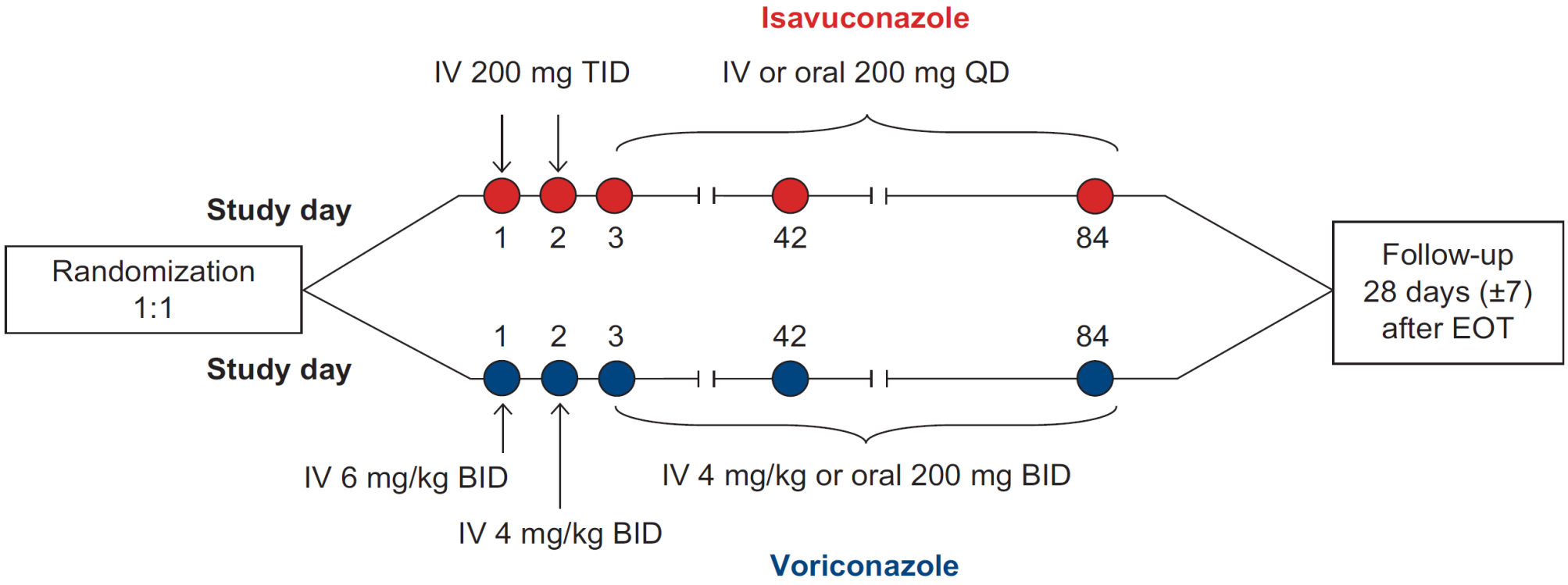
ISAVUCONAZOLE AND TDM

- The case for TDM of isavuconazole is uncertain at the present time
- Analysis of clinical trial data does not reveal any relationship between various measures of drug exposure (e.g. AUC, C_{min}) and efficacy endpoints (all-causemortality, clinical response) or safety endpoints, although this information is only available in abstract form at present

EXPOSURE-RESPONSE RELATIONSHIPS FOR ISAVUCONAZOLE IN PATIENTS WITH INVASIVE ASPERGILLOSIS AND OTHER FILAMENTOUS FUNGI

Desai AV et al. *Antimicrob Agents Chemother* 2017 Sep 18. pii: AAC.01034-17

STUDY DESIGN (SECURE TRIAL)



Maximum therapy duration was 84 days.

EXPOSURE-RESPONSE RELATIONSHIPS FOR ISAVUCONAZOLE IN PATIENTS WITH INVASIVE ASPERGILLOSIS AND OTHER FILAMENTOUS FUNGI

Desai AV et al. *Antimicrob Agents Chemother* 2017 Sep 18. pii: AAC.01034-17

SUMMARY OF PATIENT CHARACTERISTICS

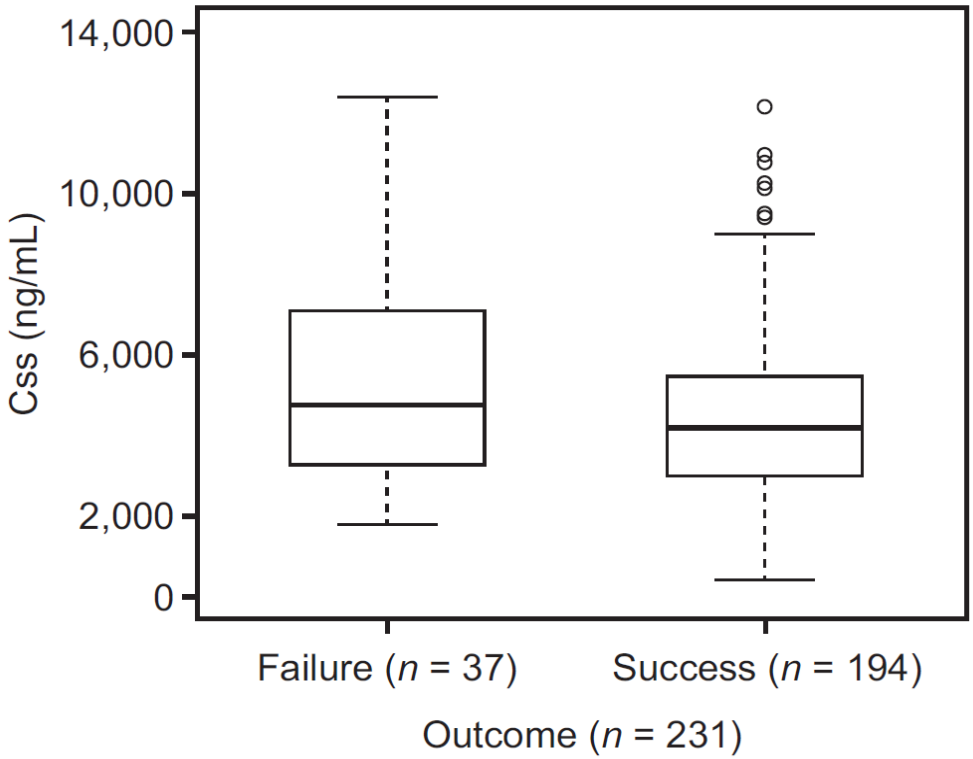
Patient characteristics	ITT population (*n* = 231)		mITT population (*n* = 129)	
	Yes	No	Yes	No
Hematological malignancy	191	40	100	29
Uncontrolled malignancy	156	75	79	50
Neutropenia	150	81	79	50
Elevated serum galactomannan at baseline[a]	54	150	51	62
Lower respiratory tract disease	182	49	104	25
Duration of therapy (Median)	51 days		59 days	

EXPOSURE-RESPONSE RELATIONSHIPS FOR ISAVUCONAZOLE IN PATIENTS WITH INVASIVE ASPERGILLOSIS AND OTHER FILAMENTOUS FUNGI

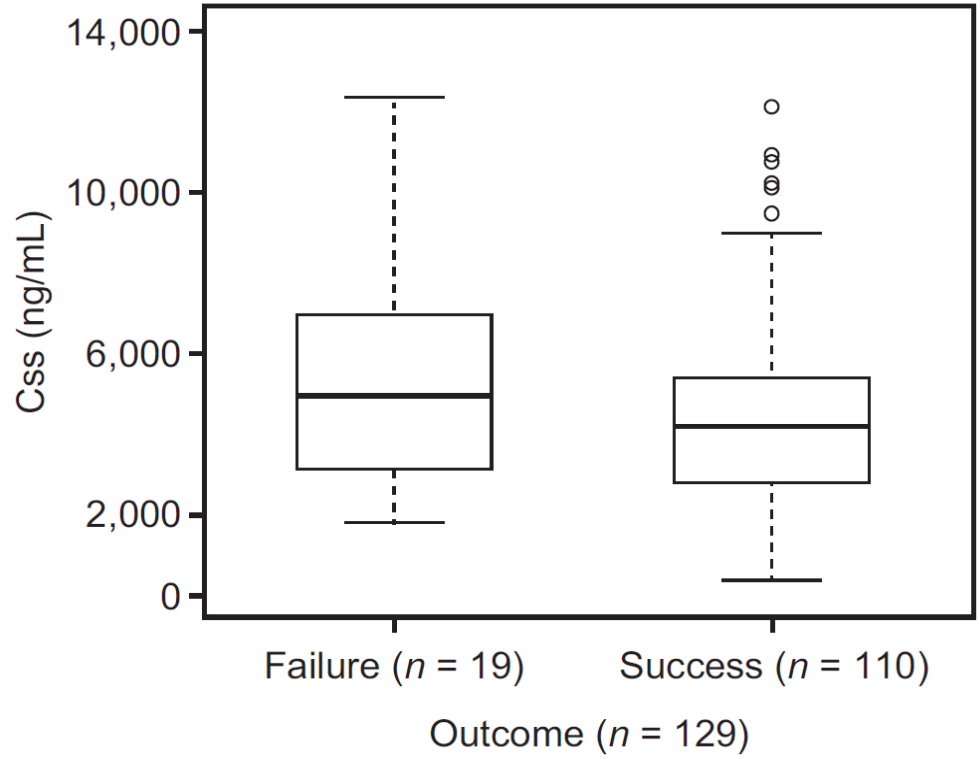
Desai AV et al. *Antimicrob Agents Chemother* 2017 Sep 18. pii: AAC.01034-17

BOX AND WHISKER PLOTS OF C_{SS} VS MORTALITY AT DAY 42 FOR

ITT POPULATION



MITT POPULATION

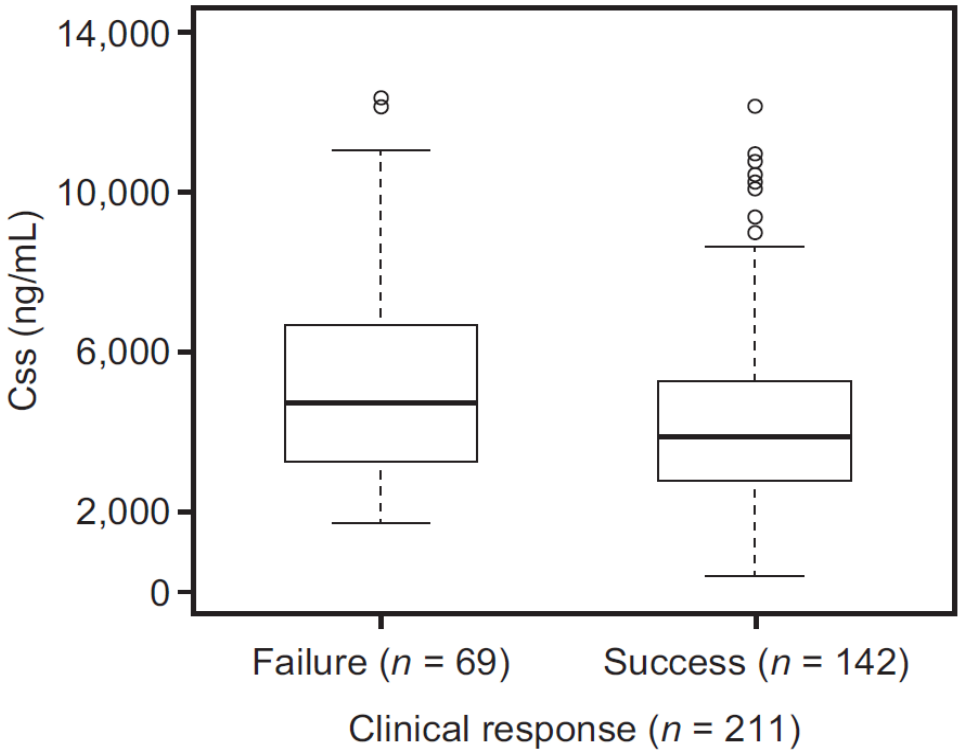


EXPOSURE-RESPONSE RELATIONSHIPS FOR ISAVUCONAZOLE IN PATIENTS WITH INVASIVE ASPERGILLOSIS AND OTHER FILAMENTOUS FUNGI

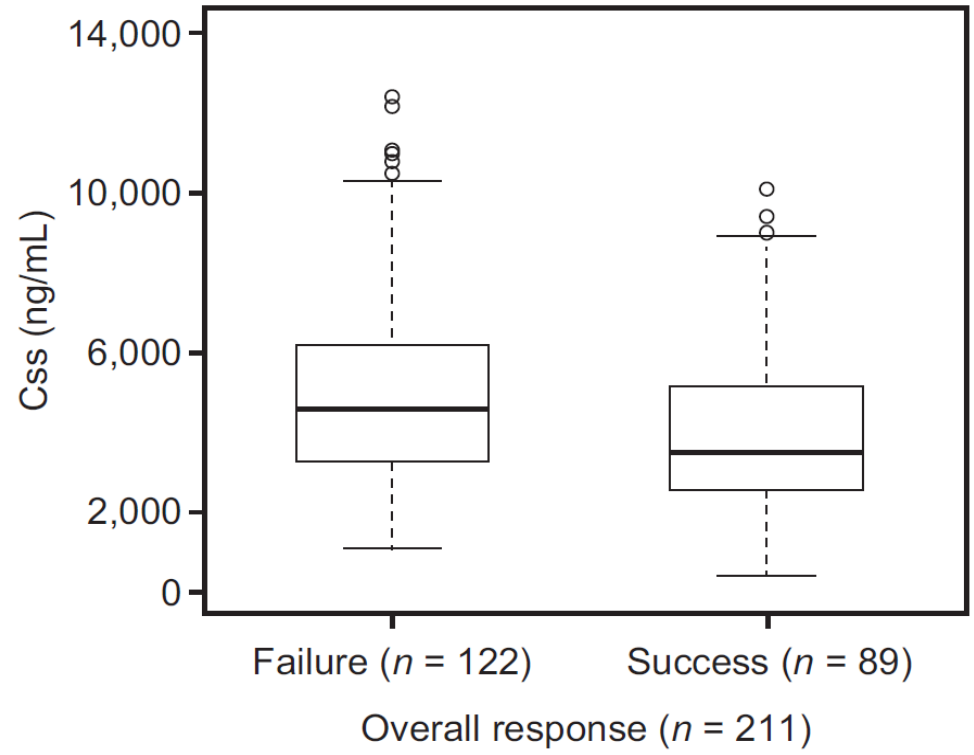
Desai AV et al. *Antimicrob Agents Chemother* 2017 Sep 18. pii: AAC.01034-17

BOX AND WHISKER PLOTS OF C_{SS} VS RESPONSE AT EOT FOR ITT POPULATION

CLINICAL RESPONSE



OVERALL RESPONSE

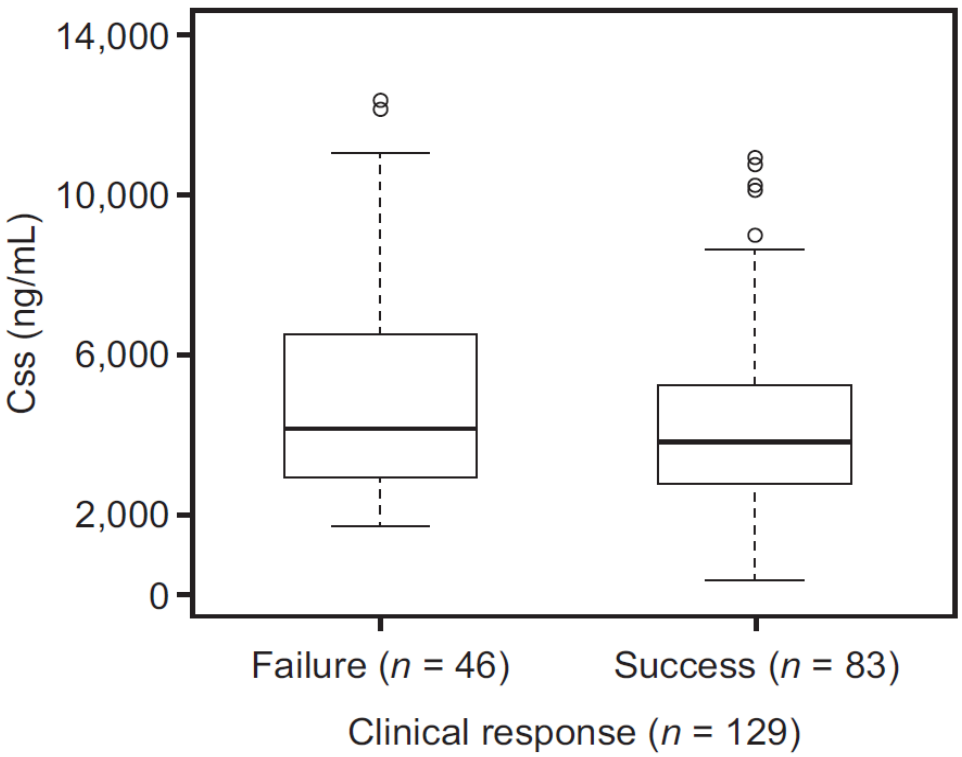


EXPOSURE-RESPONSE RELATIONSHIPS FOR ISAVUCONAZOLE IN PATIENTS WITH INVASIVE ASPERGILLOSIS AND OTHER FILAMENTOUS FUNGI

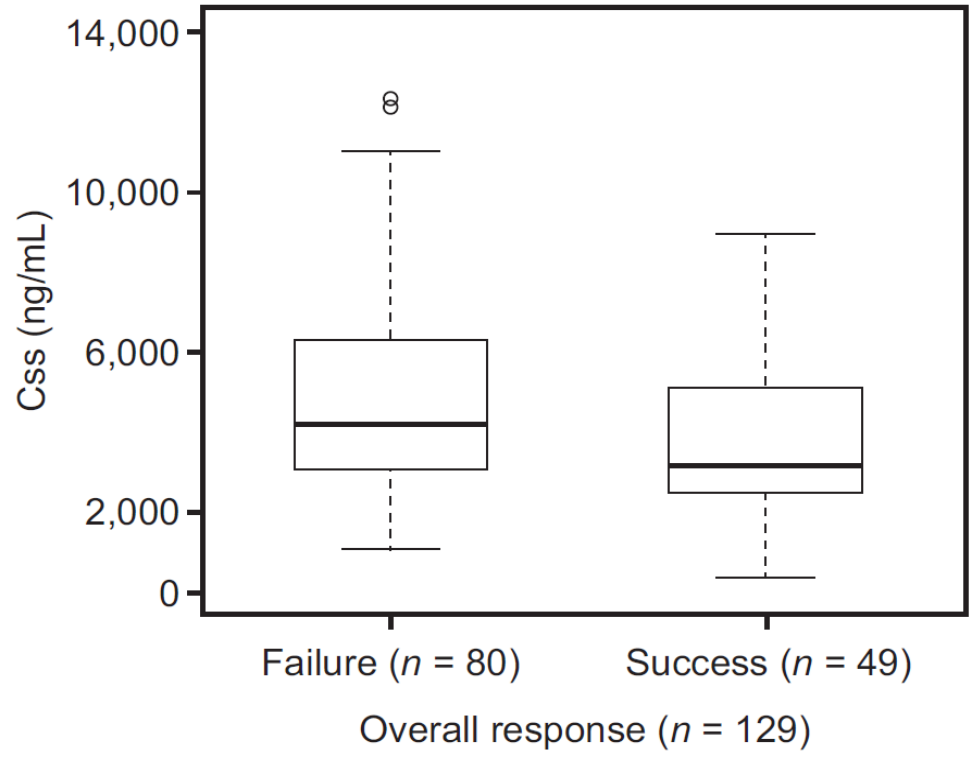
Desai AV et al. *Antimicrob Agents Chemother* 2017 Sep 18. pii: AAC.01034-17

BOX AND WHISKER PLOTS OF C_{SS} VS RESPONSE AT EOT FOR MITT POPULATION

CLINICAL RESPONSE



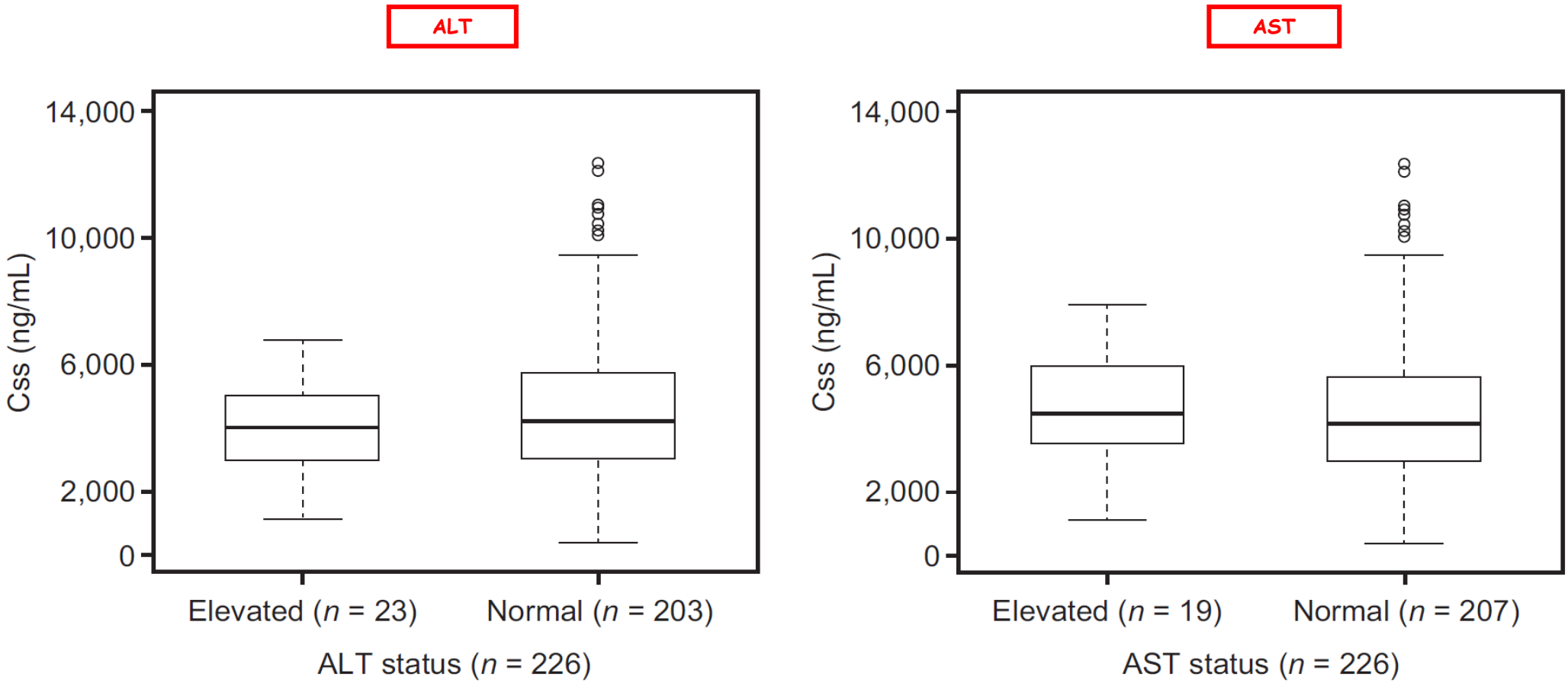
OVERALL RESPONSE



EXPOSURE-RESPONSE RELATIONSHIPS FOR ISAVUCONAZOLE IN PATIENTS WITH INVASIVE ASPERGILLOSIS AND OTHER FILAMENTOUS FUNGI

Desai AV et al. *Antimicrob Agents Chemother* 2017 Sep 18. pii: AAC.01034-17

BOX AND WHISKER PLOTS OF C_{SS} VS AST/ALT LEVELS AT EOT FOR ITT POPULATION



EXPOSURE-RESPONSE RELATIONSHIPS FOR ISAVUCONAZOLE IN PATIENTS WITH INVASIVE ASPERGILLOSIS AND OTHER FILAMENTOUS FUNGI

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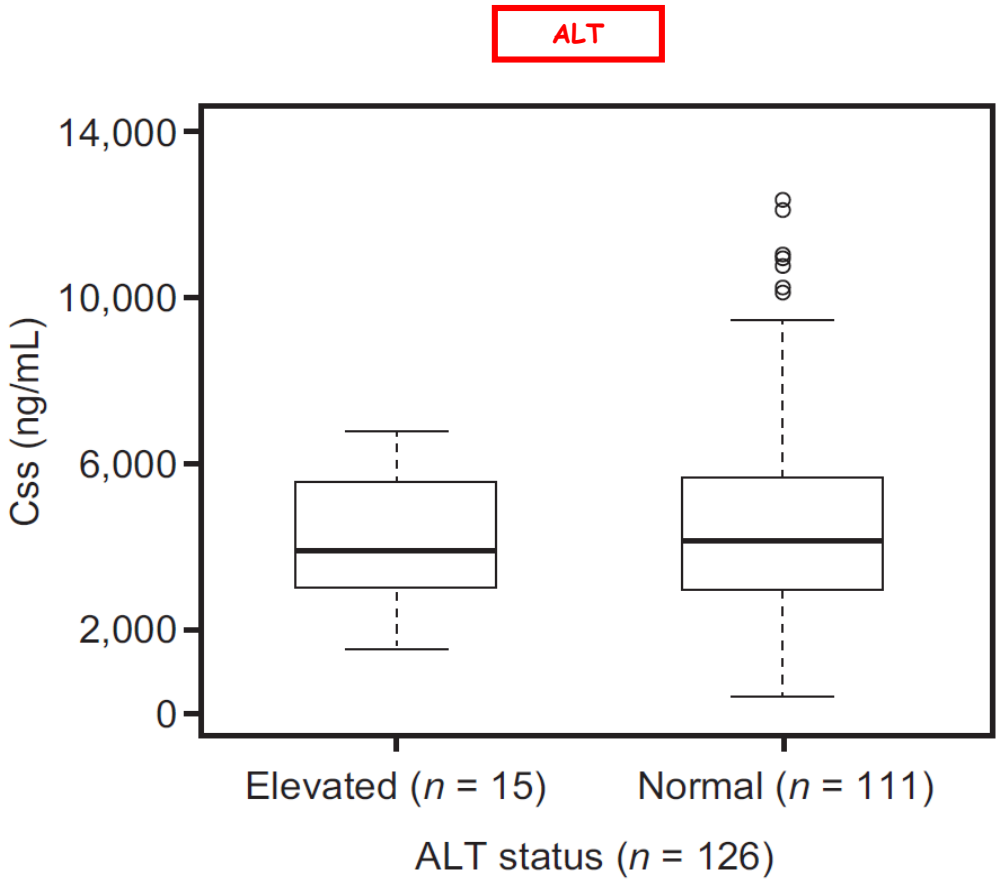
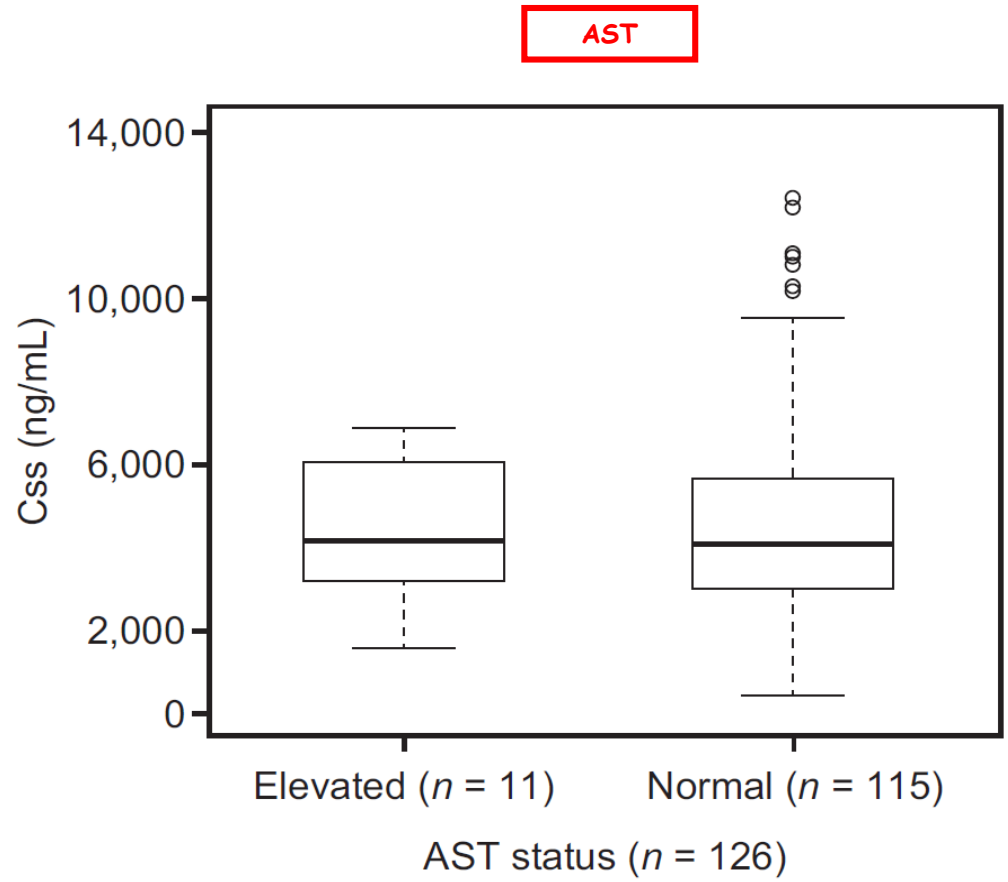
BOX AND WHISKER PLOTS OF C_{SS} VS AST/ALT LEVELS AT EOT FOR MITT POPULATION





EXPOSURE-RESPONSE RELATIONSHIPS FOR ISAVUCONAZOLE IN PATIENTS WITH INVASIVE ASPERGILLOSIS AND OTHER FILAMENTOUS FUNGI

Desai AV et al. *Antimicrob Agents Chemother* 2017 Sep 18. pii: AAC.01034-17

SUMMARY OF EXPOSURE PARAMETERS

	Css (ng/mL)	C7 (ng/mL)	C14 (ng/mL)
Mean (SD)	3633 (2023)	2631 (1033)	3049 (1397)
Median	3218	2477	2923
Range	174-10969	189-5627	174-7512

EXPOSURE-RESPONSE RELATIONSHIPS FOR ISAVUCONAZOLE IN PATIENTS WITH INVASIVE ASPERGILLOSIS AND OTHER FILAMENTOUS FUNGI

Desai AV et al. *Antimicrob Agents Chemother* 2017 Sep 18. pii: AAC.01034-17

CONCLUSIONS

- There could be several reasons for any lack of relationship between drug exposure and clinical outcomes from this analysis
- Firstly, even though there were some extremes in predicted exposures, the variability was only 62% in 211 patient population
- Secondly, it is possible there was a degree of bias in the PPK model. The PPK model was fitted to data from both phase 1 and sparse data from phase 3 data
- Even though there were 231 patients in the SECURE study, sparse data may potentially have led to biased estimates of exposure and Css values
- Poor compliance to the study drug could also have led to biased estimates of drug exposures

EXPOSURE-RESPONSE RELATIONSHIPS FOR ISAVUCONAZOLE IN PATIENTS WITH INVASIVE ASPERGILLOSIS AND OTHER FILAMENTOUS FUNGI

Desai AV et al. *Antimicrob Agents Chemother* 2017 Sep 18. pii: AAC.01034-17

CONCLUSIONS

- The lack of association between exposure and response is consistent with the proposition that the isavuconazole exposures achieved by the clinical dosage regimen were near maximal for treating the infecting organisms in the SECURE study
- There is no apparent relationship between exposure and efficacy to suggest routine TDM for isavuconazole.
- However, it is reasonable to continue observing real-world patients who are administered isavuconazole and monitor their exposures when necessary to ensure they do not require TDM

TDM FOR INVASIVE MOULD INFECTIONS AND DISEASE: PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

Scott KE and Hope WW. *J Antimicrob Chemother* 2017; 72 Suppl 1: i12–i18

ISAVUCONAZOLE AND TDM

- TDM could be considered in selected clinical cases where drug exposure needs to be confirmed (e.g. severe gut disease from GVHD where oral absorption may be problematic, treatment of CNS disease, or treatment of a non-wild-type fungal pathogen).
- TDM may also be indicated in circumstances where there is currently little information (e.g. dosing in children or adolescents).

ISAVUCONAZONIUM SULFATE: A TRIAZOLE PRODRUG FOR INVASIVE FUNGAL INFECTIONS

Murrell D et al. *Int J Pharm Pract* 2017; 25: 18–30

ADVANTAGES OF ISZ OVER OTHER AVAILABLE TRIAZOLE AGENTS

Characteristic	ISZ[86, 87]	POS[78, 79]	VCZ[80–84]	Itraconazole[85, 86]
Anti-aspergillus and mucorales activity	Aspergillus + mucorales	Aspergillus + mucorales	Aspergillus	Aspergillus
Formulation	Oral/IV	Oral/IV	Oral/IV	Oral/IV
Oral bioavailability	Equivalent to intravenous	Depends on dosing frequency and food (range of 8%–47%)	90%–95%	30% tablet 50% solution
Food requirement for absorption	Not required	Increased absorption (with a fatty meal)	Decreased absorption (with a fatty meal)	Increased absorption with acidity
Kinetics	Linear and predictable	Nonlinear	Nonlinear	Nonlinear
Interpatient variability	Minimal	Significant	Significant	Significant
Half-life ($t_{1/2}$)	56–104 h	24–30 h	16–35 h	24–30 h
Cyclodextrin (for solubility)	Not required	Not required	Required	Not required
Cyp450 effects (resulting in multiple drug interactions)	Minimal (Cyp3A4)	Moderate (Cyp3A4, Cyp2C9, Cyp2C19)	High (Cyp3A4, Cyp2C8, Cyp2C9, Cyp2C19, Cyp2D)	High (Cyp3A4, Cyp2C9, Cyp2C19)

CYP INHIBITORS

Fluconazole
Ketoconazole
Voriconazole

Fluconazole
Ketoconazole
Voriconazole

Isavuconazole
Posaconazole
Ketoconazole
Itraconazole
Fluconazole
Voriconazole

CYP1A2

- Teophyillin
- Verapamil
- R-warfarin
- Aloperidol
- Naproxene
- Ondansetron
- Propranolol

CYP2C9

- Antiepileptics (phenytoin)
- S-warfarin
- NSAIDs (diclofenac, flurbiprofene, ibuprofene, naproxene, piroxicam)

CYP2C19

- Antiepileptics (phenytoin)
- Proton pump inhibitors (lansoprazole, omeprazole)
- Others (diazepam, imipramine)

CYP2D6

- Beta-blockers (metoprolol, propranolol, timolol)
- Antidepressant (amitriptiline, clomipramine, desipramine, imipramine)
- Antipsychotics (thioridazine)

CYP3A4-5

- Macrolides
- Benzodiazepins (alprazolam, midazolam, triazolam)
- Immunosuppressants (cyclosporine, tacrolimus, sirolimus)
- Antiepiletics (carbamazepine)
- Opioid analgesics (alfentanil, fentanil, sufentanil)
- Antiarrrhythmics (disopiramide, quinidine)
- Calcium-antagonists (felodipine, nifedipine)
- R-warfarin
- Vinka alkaloids
- HMG-CoA reductase inhibitors (lovastatine, simvastatine)

Modified from Pea F. & Furlanut M. *Clin Pharmacokinet* 2001; 11: 833-868

PK ASSESSMENT OF DRUG–DRUG INTERACTIONS OF ISAVUCONAZOLE WITH THE IMMUNOSUPPRESSANTS CYCLOSPORINE, MYCOPHENOLIC ACID, PREDNISOLONE, SIROLIMUS, AND TACROLIMUS IN HEALTHY ADULTS

Groll AH et al. *Clin Pharmacol Drug Dev.* 2017; 6: 76-85

STATISTICAL ANALYSIS OF THE EFFECT OF ISAVUCONAZOLE ON THE PHARMACOKINETICS OF IMMUNOSUPPRESSIVE AGENTS

	Geometric least-squares mean ratio, % (90% CI)				
Parameter	Cyclosporine	Mycophenolic acid	Prednisolone	Sirolimus	Tacrolimus
$AUC_{0-\infty}$	129 (115, 144)	135 (127, 145)	108 (102, 114)	184 (159, 213)	225 (191, 266)
AUC_{last}	129 (115, 144)	132 (124, 141)	108 (102, 114)	208 (181, 239)	227 (192, 268)
C_{max}	106 (95, 119)	89 (76, 103)	96 (90, 102)	165 (141, 192)	142 (122, 164)

AUC, area under the concentration–time curve; CI, confidence interval; C_{max}, maximum concentration.

DRUG INTERACTION PROFILES OF ISAVUCONAZOLE, VORICONAZOLE AND POSACONAZOLE WITH IMMUNOSUPPRESSANTS METABOLIZED BY CYP450 3A4

Townsend R et al. P464 at the 7th Congress on Trends in Medical Mycology; Lisbon, Portugal; 9–12 October, 2015

EFFECT OF CONCOMITANT ADMINISTRATION OF TRIAZOLES ON THE AUC OF CICLOSPORIN, SIROLIMUS AND TACROLIMUS

Immunosuppressant	n-fold increase in the AUC of immunosuppressants by triazoles		
	ISA		
Ciclosporin	1.3[a]	1.7[b]	1.5[c]
Sirolimus[a]	1.8	11.0	8.9
Tacrolimus[a]	2.3	3.0	4.6

[a]Study in healthy subjects
[b]Study in renal-transplant patients
[c]Predicted value from a study in heart-transplant patients

DRUG INTERACTION PROFILES OF ISAVUCONAZOLE, VORICONAZOLE AND POSACONAZOLE WITH IMMUNOSUPPRESSANTS METABOLIZED BY CYP450 3A4

Townsend R et al. P464 at the 7th Congress on Trends in Medical Mycology; Lisbon, Portugal; 9–12 October, 2015

CURRENT RECOMMENDATIONS IN THE US PRESCRIBING INFORMATION FOR DOSE ADJUSTMENT FOR TRIAZOLES WITH CICLOSPORIN, SIROLIMUS AND TACROLIMUS

Ongoing immunosuppression	ISAV	VRC	POS
Ciclosporin	Use with caution. Concomitant administration of ISAV and ciclosporin results in an increase in ciclosporin exposure. Monitor drug concentrations of ciclosporin and adjust dose as needed	Reduce ciclosporin dose to ½ of the starting dose with frequent monitoring of ciclosporin blood levels. When VRC is discontinued, ciclosporin levels must be carefully monitored and dose increased as necessary	Reduce ciclosporin dose to ~¾ of the current dose with frequent monitoring of ciclosporin blood levels during co-administration, and upon discontinuation of POS; ciclosporin dose should be adjusted as necessary
Sirolimus	Same recommendation as for ciclosporin	Contraindicated	Contraindicated
Tacrolimus	Same recommendation as for ciclosporin	Reduce tacrolimus dose to ⅓ of the starting dose with frequent monitoring of tacrolimus blood levels. When VRC is discontinued, tacrolimus levels must be carefully monitored and dose increased as necessary	Reduce tacrolimus dose to ⅓ of the starting dose with frequent monitoring of tacrolimus blood levels. When POS is discontinued, tacrolimus levels must be carefully monitored and dose increased as necessary

ISAVUCONAZONIUM SULFATE: A TRIAZOLE PRODRUG FOR INVASIVE FUNGAL INFECTIONS

Murrell D et al. *Int J Pharm Pract* 2017; 25: 18–30

CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS WITH ISAVUCONAZOLE

Drug	Result of interaction	Recommendation
Cyclosporine	Increased the exposure of cyclosporine by ~1.3-fold	Caution when used concurrently
Tacrolimus	Increased the exposure of tacrolimus by ~2.25-fold	Caution when used concurrently
Atorvastatin	Increased the exposure of atorvastatin by ~1.4-fold	Caution when used concurrently
Lopinavir/ritonavir	Increased exposure of isavuconazole by 2-fold and a decrease in lopinavir/ritonavir exposure	Caution when used concurrently
Warfarin	No effect	No dose adjustment necessary
Ketoconazole	Increased isavuconazole exposure by 5-fold	Contraindicated
Bupropion	Decreased the exposure of bupropion by ~1.4-fold	Caution when used concurrently
Mycophenolate mofetil	Increased mycophenolate mofetil exposure	Caution when used concurrently, monitor for toxicities
Dabigatran etexilate	Increased dabigatran exposure	Caution when used concurrently, monitor for toxicities
Carbamazepine	Decreased exposure of isavuconazole	Contraindicated

EFFECTS OF ISAVUCONAZOLE ON THE PLASMA CONCENTRATIONS OF TACROLIMUS AMONG SOLID ORGAN TRANSPLANT PATIENTS

Rivosecchi RM et al. *Antimicrob Agents Chemother* 2017 Sept; 61(9). pii: e00970-17

TACROLIMUS DOSING PROTOCOLS AND DURATION OF ISAVUCONAZOLE PROPHYLAXIS ACCORDING TO ORGAN TRANSPLANT

Transplant type	Initial dosage of tacrolimus (mg/12 h)	Initial target concentration range of tacrolimus (ng/ml)[b]	Duration of isavuconazole prophylaxis (mo)
Kidney	2	8–12	1
Liver	1	8–10	1
Heart	2	10–12	1
Lung	0.5	12–15	3–4

EFFECTS OF ISAVUCONAZOLE ON THE PLASMA CONCENTRATIONS OF TACROLIMUS AMONG SOLID ORGAN TRANSPLANT PATIENTS

Rivosecchi RM et al. *Antimicrob Agents Chemother* 2017 Sept; 61(9). pii: e00970-17

CLINICAL CHARACTERISTICS OF PATIENTS INCLUDED IN THIS STUDY

Clinical characteristic[a]	All patients (n = 55)	Kidney transplant (n = 20)	Liver transplant (n = 18)	Heart transplant (n = 9)	Lung transplant (n = 8)	P value
Age (median [range]) (yrs)	60 (22–74)	53.5 (22–74)	60.5 (43–69)	64 (58–69)	66 (56–68)	0.006
Male (n [%])	47 (85)	17 (85)	13 (72)	7 (78)	7 (88)	0.73
Race, white (n [%])	46 (84)	16 (80)	15 (83)	7 (78)	7 (88)	0.95
Wt (median [range]) (kg)	82 (52–180)	93 (65–146)	88 (58–180)	77 (59–112)	69 (60–74)	0.005
Body mass index (median [range]) (kg/m^2)	28 (13–41)	30 (25–41)	30 (21–40)	26 (19–31)	23 (17–27)	0.002
Concomitant PPI (n [%])	43 (78)	16 (80)	14 (78)	5 (63)	8 (100)	0.17
Duration of intravenous therapy (median [range]) (days)[b]	3 (0–21)	2 (0–4)	5 (0–18)	5 (3–21)	10 (6–21)	<0.001
On isavuconazole, day 8–21						
Tacrolimus C/D (median [IQR])[c]	125 (94–188)	124 (76–181)	192 (127–259)	105 (84–150)	106 (80–109)	<0.001
Tacrolimus daily dose (median [IQR]) (mg)	6 (4–10)	7.5 (6–11.75)	4 (2.75–6)	7.5 (6–12.25)	8.5 (5.5–10)	0.0001
Tacrolimus trough levels (median [IQR]) (ng/ml)	10.5 (9–12.25)	10.5 (9–12.75)	8.5 (7.75–10.25)	12 (9.7–14)	12.5 (11.5–13)	0.001
Off isavuconazole, day 28–60						
Tacrolimus C/D (median [IQR])	120 (62–171)	154 (59–187)	101 (60–161)	103 (79–154)	87 (38–163)	0.59
Tacrolimus daily dose (median [IQR]) (mg)	8 (5–10)	6.5 (5–12.25)	6 (4–8)	9.5 (7.75–10.75)	9.5 (5.75–15)	0.03
Tacrolimus trough levels (median [IQR]) (ng/ml)	9 (7–11)	7 (6–9.5)	11 (9.75–12.25)	11 (9.75–12.25)	11 (8.75–12.25)	0.002
Actual tacrolimus dose taken off isavuconazole/calculated estimated tacrolimus dose[d]	1.3 (1.0–2.1)	1.3 (1.0–1.5)	1.9 (1.1–2.9)	1.1 (0.7–1.9)	1.4 (0.9–2.6)	0.28

[a]PPI, proton pump inhibitor; C/D, concentration-to-dose ratio ([ng/ml]/[mg/kg]); IQR, interquartile range.

ISAVUCONAZONIUM SULFATE: A TRIAZOLE PRODRUG FOR INVASIVE FUNGAL INFECTIONS

Murrell D et al. *Int J Pharm Pract* 2017; 25: 18–30

ADVANTAGES OF ISZ OVER OTHER AVAILABLE TRIAZOLE AGENTS

Characteristic	ISZ[86, 87]	POS[78, 79]	VCZ[80–84]	Itraconazole[85, 86]
Anti-aspergillus and mucorales activity	Aspergillus + mucorales	Aspergillus + mucorales	Aspergillus	Aspergillus
Formulation	Oral/IV	Oral/IV	Oral/IV	Oral/IV
Oral bioavailability	Equivalent to intravenous	Depends on dosing frequency and food (range of 8%–47%)	90%–95%	30% tablet 50% solution
Food requirement for absorption	Not required	Increased absorption (with a fatty meal)	Decreased absorption (with a fatty meal)	Increased absorption with acidity
Kinetics	Linear and predictable	Nonlinear	Nonlinear	Nonlinear
Interpatient variability	Minimal	Significant	Significant	Significant
Half-life ($t_{1/2}$)	56–104 h	24–30 h	16–35 h	24–30 h
Cyclodextrin (for solubility)	Not required	Not required	Required	Not required
Cyp450 effects (resulting in multiple drug interactions)	Minimal (Cyp3A4)	Moderate (Cyp3A4, Cyp2C9, Cyp2C19)	High (Cyp3A4, Cyp2C8, Cyp2C9, Cyp2C19, Cyp2D)	High (Cyp3A4, Cyp2C9, Cyp2C19)
Antacids/proton pump inhibitors	No change	Decreased level	Decreased	Decreased
With warfarin	No interaction	Prolonged PT/INR	Prolonged PT/INR	Prolonged PT/INR
Renal toxicity	None	None	Reported with intravenous formulation	None
Phototoxicity	None	None	Reported	Reported
Skin cancer	None	None	Reported	None
Neurological effects	Minimal	Sensorimotor, mono- and polyneuropathy	Sensorimotor, mono- and polyneuropathy	Sensorimotor, mono- and polyneuropathy
Visual toxicity	None	Hallucinations	Hallucinations	Hallucinations

ISAVUCONAZOLE VERSUS VORICONAZOLE FOR PRIMARY TREATMENT OF INVASIVE MOULD DISEASE CAUSED BY ASPERGILLUS AND OTHER FI LAMENTOUS FUNGI (SECURE): A PHASE 3, RANDOMISED-CONTROLLED, NON-INFERIORITY TRIAL

Maertens JA et al. *Lancet* 2016 Feb 20;387(10020):760-9

TREATMENT-EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS

	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0·122
Gastrointestinal disorders	174 (68%)	180 (69%)	0·705
Infections and infestations	152 (59%)	158 (61%)	0·719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0·658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0·859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0·289
Nervous system disorders	95 (37%)	89 (34%)	0·582
Skin and subcutaneous tissue disorders*	86 (33%)	110 (42%)	0·037¶
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0·357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0·703
Psychiatric disorders†	70 (27%)	86 (33%)	0·151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0·495
Vascular disorders	67 (26%)	77 (30%)	0·378
Renal and urinary disorders	55 (21%)	58 (22%)	0·832
Cardiac disorders	43 (17%)	57 (22%)	0·148
Eye disorders‡	39 (15%)	69 (27%)	0·002¶
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0·526
Hepatobiliary disorders§	23 (9%)	42 (16%)	0·016¶
Immune system disorders	20 (8%)	25 (10%)	0·533
Neoplasms benign, malignant and unspecified	19 (7%)	31 (12%)	0·101
Ear and labyrinth disorders	14 (5%)	13 (5%)	0·846
Reproductive system and breast disorders	8 (3%)	13 (5%)	0·373
Endocrine disorders	5 (2%)	3 (1%)	0·503
Congenital, familial, and genetic disorders	3 (1%)	2 (1%)	0·685
Social circumstances	0	1 (<1%)	>0·999

ISAVUCONAZOLE: A ROLE FOR THE NEWEST BROAD-SPECTRUM TRIAZOLE

Slavin M et al. *Lancet* 2016: 387: 726-727

EDITORIAL

- The approach to patients with previous triazole exposure has not been addressed in this clinical study, but will probably be a common clinical scenario.

REAL-LIFE USE OF ISAVUCONAZOLE IN PATIENTS INTOLERANT TO OTHER AZOLES

Ordaya EE et al. *Clin Infect Dis* 2016 (Dec 1); 63 (11): 1529-30

CLINICAL CHARACTERISTICS, INDICATIONS FOR TREATMENT, AND OUTCOMES IN PATIENTS WHO RECEIVED ISAVUCONAZOLE AS ALTERNATIVE THERAPY (N = 11)

Patient Details	Patients, No. (%)
Male sex	8 (73)
Age, median (range), y	52 (17–81)
IFD cases	
Proven	8 (73)
Probable	3 (27)
Fungal pathogen	
Aspergillus spp.	5 (46)
Mucorales molds[a]	2 (18)
Chaetomium sp.	1 (9)
Candida glabrata	1 (9)
Cryptococcus neoformans	1 (9)
Rhodotorula mucilaginosa	1 (9)
Antifungals used before switch to ISV	
Voriconazole	9 (82)
Posaconazole	2 (18)

Patient Details	Patients, No. (%)
Adverse effects that led to ISV therapy	
Elevated transaminase level	4 (37)
Neurovisual changes	3 (27)
Cardiotoxicity	2 (18)
Drug interactions	1 (9)
Photosensitivity	1 (9)
Duration of ISV therapy, median (range), d	87 (3–365)
Adverse effects of ISV	
Elevated transaminase level	1 (9)
Discontinuation of ISV	0
Response to ISV	
Complete	3 (27)
Partial	6 (55)
Failure	2 (18)
Death	2 (18)

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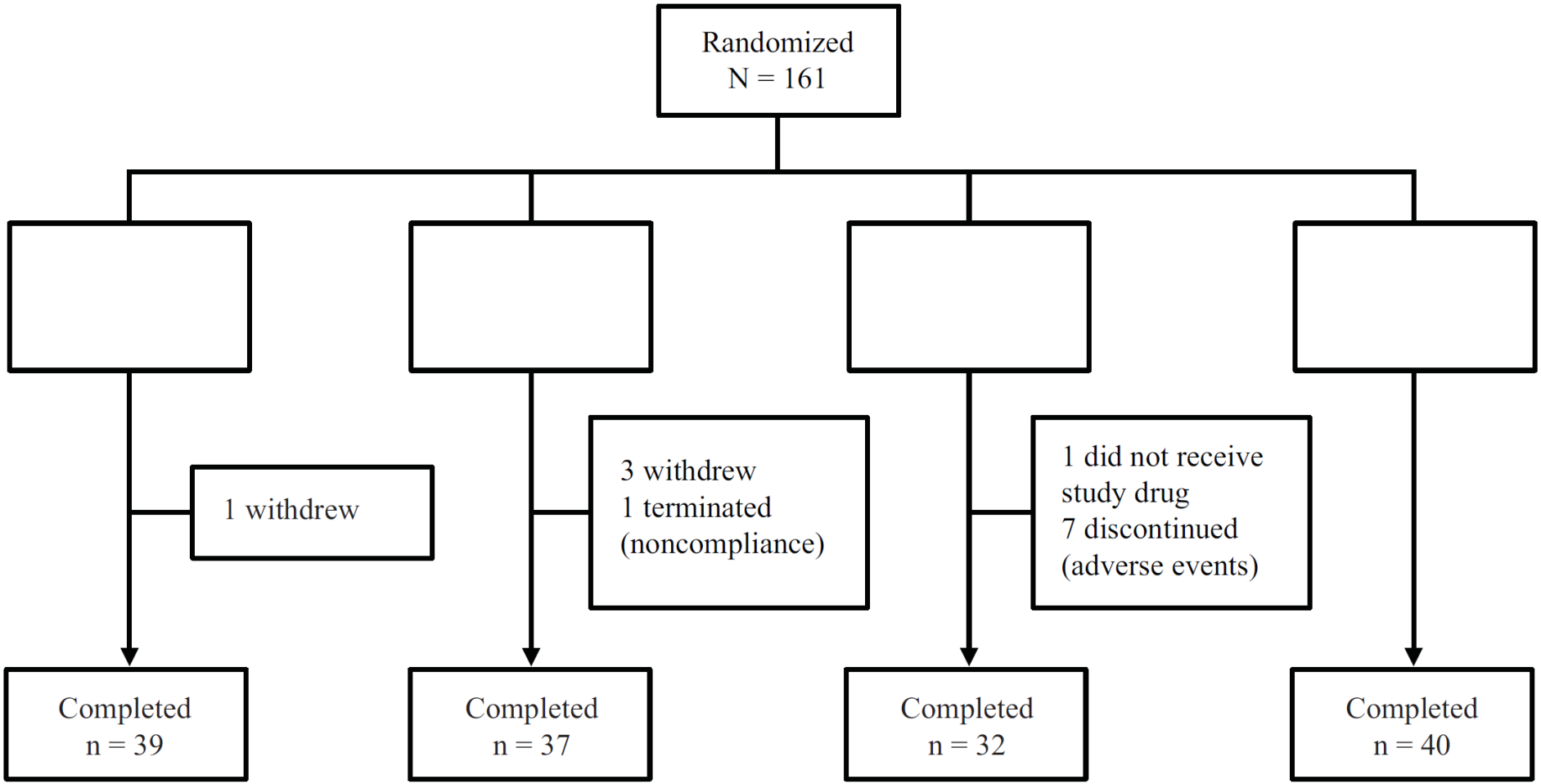
Renal toxicity	None	None	Reported with intravenous formulation	None
Phototoxicity	None	None	Reported	Reported
Skin cancer	None	None	Reported	None
Neurological effects	Minimal	Sensorimotor, mono- and polyneuropathy	Sensorimotor, mono- and polyneuropathy	Sensorimotor, mono- and polyneuropathy
Visual toxicity	None	Hallucinations	Hallucinations	Hallucinations
QTc interval	Shortening (significance unknown)	Prolongation	Prolongation	Prolongation

QT INTERVAL SHORTENING WITH ISAVUCONAZOLE: *In Vitro* AND *In Vivo* EFFECTS ON CARDIAC REPOLARIZATION

Keirns J et al. *Clin Pharmacol Ther.* 2017 Jun; 101(6): 782-790

SUBJECT DISPOSITION IN THE PHASE I CLINICAL STUDY



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DEMOGRAPHICS OF ALL SUBJECTS IN THE SAFETY ANALYSIS SET

		Isavuconazole		
Parameter	**Placebo (*n* = 40)**	**200 mg (*n* = 41)**	**600 mg (*n* = 39)**	**Moxifloxacin (*n* = 40)**
Age [years], mean ± SD	33.4 ± 9.8	33.0 ± 10.6	31.5 ± 9.2	32.2 ± 9.5
Sex, *n* (%)				
Male	22 (55.0)	17 (41.5)	20 (51.3)	22 (55.0)
Female	18 (45.0)	24 (58.5)	19 (48.7)	18 (45.0)
Race, *n* (%)				
White	22 (55.0)	20 (48.8)	29 (74.4)	16 (40.0)
Black or African American	10 (25.0)	17 (41.5)	7 (17.9)	14 (35.0)
Asian	4 (10.0)	2 (4.9)	2 (5.1)	4 (10.0)
American Indian/Alaska Native	2 (5.0)	0	0	1 (2.5)
Native Hawaiian/Pacific Islander	1 (2.5)	0	0	0
Other	1 (2.5)[a]	2 (4.9)[b]	1 (2.6)[c]	5 (12.5)[d]
Weight [kg], mean (SD)	71.4 (13.2)	69.5 (12.1)	70.6 (11.1)	76.8 (13.0)
Body mass index [kg/m^2], mean (SD)	24.5 (3.0)	24.0 (3.2)	24.2 (2.8)	25.3 (2.8)

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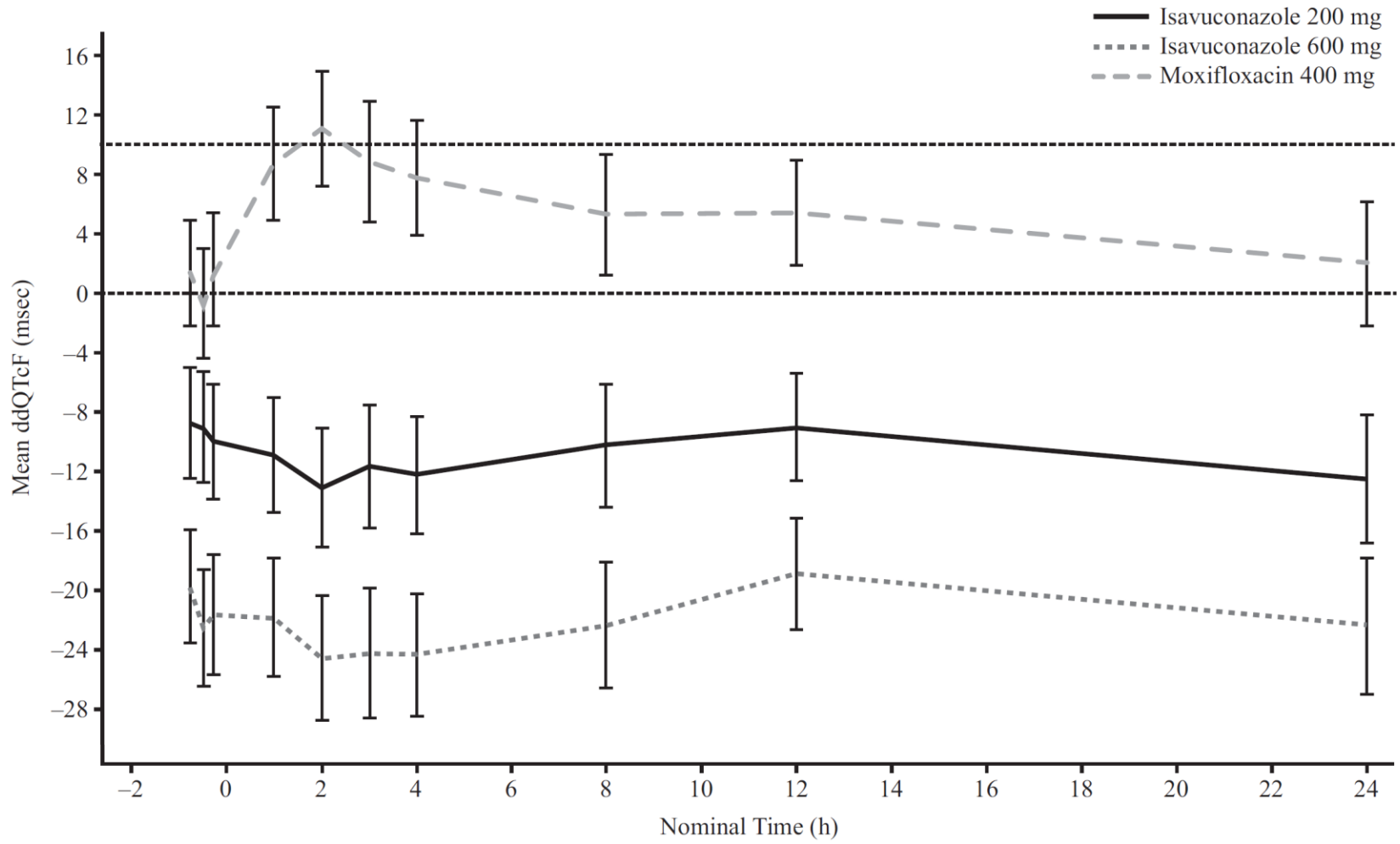
MEAN CHANGE COMPARED WITH PLACEBO IN BASELINE-ADJUSTED* QTCF OVER TIME ON DAY 13



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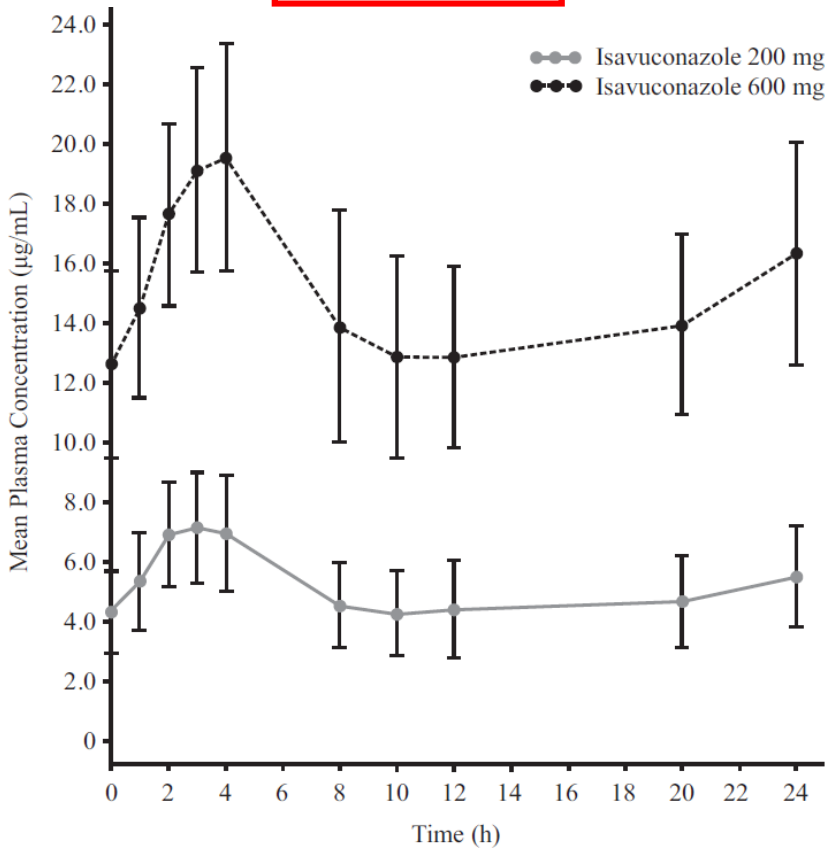
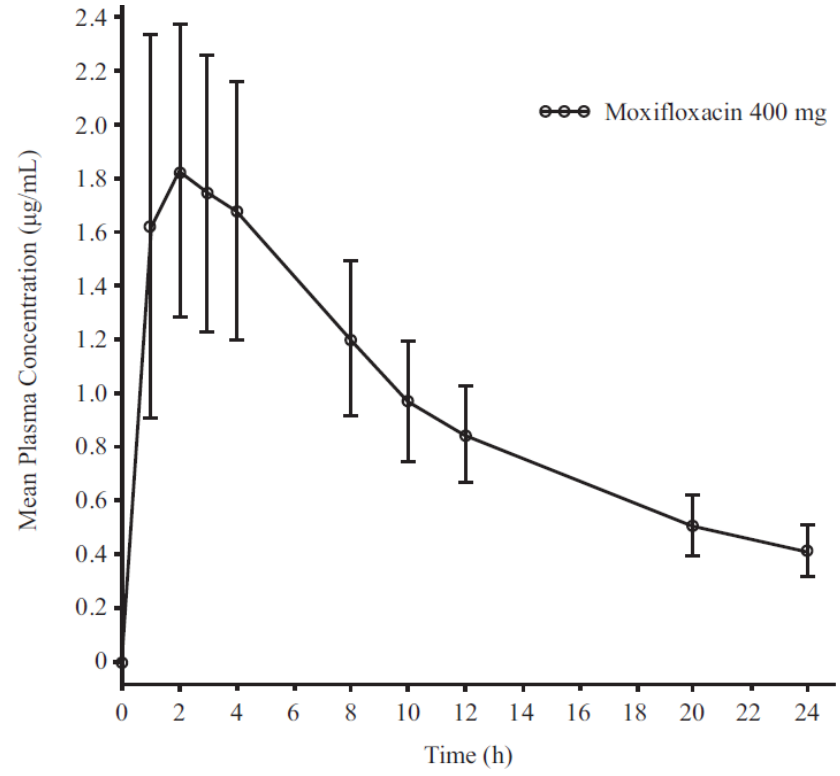
MEAN (± SD) PLASMA CONCENTRATIONS FOLLOWING THE DAY 13 DOSE

ISAVUCONAZOLE



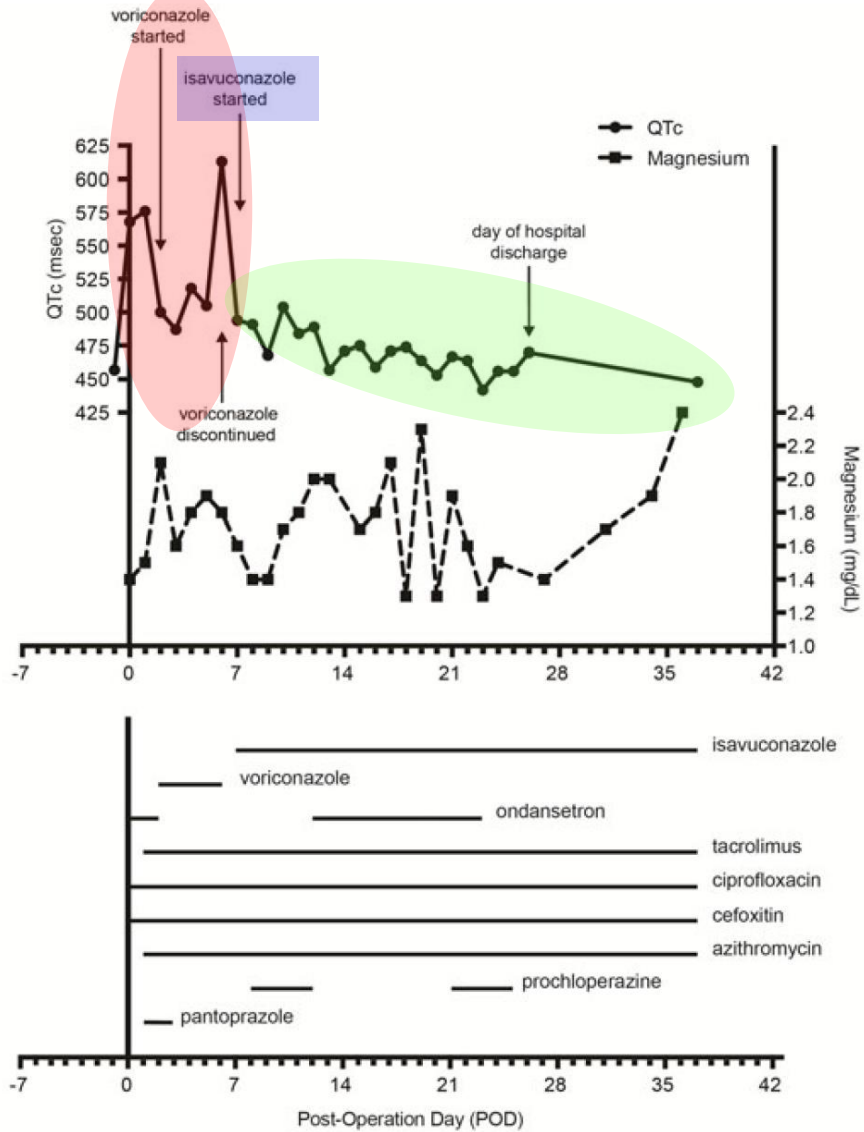
MOXIFLOXACIN



USE OF ISAVUCONAZOLE IN A PATIENT WITH VORICONAZOLE-INDUCED QTc PROLONGATION

Trang TP et al. *Transpl Infect Dis* 2017 Aug; 19 (4). e12712

TIMING OF QTC PROLONGATION, MAGNESIUM LEVELS, AND MEDICATIONS RECEIVED IN A CYSTIC FIBROSIS PATIENT FOLLOWING LUNG TRANSPLANTATION



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The 'cephalosporin era' of triazole therapy: isavuconazole, a welcomed newcomer for the treatment of invasive fungal infections

Maria N Chitasombat MD & Dimitrios P Kontoyiannis MD ScD