Isavuconazole IV to Oral Step-Down Therapy Versus Caspofungin followed by Voriconazole Oral Step-Down Therapy in the Treatment of Candidaemia and Invasive Candidiasis (IC): the ACTIVE trial

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Introduction

- Isavuconazole is a novel, broad-spectrum, triazole antifungal agent that demonstrates potent *in vitro* activity against *Candida* spp. and AUC:MIC-dependent *in vivo* efficacy in preclinical disseminated candidiasis models.[1–4]
- Isavuconazole failed to show non-inferiority to caspofungin at the primary endpoint for overall success at end of intravenous (IV) therapy (EOIVT) in the ACTIVE trial.
- However, overall success at the secondary endpoint of end of therapy (EOT) + 2 weeks was comparable between isavuconazole and caspofungin.[5]
- The objective of the current analysis is to evaluate the efficacy of treatment with isavuconazole in the subset of patients who switched from IV to oral (PO) therapy in the ACTIVE trial.

AUC:MIC, Area under the concentration curve:minimum inhibitory concentration ratio.

[1]Lepak et al 2013 *Antimicrob Agents Chemother;* [2]Rybak et al. 2015 *Pharmacotherapy;* [3]Pfaller et al. 2014 *Diagn Microbiol and Infect Dis;* [4]Pfaller et al. 2015 *Diagn Microbiol and Infect Dis;* [5]Kullberg et al. 2016 *ECCMID Presentation #1239*

Analysis overview

Study design	International, double-blind, randomised, non-inferiority study of IV isavuconazole followed by PO isavuconazole versus IV caspofungin followed by PO voriconazole; switch to PO treatment allowed from Day 11
Analysis population	All ITT patients with documented IC or candidaemia at baseline as assessed by the DRC (mITT population) who progressed to PO therapy and received at least one PO dose of either isavuconazole or voriconazole
Efficacy endpoints*	Overall response[#] at EOIVT, EOT and EOT + 2 weeks, as determined by an independent, blinded DRC in the mITT population; ACM at Day 56 and safety also were assessed

ACM, All-cause mortality; DRC, data review committee; EOIVT, end of IV treatment; EOT, end of treatment; IC, invasive candidiasis; ITT, intent to treat; IV, intravenous; mITT, modified intent to treat; PO, oral

*Due to small patient numbers the analysis was not powered to detect any post-EOIVT outcome differences.

[#]Successful overall response required successful clinical and mycological response plus no use of alternative systemic antifungal therapy within 48 hours after the last dose of study drug.

Dosing and oral step down

IV Dosing (Days 1–10)

- Isavuconazole (200 mg QD; loading doses Days 1 and 2)
- Caspofungin (50 or 70 mg QD; loading dose Day 1)

PO Switch (Days 11–EOT)*

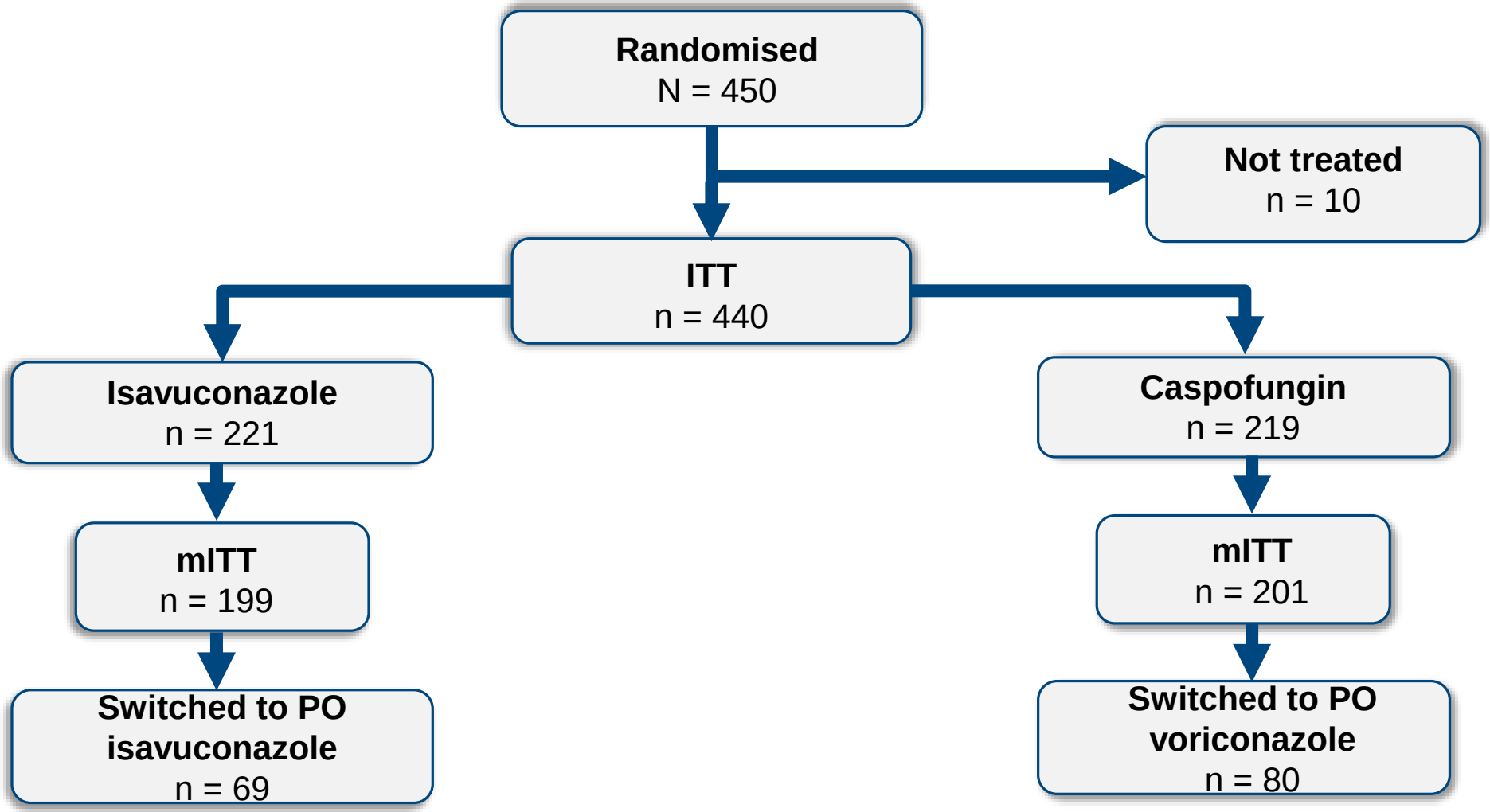
- Switch from IV to PO at the discretion of the investigator
- Switch from IV isavuconazole (200 mg QD) to PO isavuconazole (200 mg QD)

  OR

- Switch from IV caspofungin (50 or 70 mg QD) to PO voriconazole (200 mg BID; loading dose Day 1)

*Minimum treatment duration 14 days after sterile blood cultures; maximum treatment duration 56 days

Patient disposition



Intent-to-treat (ITT): all randomised patients who received at least one dose of study medication.
Modified ITT (mITT): ITT patients with documented candidaemia or invasive candidiasis at baseline based on the assessment of the independent blinded DRC.

Demographic and Baseline Characteristics of Patients Who Received at Least One Oral Dose

Category	Isavuconazole IV → isavuconazole PO (N = 69)	Caspofungin IV → voriconazole PO (N = 80)	Total (N = 149)
Age, mean ± SD years	57 ± 18	58 ± 15	57 ± 17
Sex, n (%)			
Male	44 (63.8)	46 (57.5)	90 (60.4)
Geographic region, n (%)			
North America	15 (21.7)	14 (17.5)	29 (19.5)
Western Europe	16 (23.2)	23 (28.8)	39 (26.2)
Other	38 (55.1)	43 (53.8)	81 (54.4)
Baseline parameters			
APACHE II Score, mean ± SD	12 ± 7	13 ± 6	12 ± 7
Neutropenia, n (%)	8 (11.6)	11 (13.8)	19 (12.8)
BMI [kg/m^2], mean ± SD	24 ± 6	24 ± 6	24 ± 6

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; SD, standard deviation.
Percentages may not add to 100 due to rounding

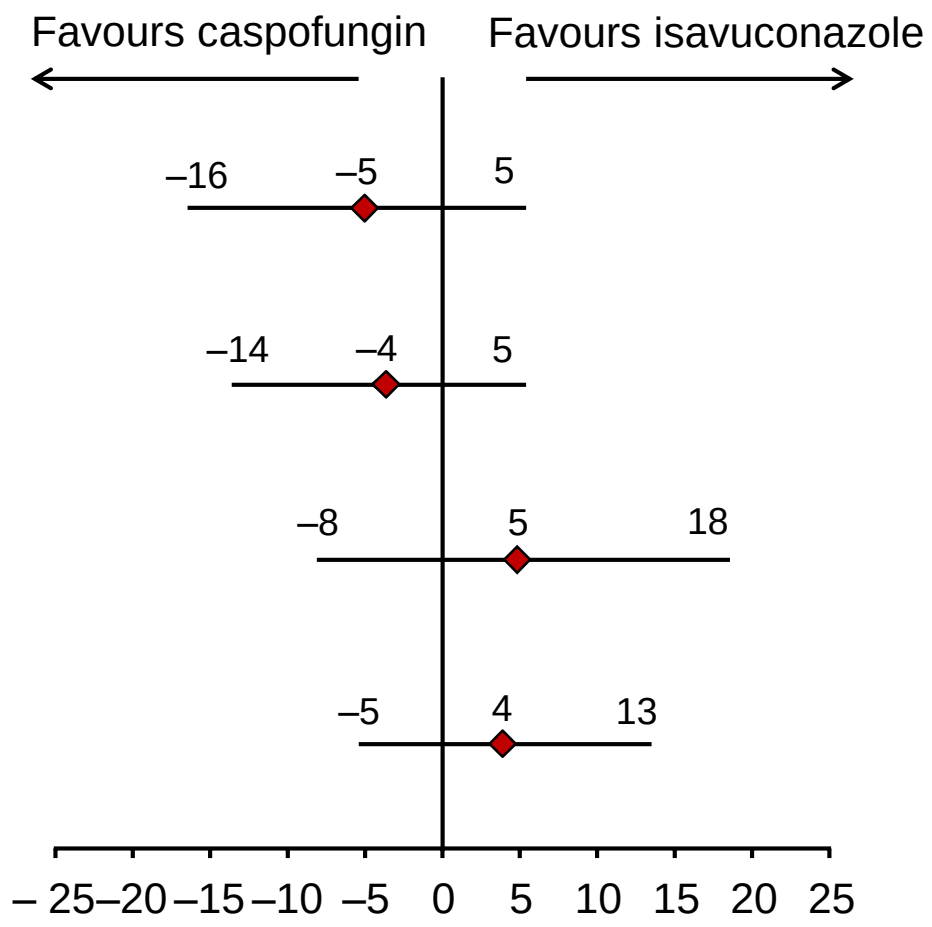
Treatment duration

	Isavuconazole IV → isavuconazole PO (N = 69)	Caspofungin IV → voriconazole PO (N = 80)
Total duration [days], median (min–max)	20.0 (12–57)	19.5 (11–59)
IV duration [days], median (min–max)	11.0 (10–44)	10.0 (10–30)
Oral duration [days], median (min–max)	8.0 (1–47)	8.0 (1–45)

Efficacy outcomes

Category, n (%)	Isavuconazole (N = 69)	Caspofungin (N = 80)
Successful overall response at EOIVT*	**58 (84.1)**	**71 (88.8)**
Successful overall response at EOT	60 (87.0)	73 (91.3)
Successful overall response at EOT + 2 weeks	57 (82.6)	62 (77.5)
All-cause mortality Day 56	5 (7.2)	9 (11.3)

*Stratified by geographical region and baseline neutropenia status.
Successful overall response required successful clinical and mycological response plus no use of alternative systemic antifungal therapy within 48 hours after the last dose of study drug.



Adjusted difference (%; 95% CI) between isavuconazole versus caspofungin.

Shift of overall response

Time point and shift of outcome, n (%)	Isavuconazole IV → isavuconazole PO (N = 69)	Caspofungin IV → voriconazole PO (N = 80)	Adjusted Difference*, %, (95% CIs)
EOIVT–EOT			
Success → success	57 (82.6)	68 (85.0)	−3.0 (−14.5, 8.4)
Success → failure	1 (1.4)	3 (3.8)	
Failure → success	3 (4.3)	5 (6.3)	
Failure → failure	8 (11.6)	4 (5.0)	
EOT–EOT + 2 weeks			
Success → success	56 (81.2)	61 (76.3)	4.9 (−8.1, 17.8)
Success → failure	4 (5.8)	12 (15.0)	
Failure → success	1 (1.4)	1 (1.3)	
Failure → failure	8 (11.6)	6 (7.5)	

*Adjusted difference (isavuconazole−caspofungin) is calculated by a stratified Cochran-Mantel-Hanszel method stratified by geographical region and baseline neutropenia status.

Percentages may not add to 100 due to rounding.

Reasons for shift of overall response from success to failure

Time point and reason	Isavuconazole IV → isavuconazole PO n (%)	Caspofungin IV → voriconazole PO n (%)
EOIVT–EOT	**n = 1**	**n= 3**
Death	0	1
Unevaluable*	1	0
Use of alternative systemic antifungal therapy	0	2
EOT–EOT + 2 weeks	**n = 4**	**n = 12**
Death	2	4
Recurrent infection	1	0
Emergent infection	0	1#
Unevaluable*	1	7

*Patients were deemed unevaluable as a result of not having a follow-up assessment made by the investigator; either patients did not have a culture available to confirm eradication or their clinical response was not evaluated.
#Required use of alternative systemic antifungal therapy.

Safety and tolerability

Overview of treatment-emergent adverse events (TEAEs) and death in patients that received at least one oral dose

Safety population, n (%)	Isavuconazole IV → isavuconazole PO (N = 69)	Caspofungin IV → voriconazole PO (N = 80)
Number of subjects ≥1 TEAE	66 (95.7)	77 (96.3)
Study drug-related TEAE	31 (44.9)	31 (38.8)
Serious TEAE	20 (29.0)	26 (32.5)
Study drug-related serious TEAE	4 (5.8)	3 (3.8)
TEAE leading to discontinuation of study drug	1 (1.4)	6 (7.5)
Study drug-related TEAE leading to discontinuation	0	4 (5.0)*
Study drug-related TEAE leading to death	1 (1.4)	0
Death	5 (7.2)	10 (12.5)

*Three patients discontinued while on caspofungin and 1 patient discontinued after switching to PO voriconazole.

Safety and tolerability

Frequency of TEAEs reported in ≥10% of patients

Safety population, n (%)	Isavuconazole IV → isavuconazole PO (N = 69)	Caspofungin IV → voriconazole PO (N = 80)
Vomiting	12 (17.4)	18 (22.5)
Diarrhoea	9 (13.0)	20 (25.0)
Hypokalaemia	12 (17.4)	16 (20.0)
Pyrexia	13 (18.8)	14 (17.5)
Nausea	13 (18.8)	13 (16.3)
Constipation	12 (17.4)	12 (15.0)
Oedema peripheral	8 (11.6)	9 (11.3)
Dyspnoea	8 (11.6)	8 (10.0)
Anaemia	5 (7.2)	10 (12.5)
Cough	6 (8.7)	8 (10.0)
Anxiety	7 (10.1)	5 (6.3)
Gamma-glutamyltransferase increased	4 (5.8)	8 (10.0)
Hypomagnesaemia	3 (4.3)	8 (10.0)

Summary

- This analysis was limited by a small number of patients and was therefore not powered to detect any post-EOIVT outcome differences.
  - All differences reported are not statistically significant.
- The majority of patients who had an overall successful response at EOIVT maintained a successful response at EOT in both treatment arms.
- The majority of patients who had an overall successful response at EOT maintained a successful response at EOT + 2 weeks in both treatment arms.
  - However, by EOT + 2 weeks, more patients in the caspofungin arm (15%) transitioned to failure compared with the isavuconazole arm (5.8%).
- Efficacy outcomes were comparable between the isavuconazole and caspofungin treatment arms in patients who received at least one dose of PO therapy.

Conclusions

- At EOIVT and EOT, overall success was numerically higher in the caspofungin arm; outcomes in patients switching from IV to PO therapy in both treatment arms were largely sustained.

- However, successful outcomes were sustained in a numerically larger proportion of patients in the isavuconazole arm at EOT + 2 weeks, although this difference was not significant.

- The fact that there were few treatment failures observed in patients treated with PO isavuconazole suggests a potential role of isavuconazole as a PO step-down option in the treatment of candidaemia or IC.

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Thank you

Back-up slides

Shift of clinical response

Time point and shift of outcome, n (%)	Isavuconazole (N = 69)	Caspofungin (N = 80)	Adjusted Difference, %, (95% CIs)
EOIVT–EOT			
Success to success	69 (100)	79 (98.8)	1.3 (−1.2, 3.9)
Success to failure	0	0	
Failure to success	0	1 (1.3)	
Failure to failure	0	0	
EOT–EOT + 2 weeks			
Success to success	63 (91.3)	68 (85.0)	6.4 (−4.1, 16.9)
Success to failure	6 (8.7)	12 (15.0)	
Failure to success	0	0	
Failure to failure	0	0	

Percentages may not add to 100 due to rounding.

Shift of mycological response

Time point and shift of outcome, n (%)	Isavuconazole (N = 69)	Caspofungin (N = 80)	Adjusted Difference, %, (95% CIs)
EOIVT–EOT			
Success to success	58 (84.1)	74 (92.5)	−9.1 (−19.2, 1.0)
Success to failure	1 (1.4)	0	
Failure to success	3 (4.3)	4 (5.0)	
Failure to failure	7 (10.1)	2 (2.5)	
EOT–EOT + 2 weeks			
Success to success	58 (84.1)	65 (81.3)	3.6 (−8.5, 15.8)
Success to failure	3 (4.3)	13 (16.3)	
Failure to success	1 (1.4)	1 (1.3)	
Failure to failure	7 (10.1)	1 (1.3)	

Percentages may not add to 100 due to rounding.