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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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Background: In a phase 3, randomised, double-blind, multinational trial in patients with proven candidaemia or IC (ACTIVE; NCT00413218), isavuconazole did not demonstrate non-inferiority compared with caspofungin for the primary endpoint of overall success at end of intravenous (IV) therapy (EOIVT); however, overall responses for the secondary endpoints were similar between the treatment groups. We report the analysis conducted to evaluate the efficacy in the subset of patients who switched from IV to oral therapy.

Material/methods: Adults with candidaemia or IC were randomised 1:1 to isavuconazole (200 mg IV TID for 2 days, followed by 200 mg IV QD) or caspofungin (70 mg IV QD on Day 1, followed by 50 mg IV QD) for a maximum of 56 days. After day 10, patients could switch to oral isavuconazole at 200 mg QD (isavuconazole arm) or oral voriconazole at 400 mg BID Day 1, followed by 200 mg BID (caspofungin arm). Successful overall response (positive clinical and mycological responses, and no alternative systemic antifungal therapy) was assessed at EOIVT, the end of all therapy (EOT), and 2 weeks after EOT (EOT + 2 weeks) in the modified intent-to-treat (mITT) population (patients with proven infection who received ≥1 dose of study drug).

Results: Of 400 mITT patients, 69 (34.7%) isavuconazole and 80 (39.8%) caspofungin→voriconazole patients switched from IV to oral therapy. The mean (SD) total duration of therapy was 22.9 (11.0) days for isavuconazole and 23.9 (11.8) days for caspofungin→voriconazole. Successful overall response at EOIVT was 84.1% and 88.8%, respectively (**Table 1**). By EOT + 2 weeks, more patients in the caspofungin→voriconazole arm (15%) transitioned to failure compared with the isavuconazole arm (5.8%).

Conclusions: Outcomes in these patients were largely sustained after switching from IV to oral therapy, with a trend of more sustained responses at EOT + 2 weeks in the isavuconazole arm. Differences in outcomes observed between EOIVT and EOT +2 weeks in the treatment groups during the step-down suggest a potential role of isavuconazole as a step-down option in the treatment of candidaemia or IC.

Table 1. Patient outcomes (mITT)

Parameter **Success n (%)** **95% CIs (%)**	**Isavuconazole (n=69)**	**Caspofungin →Voriconazole (n=80)**	**Adjusted difference** **% (95% CI)**
EOIVT	58 (84.1%) (73.3, 91.8)	71 (88.8%) (79.7, 94.7)	–5.2 (–15.8, 5.4)
EOT	60 (87.0%) (76.7, 93.9)	73 (91.3%) (82.8, 96.4)	–4.4 (–13.9, 5.2)
Success→Failure	1 (1.4%)	3 (3.8%)	
Failure→Success	3 (4.3%)	5 (6.3%)	
Success→Success	57 (82.6%)	68 (85.0%)	
Failure→Failure	8 (11.6%)	4 (5.0%)	
EOT + 2 weeks	57 (82.6%) (71.6, 90.7)	62 (77.5%) (66.8, 86.1)	4.8 (–7.9, 17.5)
Success→Failure	4 (5.8%)	12 (15.0%)	
Failure→Success	1 (1.4%)	1 (1.3%)	
Success→Success	56 (81.2%)	61 (76.3%)	
Failure→Failure	8 (11.6%)	6 (7.5%)	