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A comparison of the safety profiles of isavuconazole vs voriconazole in the Phase 3 SECURE study in patients with invasive mould infections

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Introduction and Purpose

Isavuconazole (ISAV) is the active moiety of isavuconazonium sulfate, a water-soluble prodrug for oral and intravenous administration. ISAV has broad-spectrum antifungal activity against pathogens causing invasive mould disease (IMD). SECURE, a large (N=516), Phase 3, double-blind, randomized trial, demonstrated the non-inferiority of ISAV compared with voriconazole (VRC) for Day 42 all-cause mortality (ISAV 18.6%, VRC 20.2%) in primary treatment of IMD caused by *Aspergillus* spp. and other filamentous fungi. Assessment of safety was a main study objective which is is of particular importance in severely-ill IMD patients with multiple co-morbidities.

Methods

Any adverse event (AE) that occurred in the time period between the first study-drug administration and 28 days after last dosing was considered to be a treatment-emergent AE (TEAE). TEAEs were recorded and assessed at every study visit. The number (%) of patients with TEAEs were summarized by System Organ Class (SOC) and Preferred Term (PT) (MedDRA v12.1), and were compared to VRC by SOC using Fisher's exact test. Alanine-aminotransferase/aspartate-aminotransferase (ALT/AST) levels were summarized on Days 7, 14, 28, 42, at end-of-treatment, and 4 weeks thereafter, and expressed relative to the upper limit of normal (ULN). Values were categorized by exceeding threshold multiples of the ULN. TEAEs considered by the investigator as remotely, possibly, or probably related to study drug were considered 'drug-related'. A post-hoc analysis was performed to analyze TEAEs in patients with proven or probable IFD vs possible or no IFD. The cumulative proportion of TEAEs over the study period was also assessed.

Results

Overview of deaths and treatment-emergent adverse events

97% of patients reported at least one TEAE regardless of causality (ISAV 96% [247/257], VRC 98% [255/259]), which was expected considering the severely-ill study population.

The total number of TEAEs was 2829 in ISAV-treated vs 3463 in VRC-treated patients. The proportion of moderate or severe, drug-related and of TEAEs leading to permanent discontinuation of study drug were significantly lower in the ISAV treatment group than in the VRC treatment group (**Table 1**). Average treatment durations, reported TEAE rates and relative risks (RR= ISAV/VRC) were similar across the DRC assessed categories of proven, probable and possible IFD but treatment duration was shorter in patients with no IFD. A sensitivity analysis (not shown) was therefore performed in the Safety population excluding "no IFD" which confirmed the results in the overall Safety population.

Table 1. Overview of treatment duration and TEAEs in various analysis populations

	Safety population			Proven IFD			Probable IFD		
	ISAV N=257	VRC N=259		ISAV N=29	VRC N=36		ISAV N=114	VRC N=93	
Mean (SD) tx duration (d)	46.9 (32.3)	46.5 (32.1)		52.8 (36.4)	51.1(32.5)		48.3 (31.8)	45.9 (32.9)	
Median (min-max) tx duration (d)	45.0 (1-102)	47.0 (1-88)		77.0 (3-98)	53.5 (3-87)		49.0 (1-102)	42.0 (1-88)	
Total number of TEAEs	2829	3463		229	464		1362	1413	
Subjects with at least 1	ISAV N=257 %	VRC N=259 %	RR	ISAV N=29 %	VRC N=36 %	RR	ISAV N=114 %	VRC N=93 %	RR
TEAE	96	98	0.98	93	97	0.96	97	98	1
Drug-related TEAE	42*	60	0.71	31*	61	0.51	42*	61	0.69
Serious TEAE	52	58	0.91	52	61	0.85	59	66	0.9
TEAE leading to discontinuation	14*	23	0.63	7	11	0.62	18*	30	0.58
Moderate or severe TEAE	82*	89	0.92	72	83	0.87	88	91	0.96
	Safety population excluding no IFD			**Possible IFD**			**No IFD**		
	ISAV N=231	VRC N=237		ISAV N=88	VRC N=108		ISAV N=26	VRC N=22	
Mean (SD) tx duration (d)	48.1 (32.4)	47.0 (31.9)		46.4 (32.1)	46.6 (31.1)		36.2 (30.0)	40.9 (34.0)	
Median (min-max) tx duration (d)	47.0 (1-102)	48.0 (1-88)		42.5 (2-87)	45.5 (1-88)		31.5 (1-86)	38.0 (2-86)	
Total number of TEAEs	2615	3263		1024	1386		214	200	
Subjects with at least 1	ISAV N=231 %	VRC N=237 %	RR	ISAV N=88 %	VRC N=108 %	RR	ISAV N=26 %	VRC N=22 %	RR
TEAE	97	99	0.98	98	100	0.98	88	95	0.93
Drug-related TEAE	43*	61	0.71	49	60	0.81	35	50	0.69
Serious TEAE	54	59	0.92	49	53	0.93	35	41	0.85
TEAE leading to discontinuation	15*	23	0.63	14	21	0.64	12	18	0.63
Moderate or severe TEAE	85*	91	0.93	85	94	0.91	54	68	0.79

*p<0.05

Analysis of treatment-emergent adverse events by System Organ Class

When analyzed by SOC, TEAE rates were lower with ISAV than VRC in 19 of the 24 SOCs with reported TEAEs (**Figure 1**, Safety population). TEAE rates were ≥ 5% lower with ISAV compared to VRC in the following SOCs under the PTs: Eye (15% vs 27%, p<0.01), Skin (33% vs 42%, p<0.05), Hepatobiliary (9% vs 16%, p<0.05), Psychiatric (27% vs 33 %, ns) and Cardiac (17% vs 22%, ns). Moderate or severe TEAEs were lower with ISAV than VRC in 21 of the 24 SOCs. The events that contributed to the observed safety advantage of ISAV under these SOCs are provided by PT in **Table 2**.

Figure 1. TEAEs by SOC

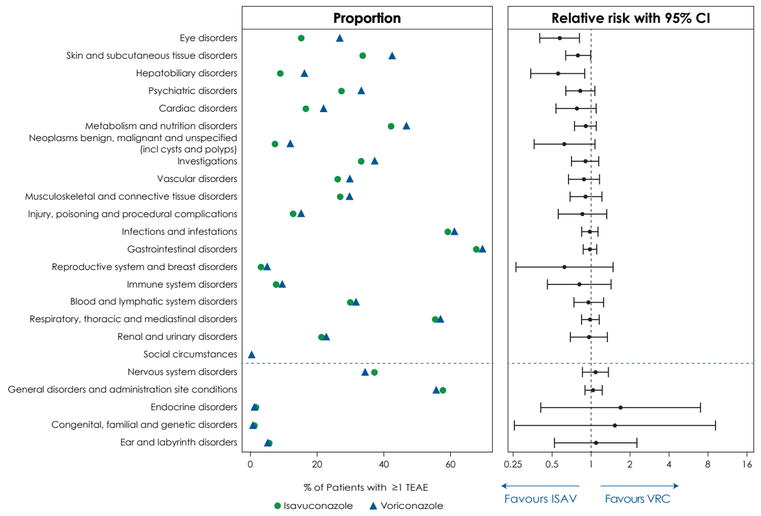


Table 2. TEAEs by Preferred Term (Hepatobiliary, Eye, Skin, Psychiatric and Cardiac Disorders)

SOC (Disorder)	TEAE Preferred Term (Safety population)
Hepatobiliary (ISAV 8.9%, VRC 16.2%)	Hyperbilirubinaemia (5, 1.9% vs 10, 3.9%), hepatic function abnormal (4, 1.6% vs 9, 3.5%), jaundice (1, 0.4% vs 6, 2.3%), cholestasis (1,0.4% vs 6, 2.3%)
Eye (ISAV 15.2%, VRC 26.6%)	Visual impairment (4, 1.6% vs 19, 7.3%), photophobia (2, 0.8% vs 6, 2.3%), visual acuity reduced (1, 0.4% vs 6, 2.3%), retinal haemorrhage (0 vs 5, 1.9%)
Skin and Subcutaneous Tissue (ISAV 33.5%, VRC 42.5%)	Rash (17, 6.6% vs 28, 10.8%), erythema (9, 3.5% vs 15, 5.8%), skin lesion (4, 1.6% vs 8, 3.1%), drug eruption (3, 1.2% vs 11, 4.2%)
Psychiatric (ISAV 27.2%, VRC 33.2%)	Hallucination (6, 2.3% vs 11, 4.2%), visual hallucination (3, 1.2% vs 11, 4.2%), agitation (2, 0.8% vs 7, 2.7%)
Cardiac (ISAV 16.7%, VRC 22.0%)	Tachycardia (12, 4.7% vs 21, 8.1%), cardiac arrest (1, 0.4% vs 6, 2.3%)

Drug-related events

Overall, the rate of treatment-related TEAEs was significantly lower with ISAV (42%) than with VRC (60%) (p<0.001). This difference in favor of ISAV compared to VRC was primarily influenced by disorders of eye (3% vs 11%, p<0.01), hepatobiliary disorders (2% vs 10%, p<0.01), investigations (including hepatic enzyme elevations) (10% vs 18%, p<0.01) and psychiatric disorders (2% vs 11%, p<0.01). TEAEs of respiratory disorders were lower with VRC (2%) than with ISAV (6%, p<0.05).

Hepatobiliary events

Hepatobiliary TEAEs (overall) and drug-related hepatobiliary TEAEs were significantly lower with isavuconazole compared to voriconazole. The lower rate of drug-related hepatobiliary events with ISAV compared to VRC was primarily influenced by PTs of Hepatic Function Abnormal, Hyperbilirubinemia, Cholestasis, and Hepatic Failure and Jaundice. This was further supported by a lower rate of ALT/AST (>3 × ULN) plus bilirubin (>2 × ULN) elevations at the end-of-study visit (ISAV 0.4% vs VRC 2.7%) (**Figure 2**). Analysis of the cumulative incidence shows that the difference in drug-related hepatobiliary events becomes evident within the first days of study treatment.

Figure 2. Drug-related hepatobiliary TEAEs and transaminase elevations

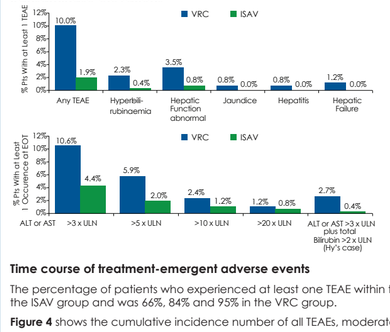
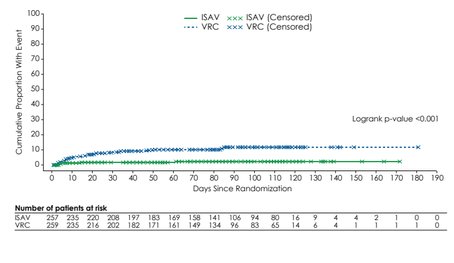


Figure 3. Cumulative incidence of drug-related hepatobiliary TEAEs

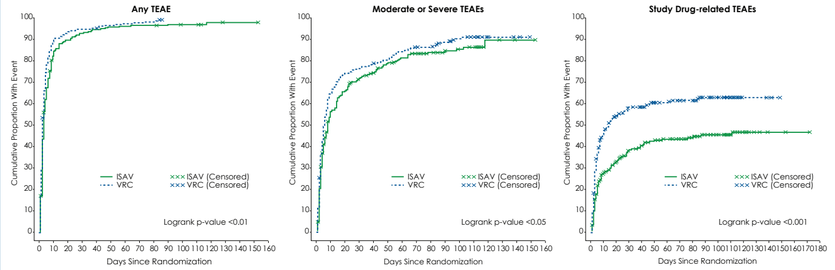


Time course of treatment-emergent adverse events

The percentage of patients who experienced at least one TEAE within the first 3 days, first 7 days and first 28 days in the study was 56%, 75% and 92% in the ISAV group and was 66%, 84% and 95% in the VRC group.

Figure 4 shows the cumulative incidence number of all TEAEs, moderate or severe TEAEs, and drug-related TEAEs over the study period.

Figure 4. Cumulative incidence of TEAEs over the study period



Conclusions

In the SECURE study, ISAV was better tolerated than VRC. This difference was most evident for hepatic (both clinical events and transaminase elevations), skin, eye and psychiatric AEs. The consistency of the differences in favor of ISAV in moderate or severe TEAEs underlines the potential clinical relevance of these safety results.

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