Table 2. Global Response Success Rates of Voriconazole in the IC–EC Study

	IC			EC		
	2 to < 12 y	12 to < 18 y	Overall	2 to < 12 y	12 to < 18 y	Overall
C. albicans, n/N (%)	1/2 (50.0)	0	1/2 (50.0)	2/2 (100)	5/8 (62.5)	7/10 (70.0)
C. glabrata, n/N (%)	1/1 (100)	0	1/1 (100)	0	0	0
C. parapsilosis, n/N (%)	1/1 (100)	0	1/1 (100)	0	0	0
C. tropicalis n/N (%)	3/3 (100)	0	3/3 (100)	0	0	0

IC, invasive candidiasis; EC, esophageal candidiasis; n/N, number of patients responding out of total population.
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Table 3. Global Response Success Rate in the IA Study

	2 to < 12 y, n = 5	12 to < 18 y, n = 9	Overall, n = 14
Week 6, n (%) [95% CI]	2 (40.0) [5.3 to 85.3]	7 (77.8) [40.0 to 97.2]	9 (64.3) [35.1 to 87.2]
EOT, n (%) [95% CI]	2 (40.0) [5.3 to 85.3]	7 (77.8) [40.0 to 97.2]	9 (64.3) [35.1 to 87.2]

EOT, end of treatment; IA, invasive aspergillosis.
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The investigators concluded that the data from these analyses suggest that treatment of pediatric IC, EC, or IA with voriconazole was safe and effective, and consistent with previous studies in adults.

Isavuconazole Effective in UncCAs and HMs

Written by Emma Hitt Nichols, PhD

Patients with invasive fungal disease (IFD) and comorbid conditions such as hematologic malignancy (HM) and uncontrolled malignancy (UncCA) were successfully treated with the novel triazole antifungal agent isavuconazole, regardless of minimum inhibitory concentrations (MICa) required by baseline *Aspergillus* spp isolates. Andrew J. Ullmann, MD, Julius Maximilians University, Würzburg, Germany, presented data according to type of malignancy from the Isavuconazole (BAL8557) for Primary Treatment of Invasive Aspergillosis trial [SECURE; NCT00412893].

IFD is a challenge, particularly in immunocompromised patients [Leventakos K et al. *Clin Infect Dis* 2010; Kontoyiannis DP et al. *Clin Infect Dis* 2010; Pappas PG et al. *Clin Infect Dis* 2010], and patients with UncCA [Bohme A et al. *Ann Hematol* 2009] and HM [Pagano L et al. *Haematologica* 2006]. In addition, mortality rates remain high in populations such as organ or hematopoietic stem cell transplant recipients who have invasive aspergillosis (IA) [Baddley JW et al. *Clin Infect Dis* 2010]. The broad-spectrum triazole antifungal agent, isavuconazole, demonstrated efficacy against multiple pathogens, including *Aspergillus* spp, *Candida* spp, *Cryptococcus* spp, and Mucorales in vitro, as well as IA, invasive candidiasis, mucormycosis, and cryptococcosis in animal models [Lepak A et al. *Antimicrob Agents Chemother* 2013; Lepak A et al. *Antimicrob Agents Chemother* 2013; Luo G et al. *Antimicrob Agents Chemother* 2014]. The overarching purpose of the SECURE trial was to evaluate the safety and efficacy of isavuconazole in patients with IFD [Maertens J et al. ECCMID 2014 0230a]; the purpose of this analysis was to evaluate the outcomes of isavuconazole treatment in patients with UncCA who participated in the SECURE trial.

In the multicenter, noninferiority, Phase 3 SECURE trial, 516 patients (intention-to-treat population) age ≥ 18 years with proven or probable IFD were randomly assigned to receive 200 mg IV TID isavuconazole for 2 days followed by 200 mg (IV or oral) QD or standard-dose voriconazole. The primary end point of all-cause mortality at day 42 was 22% and 25% in the isavuconazole and voriconazole arms, respectively, with drug-related adverse events occurring more frequently in the voriconazole arm (60 vs 40%). Secondary end points included success rate, adverse events, and other safety parameters.

In the SECURE trial, 178 patients had UncCA, and they were evenly split between the isavuconazole and voriconazole arms. In patients with UncCA, the all-cause mortality at day 42 was 21% and 22% in patients who received isavuconazole compared with voriconazole, respectively, with a mean difference of –0.5 (95% CI, –9.6 to 8.6). The overall response at the end of the trial (EOT) was 36% and 34% in the isavuconazole and voriconazole arms, respectively, with a mean difference of –2.2 (95% CI, –17.4 to 13.0). Patients without UncCA demonstrated lower rates of all-cause mortality at day 42 in the intention-to-treat population; however, patients with UncCa taking isavuconazole demonstrated lower rates of all-cause mortality compared with the voriconazole arm. EOT overall response was greatest in patients infected with mold species not otherwise specified and *Aspergillus* spp only compared with non-*Aspergillus* spp only or positive serum for galactomannan.

Treatment-emergent adverse events (TEAEs) were similar among both treatment arms in patients with UncCA; however, fewer patients in the isavuconazole arm (40%) experienced drug-related adverse events compared with those treated with voriconazole (60%).

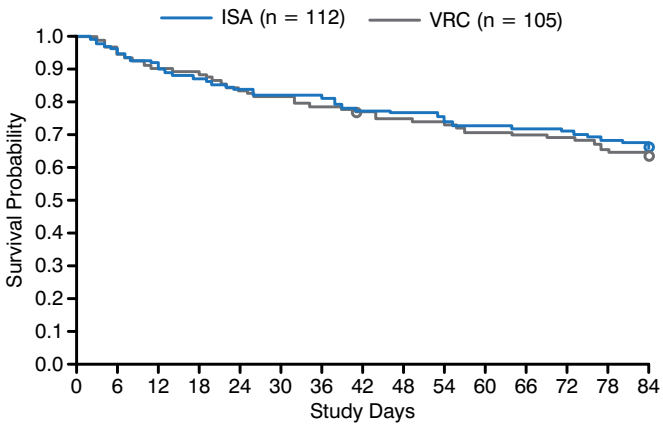
In conclusion, Prof Ullmann indicated that patients with UncCA demonstrated greater mortality rates in both treatment arms compared with patients without UncCA; however, patients treated with isavuconazole experienced fewer drug-related adverse events.

Kieren A. Marr, MD, Johns Hopkins University, Baltimore, Maryland, USA, presented an analysis of patients with HM from the SECURE trial. Out of the 516 patients in the intention-to-treat population, 433 had HM, of which 217 had proven or probable IFD.

In patients with HM, all-cause mortality at day 42 was 22% and 24% in the isavuconazole and voriconazole arms, respectively, with a mean difference of –1.5 (95% CI, –13.7 to 10.7). All-cause mortality was lowest in patients with acute myeloid leukemia compared with those with UncCA, acute lymphocytic leukemia, neutropenia, or allogenic hematopoietic stem cell transplant. At EOT, the overall response rate was 39% and 34% in the isavuconazole and voriconazole arms, respectively, with a mean difference of –5.0 (95% CI, –18.8 to 8.9).

TEAEs were similar between both treatment arms in patients with HM. 97% of patients in the ISA arm and 99% of patients in the VRC arm developed at least 1 TEAE; however, drug-related adverse events were greater in patients with HM who were treated with voriconazole (59%) compared with isavuconazole (44%). Significantly fewer ($P<.05$) TEAEs of the skin, eye, and hepatobiliary system organ classes were observed in the ISA arm of the study. In the modified intent-to-treat population, 97% of the ISA patients and 98% of the VRC patients reported TEAEs. Among this population, significantly fewer ($P<.05$) TEAEs were observed in the ISA arm than the VRC arm, including cardiac, eye, renal and urinary, and psychiatric disorders.

Figure 1. Survival Rates of Patients With Hematologic Malignancy and Invasive Fungal Disease



ISA, isavuconazole; VRC, voriconazole.

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In conclusion, Dr Marr indicated that the data suggest that treatment of IFD with isavuconazole results in comparable efficacy outcomes as with voriconazole, but with a lower risk of drug-related adverse events (Figure 1).

David Andes, MD, University of Wisconsin, Madison, Wisconsin, USA, presented data from an analysis of outcomes by MICs from the SECURE trial. In this study, *Aspergillus* spp isolates, the majority of which were *A. fumigatus*, were collected at baseline from patients enrolled in the SECURE trial for analysis of MIC values.

In patients treated with isavuconazole, the MIC_{50} and MIC_{90} values for isavuconazole were 1 and 4 µg/mL (range, 0.25 to 32). and for voriconazole they were 1 and 2 µg/mL (range, 0.12 to 32). In patients treated with voriconazole, the MIC_{50} and MIC_{90} values were 1 and 2 µg/mL (range, 0.25 to 4) for isavuconazole and voriconazole, respectively. There was no association between baseline MIC values and all-cause mortality at day 42 or successful overall response at EOT (Table 1).

In conclusion, Dr Andes indicated that the data from the MIC analysis of isolates from the SECURE trial demonstrated that successful outcomes were achieved with a range of MIC values, including higher values. In addition, patient outcomes were not associated with MIC value. Dr Andes pointed out that the MIC analysis was limited by its small sample size.

Table 1. All-Cause Mortality Stratified by Microorganism and Minimum Inhibitory Concentrations, Through Day 42

		MIC Values[a], µg/mL (%)							
Treatment	***Aspergillus* spp**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**> 16**
ISA	*Aspergillus* spp	1/9 (11.1)	1/8 (12.5)	1/10 (10.0)	2/5 (33.3)	0/6	0/1	0	1/1 (100)
	A flavus	1/2 (50.0)	0/1	0/3	0/2	0/1	0	0	0
	A fumigatus	1/8 (12.5)	0/7	1/6 (16.7)	0/2	0	0/1	0	1/1 (100.0)
	A niger	0	0	0	1/1 (100.0)	0/4	0	0	0
	A terreus	0/1	1/1 (100.0)	0/1	0/1	0/1	0	0	0
	A westerdijkiae	0	0	0	1/1 (100.0)	0	0	0	0
VRC	*Aspergillus* spp	2/2 (100)	3/5 (60)	0/12	3/5 (80)	0	0	0	0
	A flavus	0	0/1	0/4	1/2 (50.0)	0	0	0	0
	A fumigatus	2/2 (100.0)	3/4 (75.0)	0/7	2/3 (66.7)	0	0	0	0
	A terreus	0	0	0/1	0	0	0	0	0

ISA, isavuconazole; VRC, voriconazole; MIC, minimum inhibitory concentration.

[a]The denominator is the number of patients whose isolates had that MIC value: Some patients contributed multiple isolates with different MIC values or had multiple isolates with the same MIC values.

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BMS-986001 Is Effective Treatment for HIV-1-Infected Subjects

Written by Maria Vinall

BMS-986001 is a novel nucleoside analog reverse-transcriptase inhibitor (NRTI) that, in higher doses, demonstrated comparable efficacy to tenofovir (TDF) in treatment-naïve HIV-1-infected subjects. Samir Gupta, MD, Indiana University School of Medicine, Indianapolis, Indiana, United States, presented the results of this phase 2b randomized dose trial (active controlled, blinded to BMS-986001) with worldwide recruitment.

BMS-986001 was developed to better target viral transcription and minimize the toxicities associated with current NRTIs, such as increased risk of osteoporotic fracture [Bedimo R et al. *AIDS*. 2012], renal dysfunction [Scherzer R et al. *AIDS*. 2012], and adverse metabolic outcomes [Hammond E et al. *Clin Infect Dis*. 2010]. It is active against some HIV-1 isolates with NRTI resistance-associated mutations, including the K65R and L74V substitutions and the Q151M constellation (without M184V) [Li Z et al. *Antimicrob Agents Chemother*. 2013]. In a previous study [Cotte L et al. *J Acquir Immune Defic Syndr*. 2013], BMS-986001 administration for 10 days led to substantial decreases in plasma HIV-1 RNA levels and was well tolerated.

In this study, the safety and efficacy of BMS-986001 (100, 200, and 400 mg QD) was compared with TDF (300 mg QD) in treatment-naïve subjects with HIV-1. All subjects also received 600 mg of efavirenz (EFV) plus 300 mg of lamivudine (3TC) QD. The primary study end points were the efficacy and safety of BMS-986001 at week 24, determined by measuring the proportions of subjects with plasma HIV-1 RNA < 50 counts/mL and the number of adverse events (AEs). Secondary end points included the efficacy and safety of BMS-986000 through week 48, change from baseline in CD4-positive T-cell count through weeks 24 and 48, and the number of subjects experiencing virologic failure with treatment-emergent resistance-associated mutations through weeks 24 and 48.

Patients were included in the study if they were ≥ 18 years of age and antiretroviral treatment naïve and if they had plasma HIV-1 RNA > 5000 counts/mL and a CD4-positive T-cell count > 200 cells/mm^3. The exclusion criteria were resistance to 3TC, EFV, TDF, or protease inhibitors or a positive test for hepatitis B surface antigen or hepatitis C antibodies/RNA.

Baseline demographics and characteristics in the modified intent-to-treat population (received 1 dose of study drug) were similar among the 4 groups. Subjects age ranged between 29 and 34 years, and the majority were men (62% to 71%). HIV subtypes included AE, B, and C, reflecting the worldwide distribution of the