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ORIGINAL RESEARCH

Effectiveness, Safety, and Patterns of Real-World Isavuconazole Use in Europe (2015–2019)

Dionysios Neofytos · Antonio Pagliuca · Katherine Houghton · Edward Broughton · Maria Lavinea Novis de Figueiredo Valente · Lili Jiang · David A. Enoch · Beate Gruener · Raoul Herbrecht · Tobias Lahmer · Olivier Lortholary · Cléa Melenotte · Francesco Giuseppe De Rosa · Carolina Garcia-Vidal · Maria Jimenez · Maria Fernandez · Oliver Cornely

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ABSTRACT

Introduction: Real-world data from multinational observational studies are required to better understand the role and performance of isavuconazole in real-world practice in Europe.
Methods: A retrospective medical record review was conducted at 16 sites in Europe (France, Germany, Italy, Spain, and the United Kingdom). Eligible records were from patients aged ≥ 18 years at the time of isavuconazole initiation and received at least one dose of isavuconazole for suspected or confirmed invasive aspergillosis (IA) or invasive mucormycosis (IM) during the eligibility period (October 15, 2015 to June 30, 2019). Data were descriptively analysed. Success rates, overall survival, and times to these events were descriptively analysed.

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D. Neofytos
Geneva University Hospitals, Geneva, Switzerland

A. Pagliuca
King's College London, London, UK

K. Houghton (✉)
RTI Health Solutions, The Pavilion, Towers Business Park, Wilmslow Road, Didsbury, Manchester M20 2LS, UK
e-mail: kstull@rti.org

E. Broughton · L. Jiang · M. Fernandez
Pfizer Inc., New York, NY, USA

M. L. N. de Figueiredo Valente
Pfizer Inc., Sao Paulo, Brazil

D. A. Enoch
Cambridge University Hospital NHS Foundation Trust, Cambridge, UK

B. Gruener
University Hospital of Ulm, Ulm, Germany

R. Herbrecht
Institut de Cancérologie Strasbourg Europe (ICANS), University of Strasbourg, Strasbourg, France

T. Lahmer
Technical University of Munich, Munich, Germany

O. Lortholary
Centre National de Référence Mycoses Invasives et Antifongiques, Necker Enfants Malades University Hospital and Institut Pasteur, Paris, France

C. Melenotte
Necker Enfants Malades University Hospital, Paris, France

F. G. De Rosa
University of Turin, Turin, Italy

C. Garcia-Vidal
Hospital Clinic Barcelona, Barcelona, Spain

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Results: Data were abstracted from 218 patients (201, IA; 17, IM) who received isavuconazole as monotherapy (initiated as infusion, 52%; oral, 46%). Isavuconazole was initiated as primary therapy in 92 patients (42.2%) and salvage therapy in 121 patients (55.5%) (unknown for five patients). Mean (standard deviation) age was 56.8 (15.6) years, 66% were men and 62% had at least three comorbidities, most frequently haematologic malignancy (62%). Estimated clinical response rate at week 24 was 54.5% (95% confidence interval [CI], 38.2–66.5%) for primary treatment and 73.5% (95% CI, 62.7–81.1%) for salvage therapy. Overall, 45 patients (21%) experienced at least one adverse event (AE). Serious AEs were experienced by 37 patients (17%), with seven related to isavuconazole; five patients (2.3%) discontinued isavuconazole monotherapy due to the serious AE. A total of 137 patients (63%) died, with 17 deaths (12.4%) related to their invasive fungal infection, 11 of whom initiated isavuconazole as salvage therapy.
Conclusions: This study adds to the growing body of evidence that whether used as first-line therapy or after the failure of other antifungal therapies, isavuconazole appears to have a promising clinical response and a good safety profile as an antifungal agent in patients with varied underlying conditions.

Keywords: Invasive aspergillosis; Invasive mucormycosis; Isavuconazole; Real-world evidence

M. Jimenez
RTI Health Solutions, Research Triangle Park, NC, USA

O. Cornely
University of Cologne, Cologne, Germany

Key Summary Points

Why carry out this study?

Isavuconazole obtained market authorisation in the European Union in 2015. Real-world studies have documented isavuconazole to be associated with a good clinical response and safety profile, whether used as primary treatment or as salvage therapy.

Comprehensive, real-world data from multicentre, multi-national observational studies are required to better understand the role and performance of isavuconazole in real-world practice in Europe.

This study aimed to document the effectiveness and safety of isavuconazole monotherapy in patients with invasive aspergillosis or invasive mucormycosis through routine clinical practice in Europe.

What was learned from the study?

Isavuconazole is commonly administered as salvage therapy and appears to have good clinical effectiveness and safety whether used as primary or salvage treatment.

INTRODUCTION

Invasive aspergillosis (IA) and invasive mucormycosis (IM) are life-threatening invasive fungal diseases (IFDs) generally encountered in immunocompromised patients undergoing haematopoietic stem cell transplantation, solid organ transplantation, chemotherapy resulting in severe neutropenia, or prolonged steroid treatment [1]. Due to more effective treatments for cancer and other chronic illnesses, the number of immunocompromised hosts has increased, leading to a rise in the prevalence of IFD [2, 3]. Patients not classically defined as immunocompromised can also develop IA or mucormycosis, particularly in the intensive care unit (ICU) setting [4].

Recommended treatment options for suspected or confirmed IA are isavuconazole and

voriconazole [5]. Isavuconazole obtained market authorisation in the EU in 2015. Clinical trials have shown isavuconazole to be non-inferior to voriconazole in terms of all-cause mortality [6] among patients with IA and to liposomal amphotericin B (LamB) among patients with IM [7]. Real-world studies have documented isavuconazole to be associated with a good clinical response and safety profile, whether used as primary treatment or as salvage therapy [8–12]. Comprehensive, real-world data from multicentre, multinational observational studies are required to better understand the role and performance of isavuconazole in real-world practice in the EU.

This study was designed to describe the effectiveness and safety of isavuconazole monotherapy in patients with IA or IM through routine clinical practice in hospitals from five European countries (France, Germany, Italy, Spain, and the United Kingdom [UK]). Upon data review, it emerged that patients were receiving isavuconazole as either primary treatment or salvage therapy; thus, the results for these populations are described separately. However, this study was not designed to compare these populations or to detect differences in treatment outcomes.

METHODS

Study Design and Population

This was an observational retrospective cohort study of patient medical records conducted among 16 clinical sites in the EU (three in France, four in Germany, one in Italy, five in Spain, and three in the UK). Participating clinical sites were requested to determine medical record eligibility using the following criteria: aged ≥ 18 years at the time of isavuconazole initiation and received at least one dose of isavuconazole for suspected or confirmed IA or IM between October 15, 2015 and June 30, 2019. No definitions of "suspected or confirmed" were provided to participating clinical sites. Although no definitions of IA or IM were provided in the eligibility criteria, data abstractors were instructed to report how the IFD was defined according to the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) [13]. Physicians were provided with a hyperlink to the paper outlining the criteria and response options for proven, probable, possible, and unknown disease classification.

Clinical sites were identified using a convenience sampling approach: sites known to prescribe isavuconazole were contacted, and a feasibility assessment was performed to determine whether the sites had eligible medical records. Sites with eligible medical records that were willing to participate in the study were invited.

Data Retrieval Methods

Staff at the clinical sites reviewed eligible patient medical records and used a customised web-based data collection form to directly enter pertinent data. Data were retrieved from up to 12 months before isavuconazole initiation until the soonest of December 31, 2019, or death. Data after December 31, 2019, were not collected to avoid confounding due to the COVID-19 pandemic.

The data retrieved consisted of the following: demographics, comorbidities, IFD characteristics, IFD treatment history, antifungal therapy, therapeutic drug monitoring (TDM), clinical outcomes (clinical response, mycological response, radiological response), safety outcomes (adverse events [AEs], serious adverse events [SAEs], death), and healthcare resource utilisation (hospitalisation and outpatient visits).

Clinical outcomes during isavuconazole treatment and prior to January 1, 2020, were documented: physicians were asked to note whether an assessment had been made, the result of the assessment, and the date it was documented. Because this was a real-world observational study, clinical assessments could have been conducted at any time (or not at all) rather than at specific timepoints following isavuconazole initiation. No limitations were imposed on when the assessment was made during isavuconazole treatment (i.e., there was no minimum or

maximum duration of isavuconazole treatment that led to excluding clinical assessment data). Clinical response was defined as resolution or partial resolution of all attributable clinical symptoms and physical findings. Radiological response was defined as at least 50% improvement from initial assessment, or improvement of at least 25% from the initial assessment for the follow-up at 6 weeks (i.e., day 42 [±14 days]) or if the end of treatment occurred before this time. Mycological response was defined as eradication or presumed eradication of the original causative organism culture and was assessed only among patients who had a biomarker test close to treatment initiation.

Ethics

Ethical approval or waivers were received in each country. In France, a certificate of compliance with MR-004 was obtained. In Germany, a waiver was received from the primary site (Cologne; application number 21–1325). In Italy and Spain, ethics committee approval was received at the primary sites (Italy: University of Turin, Reference ID: 441/2021; Spain: Hospital Clinic Barcelona, Reference ID: G-08431173). In the UK, ethical approval was received from the London—Fulham Research Ethics Committee (Reference ID: 20/PR/0939).

Statistical Analysis

Data were reported among patients who received isavuconazole monotherapy as frequencies and percentages for categorical variables based on the number of patients with no missing data for each variable. Means, standard deviations (SDs), minimum and maximum, interquartile range, medians, and ranges were reported for continuous variables.

Time-to-event outcomes (i.e., clinical response, radiological success, mycological success, and death) by December 31, 2019 were assessed using the Kaplan–Meier (KM) method. Patients who did not experience an event by December 31, 2019 were censored at the date of the last medical record entry. The results from the KM method were reported as descriptive statistics (e.g., median time to event) with 95% confidence intervals (CIs).

Results are presented separately for the IA and IM populations and separately among patients who initiated isavuconazole monotherapy as primary treatment (i.e., the first use of an antifungal therapy for the IFD) or salvage therapy (i.e., prior antifungal[s] had been used for the IFD).

RESULTS

Data were abstracted from 218 patients who received isavuconazole as monotherapy: 201 diagnosed with IA and 17 diagnosed with IM. Isavuconazole was initiated as primary therapy in 92 patients (42.2% [92/218]; $n=87$, IA; $n=5$, IM) and as salvage therapy in 121 patients (55.5% [121/218]; $n=109$, IA; $n=12$, IM); for five patients (2.3% [5/218], all IA) it was unknown whether isavuconazole was prescribed as primary treatment or salvage therapy.

Patient Characteristics at Isavuconazole Initiation

Upon isavuconazole initiation, mean (SD) age was 56.0 (15.6) years for patients with IA and 66.5 (12.8) years for patients with IM. Most patients with IA were male (68% [136/201]); eight patients with IM were male and nine were female. Most patients were White (82%). Most patients had at least three comorbidities, with haematological malignancy being the most common (Table 1). Patient characteristics were similar independent of whether isavuconazole was initiated as primary treatment or salvage therapy (Table 1).

Common non-antifungal treatment histories within 30 days of isavuconazole initiation were antimicrobials (87%), immunosuppressants (38%), corticosteroids (35%), and surgery (25%).

Among the 121 patients who received isavuconazole as salvage therapy, 58 patients (47.9%) had received one antifungal prior to isavuconazole, 44 patients (36.3%) had received two antifungals prior to isavuconazole, and 19 patients (15.7%) had received at least three antifungals

Table 1 Patient characteristics at isavuconazole initiation

Characteristic	Total sample			IA			Mucormycosis		
	Total (*N* = 218)	Primary (*n* = 92)	Salvage (*n* = 121)	Total (*n* = 201)	Primary (*n* = 87)	Salvage (*n* = 109)	Total (*n* = 17)	Primary (*n* = 5)	Salvage (*n* = 12)
Age, mean (SD), years	56.8 (15.6)	57.6 (13.8)	56.1 (16.8)	56.0 (15.6)	57.3 (13.6)	54.8 (16.9)	66.5 (12.8)	63.0 (17.2)	67.9 (11.2)
Female sex, *n* (%)	74 (33.9)	32 (34.8)	41 (33.9)	65 (32.3)	30 (34.5)	34 (31.2)	9 (52.9)	2 (40.0)	7 (58.3)
Ethic/racial group,[a] *n* (%)									
Asian	3 (1.8)	1 (1.2)	2 (2.5)	2 (1.3)	1 (1.2)	1 (1.4)	1 (9.1)	0	1 (12.5)
Black	1 (0.6)	0	1 (1.3)	0	0	0	1 (9.1)	0	1 (12.5)
Other	1 (0.6)	1 (1.2)	0	1 (0.6)	1 (1.2)	0	0	0	0
White	139 (81.8)	73 (84.9)	61 (77.2)	130 (81.8)	70 (84.3)	55 (77.5)	9 (81.8)	3 (100.0)	6 (75.0)
Unknown	26 (15.3)	11 (12.8)	15 (19.0)	26 (16.4)	11 (13.3)	15 (21.1)	0	0	0
At least 3 comorbidities, *n* (%)	135 (61.9)	54 (58.7)	79 (65.3)	124 (61.7)	52 (59.8)	70 (64.2)	11 (64.7)	2 (40.0)	9 (75.0)
Comorbidities among at least 10% of patients,[b] *n* (%)									
Haematologic malignancy	135 (61.9)	57 (62.0)	73 (60.3)	124 (61.7)	54 (62.1)	65 (59.6)	11 (64.7)	3 (60.0)	8 (66.7)
Fever and neutropenia	64 (29.4)	34 (37.0)	29 (24.0)	60 (29.9)	33 (37.9)	26 (23.9)	4 (23.5)	1 (20.0)	3 (25.0)
Neutropenia	58 (26.6)	28 (30.4)	29 (24.0)	51 (25.4)	27 (31.0)	23 (21.1)	7 (41.2)	1 (20.0)	6 (50.0)
Stem cell transplantation	49 (22.5)	17 (18.5)	31 (25.6)	46 (22.9)	16 (18.4)	29 (26.6)	3 (17.6)	1 (20.0)	2 (16.7)
Hypertension	43 (19.7)	22 (23.9)	21 (17.4)	41 (20.4)	22 (25.3)	19 (17.4)	2 (11.8)	0	2 (16.7)
Diabetes	35 (16.1)	14 (15.2)	21 (17.4)	31 (15.4)	14 (16.1)	17 (15.6)	4 (23.5)	0	4 (33.3)

Table 1 continued

Characteristic	Total sample			IA			Mucormycosis		
	Total ($N=218$)	Primary ($n=92$)	Salvage ($n=121$)	Total ($n=201$)	Primary ($n=87$)	Salvage ($n=109$)	Total ($n=17$)	Primary ($n=5$)	Salvage ($n=12$)
Solid organ transplantation	29 (13.3)	15 (16.3)	14 (11.6)	28 (13.9)	14 (16.1)	14 (12.8)	1 (5.9)	1 (20.0)	0
Prior bacterial infection	23 (10.6)	8 (8.7)	14 (11.6)	22 (10.9)	8 (9.2)	13 (11.9)	1 (5.9)	0	1 (8.3)
Moderate-to-severe renal disease	24 (11.0)	8 (8.7)	16 (13.2)	21 (10.4)	7 (8.0)	14 (12.8)	3 (17.6)	1 (20.0)	2 (16.7)
Solid tumour	23 (10.6)	7 (7.6)	15 (12.4)	20 (10.0)	6 (6.9)	13 (11.9)	3 (17.6)	1 (20.0)	2 (16.7)
EORTC/MSG classification, *n* (%)									
Probable	107 (49.1)	49 (53.3)	56 (46.3)	100 (49.8)	46 (52.9)	52 (47.7)	7 (41.2)	3 (60.0)	4 (33.3)
Possible	71 (32.6)	39 (42.4)	29 (24.0)	67 (33.3)	37 (42.5)	27 (24.8)	4 (23.5)	2 (40.0)	2 (16.7)
Proven	33 (15.1)	2 (2.2)	31 (25.6)	28 (13.9)	2 (2.3)	26 (23.9)	5 (29.4)	0	5 (41.7)
Unknown	7 (3.2)	2 (2.2)	5 (4.1)	6 (3.0)	2 (2.3)	4 (3.7)	1 (5.9)	0	1 (8.3)
IFD localisation among at least 5% of the population, *n* (%)									
Lungs	189 (86.7)	87 (94.6)	97 (80.2)	179 (89.1)	84 (96.6)	90 (82.6)	10 (58.8)	3 (60.0)	7 (58.3)
Lungs plus other sites	14 (6.4)	1 (1.1)	13 (10.7)	13 (6.5)	1 (1.2)	12 (11.0)	1 (5.9)	0	1 (8.3)

EORTC/MSG European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group, *IFD* invasive fungal disease

[a]Data not available from patients residing in France per privacy requirements

[b]Comorbid medical conditions are not mutually exclusive and may not sum to 100%

before commencing isavuconazole. The most frequently prescribed prior antifungal therapies were voriconazole ($n=86$ [71.7%; 86/121]), LamB ($n=59$ [48.8%; 59/121]), and posaconazole ($n=52$ [43.0%; 52/121]). Most patients receiving voriconazole ($n=77/86$ [89.5%]) and LamB ($n=53/59$ [89.8%]) switched to isavuconazole for the same infection, whereas 48.1% ($n=25/52$) of patients previously receiving posaconazole switched to isavuconazole for the same infection. Patients were switched from these agents to isavuconazole primarily due to AEs (voriconazole, $n=38/77$ [49.4%]; LamB, $n=14/53$ [26.4%]; posaconazole, $n=5/25$ [20.0%]) and lack of response to treatment (voriconazole, $n=18/77$ [23.4%]; LamB, $n=17/53$ [32.1%]; posaconazole,

n = 8/25 [32.0%]). Other reasons for treatment switching were drug interaction (voriconazole, *n* = 7/77 [9.1%]; LamB, *n* = 2/53 [3.8%]; posaconazole, *n* = 2/25 [8.0%]) and unknown/other unspecified reason (voriconazole, *n* = 14/77 [18.2%]; LamB, *n* = 20/53 [37.7%]; posaconazole, *n* = 10/25 [40.0%]).

Most patients (83.1% [167/201], IA; 64.7% [11/17], IM) were classified as having probable or possible disease. Fungal infection primarily manifested in the lungs (Table 1). More patients receiving isavuconazole as primary treatment were classified as having probable or possible fungal infection versus proven fungal infection than patients initiating isavuconazole as salvage therapy (95.7% [88/92] vs. 2.2% [2/92] and 70.3% [85/121] vs. 25.6% [31/121], respectively).

Isavuconazole Therapy

Most patients initiated isavuconazole in the hospital setting (87.6% among the total population [191/218]), primarily on a haematology ward (39.8% [76/191]) or in an ICU (33.0% [63/191]). Isavuconazole was initially administered as an intravenous infusion among 51.8% of patients (113/218) and orally among 46.3% of patients (101/218) (mode of administration was not reported for 2%). Infusion administration was more frequent among patients initiating isavuconazole as primary treatment (71.7% [66/92]), whereas oral administration was more frequent among patients initiating isavuconazole as salvage therapy (61.2% [74/121]). It was not possible to assess changes in mode of administration from the mode initially received.

Patients initiating isavuconazole as primary treatment did so within a mean (SD) of 9.8 (42.0) days (median of 0 days) from a suspected diagnosis. When initiated as salvage therapy, isavuconazole was started at a mean (SD) of 67.3 (102.1) days (median of 19 days) after a suspected diagnosis.

The overall mean (SD) duration of isavuconazole monotherapy (including patients continuing to receive isavuconazole at the time of data collection) when initiated as infusion was 51.9 (103.6) days (median = 15 days) and, when initiated as oral, was 177.2 (267.3) days (median = 84 days). Among patients who initiated isavuconazole as primary treatment, the mean (SD) duration when initiated as infusion was 30.3 (59.3) days (median = 12 days) and, when initiated as oral, was 129.6 (94.8) days (median = 91 days). Among patients who initiated isavuconazole as salvage treatment, the mean (SD) duration when initiated as infusion was 86.5 (143.7) days (median = 25 days) and, when initiated as oral, was 197.7 (304.9) days (median = 83 days).

In the overall population, 203 patients (93.1%) had discontinued isavuconazole treatment at the time of data collection (187 with IA, 16 with IM). The mean (SD) time to discontinuation was 46.1 (98.3) days (median = 15 days) overall when isavuconazole was initiated as infusion and 115.8 (135.4) days (median = 77 days) when it was initiated as oral; 27.2 (54.1) days (median = 12 days) and 125.3 (94.2) days (median = 90 days) among patients who initiated primary treatment with isavuconazole as infusion or oral, respectively; and 77.2 (139.7) days (median = 19 days) and 115.4 (149.6) days (median = 65 days) among patients who initiated salvage treatment with isavuconazole as infusion or oral, respectively. The primary reason for treatment discontinuation was death unrelated to therapy (primary treatment, 41/90 [45.6%]; salvage, 35/108 [32.4%]), completion of planned course of treatment (primary treatment, 18/90 [20.0%]; salvage, 30/108 [27.8%]), and resolution of IFD (primary treatment, 11/90 [12.2%]; salvage, 21/108 [19.4%]).

Therapeutic drug monitoring was used among 33/201 patients with IA (16.4%) and 4/17 patients with IM (23.5%). The outcome of TDM was no change to treatment for 22/33 patients with IA (66.7%) and all patients with mucormycosis; for the remaining patients with IA (11/33), TDM resulted in treatment modification for 7/33 patients (21.2%), discontinuation among 2/33 patients (6.1%) and unspecified other for 2/33 patients (6.1%).

Clinical Outcomes

Clinical response to isavuconazole monotherapy was observed among 123/218 patients (56.4%).

The median time to clinical response was 1.6 months (95% CI, 1.2–2.6 months). Clinical response was documented for 112/201 patients with IA (55.7%) and 11/17 patients with IM (64.7%), and median time to clinical response for both groups matched that of the total population (Table 2). A higher proportion of patients who initiated isavuconazole as salvage therapy achieved clinical response than patients who initiated isavuconazole as primary treatment (66.1% [80/121] vs. 44.6% [41/92]). Similarly, the median time to clinical response was shorter when isavuconazole was initiated as salvage therapy compared with primary treatment (1.5 [95% CI, 0.9–2.3] months vs. 1.9 [95% CI, 1.2-not estimable] months, respectively), with a nonsignificant hazard ratio of 0.769 (95% CI, 0.524–1.129) (Fig. 1). The estimated success rate at week 24 was 73.5% (95% CI, 62.7–81.1%) for salvage therapy and 54.5% (95% CI, 38.2–66.5%) for primary treatment.

Radiological success was observed among 110/218 patients (50.5%) (IA, $n = 100/201$ [49.8%]; mucormycosis, $n = 10/17$ [58.8%]). The median time to radiological success was 2.8 months (95% CI, 1.9–4.1 months). A higher proportion of patients who initiated isavuconazole as salvage therapy achieved radiological success than did patients who initiated isavuconazole as primary treatment (62.0% [75/121] vs. 38.0% [35/92]). Similarly, the median time to radiological success was shorter when isavuconazole was initiated as salvage therapy compared with primary treatment (1.7 months [95% CI, 1.1–2.8] vs. 4.1 months [95% CI, 2.8-not estimable], respectively), with a significant hazard ratio of 0.583 (95% CI, 0.388–0.876). The estimated success rate at week 24 was 68.4% (95% CI, 57.3–76.7%) for salvage therapy and 52.6% (95% CI, 35.9–64.9%) for primary treatment.

Mycological success was reported only for patients who had a biomarker test close to treatment initiation and a follow-up test ($n = 112$). Mycological success was observed among 24/112 patients (21.4%), all of whom had IA. The median time to observed mycological success was 23.1 months (95% CI, 22.5-not estimable). A higher proportion of patients who initiated isavuconazole as salvage therapy achieved mycological success than patients who initiated isavuconazole as primary treatment (28.8% [15/52] vs. 13.6% [8/59]). The median time to mycological success was 22.5 months (95% CI, 22.5-not estimable) for salvage therapy and not estimable for primary treatment. The estimated success rate at week 24 was 28.8% (95% CI, 13.4–41.5%) for salvage therapy and 19.4% (95% CI, 5.2–31.5%) for primary treatment.

At data collection, 137/218 patients (62.8%) had died, and the primary cause of death was underlying disease complications (69.3% [95/137]). The median overall survival time from isavuconazole initiation was 9.4 months (95% CI, 5.8–13.7). The KM-estimated probability of death within 12 weeks of isavuconazole initiation was 34.6% (95% CI, 27.8–40.8%). The proportion of patients who initiated isavuconazole as primary treatment and died was 76.1% (70/92) and was 52.1% (63/121) for patients who initiated isavuconazole as salvage therapy. Similarly, the median overall survival time from isavuconazole initiation was longer when isavuconazole was initiated as salvage therapy compared with primary treatment (salvage, 17.7 months; primary, 3.9 months), with a hazard ratio of 2.359 (95% CI, 1.653–3.367) (Fig. 2). The KM-estimated probability of death within 12 weeks of isavuconazole initiation was 46.4% (95% CI, 35.0–55.7%) for patients who initiated isavuconazole as primary treatment and 29.0% (95% CI, 20.5–36.7%) for those who initiated it for salvage therapy. The KM-estimated probability of death within 6 weeks of diagnosis of IA infection was 25.3% (95% CI, 18.9–31.1%) and 5.9% (95% CI, 0.0–16.4%) for patients with IA and patients with IM, respectively; within 12 weeks of diagnosis, this was 38.5% (95% CI, 31.3–44.9%) and 12.2% (95% CI, 0.0–26.6%) for patients with IA and patients with IM, respectively; and within 6 months of diagnosis, this was 49.0% (95% CI, 41.5–55.6%) and 31.0% (95% CI, 4.2–50.3%) for patients with IA and patients with IM, respectively. Seventeen of 137 patients (12.4%) died due to IFD, 11 of whom initiated isavuconazole as salvage therapy.

Table 2 Kaplan–Meier estimate of time to clinical response from isavuconazole initiation

	Total sample			IA			Mucormycosis		
	Total ($N = 218$)	Primary ($n = 92$)	Salvage ($n = 121$)	Total ($n = 201$)	Primary ($n = 87$)	Salvage ($n = 109$)	Total ($n = 17$)	Primary ($n = 5$)	Salvage ($n = 12$)
Clinical response achieved, *n* (%)	121 (55.5)	40 (43.5)	79 (65.3)	110 (54.7)	36 (41.4)	72 (66.1)	11 (64.7)	4 (80.0)	7 (58.3)
Censored—last observation before 31 Dec 2019—no success, *n* (%)	77 (35.3)	47 (51.1)	28 (23.1)	71 (35.3)	46 (52.9)	23 (21.1)	6 (35.3)	1 (20.0)	5 (41.7)
Censored—last observation after 31 Dec 2019—no success, *n* (%)	18 (8.3)	4 (4.3)	13 (10.7)	18 (9.0)	4 (4.6)	13 (11.9)	0	0	0
Achieved success but missing date information, *n* (%)	2 (0.9)	1 (1.1)	1 (0.8)	2 (1.0)	1 (1.1)	1 (0.9)	0	0	0
Time to event, median (95% CI), months	1.6 (1.2–2.6)	1.9 (1.2–NE)	1.5 (0.9–2.3)	1.6 (1.2–2.7)	2.7 (1.4–NE)	1.5 (0.8–2.3)	1.7 (0.9–NE)	0.9 (0.1–NE)	1.9 (0.9- NE)

Table 2 continued

	Total sample			IA			Mucormycosis		
	Total (N = 218)	Primary (n = 92)	Salvage (n = 121)	Total (n = 201)	Primary (n = 87)	Salvage (n = 109)	Total (n = 17)	Primary (n = 5)	Salvage (n = 12)
Event rate (95% CI)									
Week 6	47.9 (40.2–54.6)	45.0 (32.2–55.4)	50.4 (40.1–58.9)	48.4 (40.3–55.4)	44.1 (30.7–54.9)	52.0 (41.1–61.0)	43.3 (13.0–63.0)	60.0 (0.0–86.3)	36.4 (0.5–59.3)
Week 12	62.4 (53.8–69.3)	54.5 (38.2–66.5)	67.0 (56.2–75.1)	61.4 (52.2–68.7)	52.2 (34.9–64.8)	67.2 (55.8–75.7)	68.5 (35.0–84.7)	80.0 (0.0–96.5)	63.6 (20.5–83.4)
Week 24	67.4 (58.5–74.4)	54.5 (38.2–66.5)	73.5 (62.7–81.1)	67.1 (57.5–74.5)	52.2 (34.9–64.8)	74.3 (62.9–82.2)	68.5 (35.0–84.7)	80.0 (0.0–96.5)	63.6 (20.5–83.4)

CI confidence interval, *IA* invasive aspergillosis, *NE* not estimable

Safety Outcomes

Within 6 months of initiating isavuconazole monotherapy, 45/218 patients experienced at least 1 AE (20.6% [45/218]). Of those, 34 experienced AEs in the first 6 weeks of treatment. In ten cases, the AEs were considered to be related to isavuconazole treatment (myopathy, n = 3; elevated liver chemistry, n = 2; nausea, n = 1; blisters, n = 1; delirium, n = 1; allergic reaction, n = 1; death related to isavuconazole, n = 1).[1]

Serious AEs (SAEs) were reported for 37/218 patients (17.0%) within 6 months of initiating isavuconazole monotherapy; most patients experienced the SAE within the first 6 weeks (n = 28). In seven cases, the SAE was related to isavuconazole treatment (elevated liver chemistry, n = 2; myopathy, n = 1; probable allergic reaction, n = 1; delirium, n = 1; clinical deterioration, n = 1; death related to isavuconazole, n = 1), and five patients (2.3%) discontinued isavuconazole monotherapy due to the SAE.

Healthcare Resource Use

Following initiation of isavuconazole, 128/218 patients (58.7%) were hospitalised (defined as newly hospitalised or transferred to another ward during the original hospitalisation); the mean (SD) number of hospitalisations was 3.0 (2.7). Hospitalisations were primarily due to monitoring of the underlying disease (71.1% [91/128]). Patients receiving isavuconazole as salvage therapy were more frequently hospitalised than patients receiving isavuconazole as first-line therapy (74.4% [90/121] vs. 40.2% [37/92]). Among 37 of the 128 hospitalised patients (28.9%), hospitalisation was due directly to IFD monitoring. The mean (SD) time from isavuconazole initiation to first subsequent hospitalisation was 66.5 (110.1) days (median = 27 days). The mean (SD) length of stay during rehospitalisation was 20.7 (42.6) days (median = 12 days).

[1] For one patient, progression of fungal infection was also reported; however, this is not considered to be an AE.

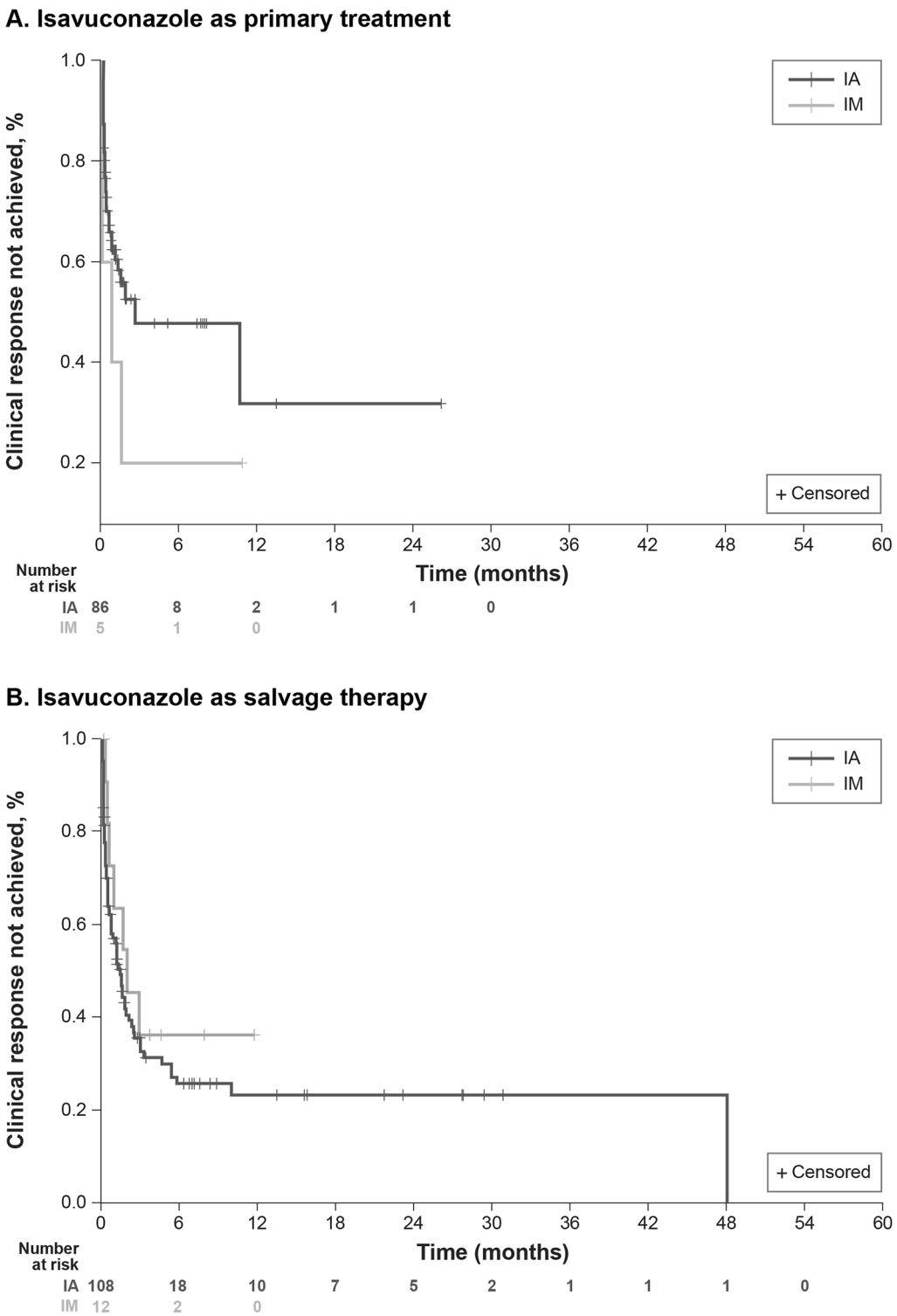

Fig. 1 Kaplan–Meier estimate of time to clinical response among patients who initiated isavuconazole monotherapy

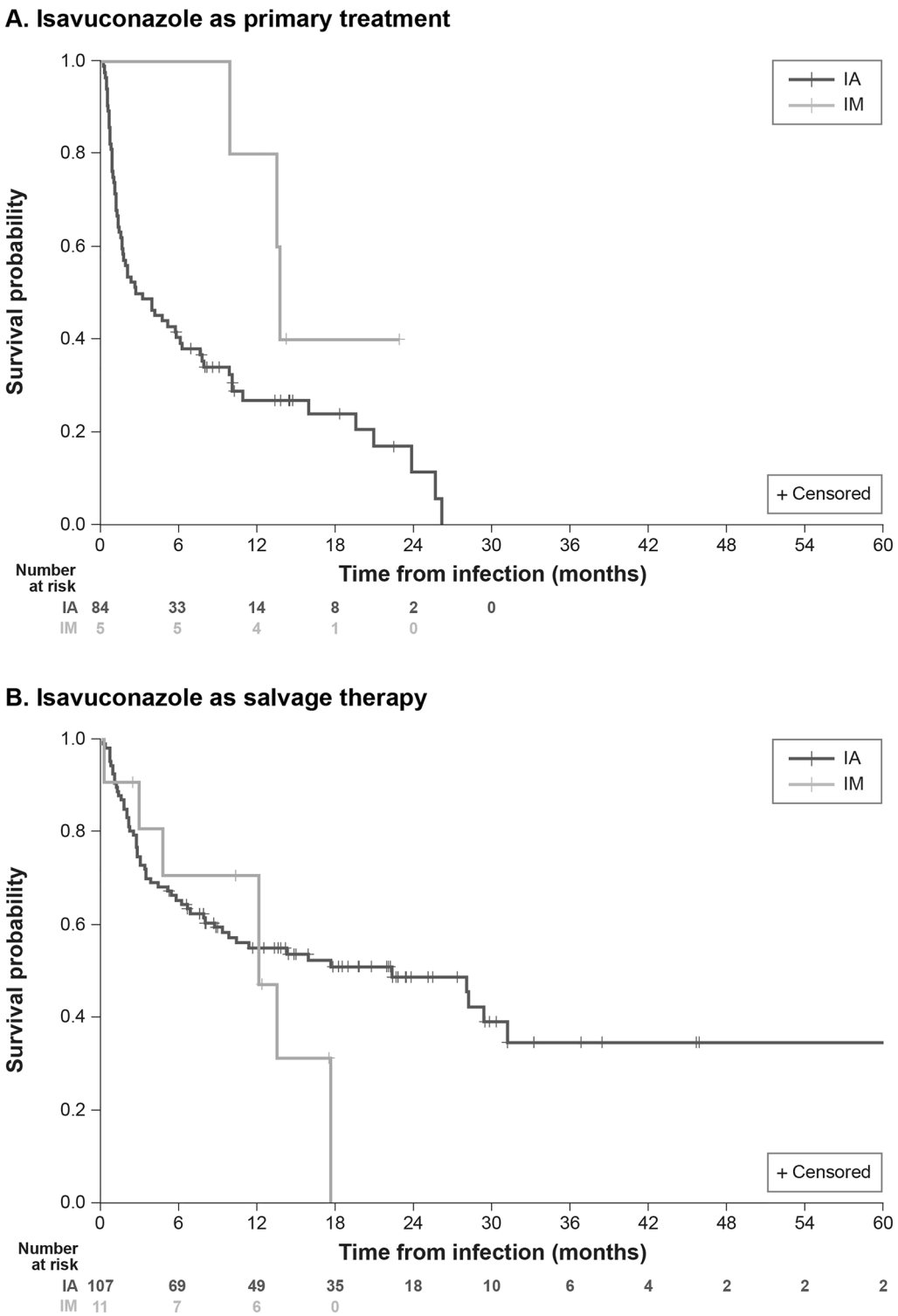

Fig. 2 Kaplan–Meier estimate of overall survival from infection diagnosis among patients who initiated isavuconazole monotherapy

An outpatient visit or referral following isavuconazole initiation was observed among 96/218 patients (44.0% [96/218]), with a mean (SD) of 8.9 (6.7) visits/referrals. Visits/referrals were primarily pre-planned for underlying disease monitoring (77/96 [80.2%]) or pre-planned for IFD monitoring (38/96 [39.6%]). Patients receiving isavuconazole as salvage therapy more frequently had an outpatient visit or referral than did patients receiving isavuconazole as first-line therapy (56.2% [68/121] vs. 30.4% [28/92]). The mean (SD) time from isavuconazole initiation to first subsequent visit/referral was 64.7 (82.8) days (median = 33 days).

DISCUSSION

This multicentre, multinational observational study describes the characteristics of patients initiating isavuconazole for treatment of IA or IM in real-world practice in Europe. This study is the first to document clinical practice and outcomes in a diverse European population since the introduction of isavuconazole to the European market.

In this real-world sample, patients had multiple comorbidities, with most patients having haematological malignancy. IA is a frequently occurring complication of treatment for haematologic malignancies [14], and haematological malignancies are often documented as comorbidities among patients with mucormycosis [15, 16]. Over a third of the sample had a history of corticosteroid treatment, a well-known risk factor for IA [17, 18]. Most patients were classified as having probable or possible disease rather than proven disease. The observed proportions are similar to those observed in the SECURE clinical trial, when 44% and 34% of patients randomised to isavuconazole had probable or possible IA, respectively [6]. Diagnosis is known to be difficult due to the non-specific range of clinical symptoms, logistical issues (sensitivity and specificity of diagnostic tools, lack of medical mycology training), lack of consideration of evolving risk factors, and new entities of IA [19–21]. Diagnosis of IM is especially difficult due to its clinical and radiological similarities to IA and to the lack of sensitive diagnostic tools [22, 23]. Disease progression with IA is rapid and often results in death. Prompt and correct diagnosis is a prerequisite for the successful treatment of patients.

Isavuconazole is recommended as primary therapy [5] for the treatment of IA and IM. However, we found that isavuconazole was used as salvage treatment in just over half of our sample. Little information is available on the use of isavuconazole as salvage therapy. The most common agents received prior to isavuconazole were voriconazole, liposomal amphotericin B, and posaconazole. Patients were switched to isavuconazole primarily due to lack of clinical response or AEs with prior antifungal treatment, consistent with prior data reported in patients receiving allogeneic bone marrow transplants [24]. European guidelines give a strong recommendation for the use of voriconazole as salvage therapy for IA but emphasise the need for changing drug classes (e.g., LamB to voriconazole); guidelines related to IM strongly recommend isavuconazole or posaconazole as salvage treatment for IM [5, 25]. Similarly, antifungal agent class and changing from one azole to another (posaconazole to isavuconazole) has been suggested as salvage treatment in cases of breakthrough mould infections [26, 27]. Previous reports have shown isavuconazole to be well tolerated and to reach therapeutic concentrations among azole-resistant patients with IA [28]. Other recent real-world studies conducted in Europe have also found that isavuconazole is commonly used as salvage therapy [28–32]. Of note, our study was not designed to detect differences among patients who receive isavuconazole as primary or salvage therapy; thus, any emergent differences are descriptive only and require further exploration in studies powered to detect such differences, with statistical accounting for differences in effect-modifying confounders between the two groups.

Isavuconazole has a more predictable pharmacokinetic profile than other available azoles and a less complicated drug interaction profile [25]. TDM is questionable with the use of isavuconazole; we found that the use of TDM was rare (17%), and results most commonly led to no treatment adjustment, suggesting that the

therapeutic levels were reached among the majority of those assessed.

Over half of the sample achieved clinical response, which is slightly lower than results from the SECURE clinical trial (62%) [6]; however, radiological response and mycological response rates were higher within our sample than those in the SECURE trial. Notably, the SECURE trial assessed response based on a data review committee, whereas the response within this retrospective study was based on an individual physician's assessment. Given that our sample was primarily made up of patients receiving salvage treatment (whereas the SECURE trial was conducted among patients receiving first-line therapy), the results provide preliminary evidence that isavuconazole as salvage therapy has good clinical effectiveness. This preliminary evidence requires confirmation in further studies.

The estimated rate of all-cause mortality at 12 weeks following infection date was similar to that observed within the SECURE trial [6], lower than that observed within the VITAL study [7], and similar to those documented in other recent real-world studies conducted in Europe [12, 29]. Our real-world sample was composed of a much more heterogeneous population than those included within clinical trials, and many of the patients were receiving salvage therapy, which represents a different treatment paradigm than that within the controlled clinical studies. We found that patients receiving isavuconazole as salvage therapy had a greater likelihood of living longer than patients receiving isavuconazole as primary treatment. This could be due to a selection bias, where patients who received salvage treatment were those more likely to survive initially compared with patients starting a primary treatment.

Patients with IA and IM are a very sick and vulnerable population that are commonly receiving multiple medications and are prone to an array of AEs [33]. When used as salvage therapy, isavuconazole has been documented to have a lower AE profile than voriconazole in real-world UK clinical settings [34]. We found that treatment-related AEs were rare despite isavuconazole being used for prolonged periods of time, providing further evidence that isavuconazole has a good safety profile in real-world clinical settings.

Limitations of this study limit the generalizability of the findings to the wider population of patients with IA or IM in Europe receiving treatment with isavuconazole. First, a small number of participating sites in each country were recruited using a convenience sampling approach and may not be representative of care throughout each country. Only patients who had initiated isavuconazole no later than June 30, 2019, were eligible (to avoid collection of clinical outcomes related to the COVID-19 pandemic) and the findings may not be representative of post-pandemic treatment and outcomes. Data available for the study was restricted to that available within medical records to which the sites had access; any relevant care received outside of the site may not have been documented. Further, the study did not assess underlying disease severity which may explain some of the differences seen in clinical outcomes. Additionally, clinicians were encouraged to use the established EORTC/MSG guideline definitions, but diagnoses were not further validated.

CONCLUSIONS

The results of this study add to the growing body of evidence that whether used as first-line therapy or after the failure of other azole and non-azole therapies, isavuconazole seems to have a promising clinical response and a good safety profile as an antifungal agent in patients with varied underlying conditions, including, but not limited to, haematological malignancy, neutropenia, and stem cell transplant.

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Houghton, Maria Jimenez, Oliver Cornely, Antonio Pagliuca. Data collection: Katherine Houghton, Maria Jiminez, David A Enoch, Beate Gruener, Raoul Herbrecht, Tobias Lahmer, Olivier Lortholary, Cléa Melenotte, Francesco Giuseppe De Rosa, Carolina Garcia-Vidal. Data analysis: Katherine Houghton, Lili Jiang, Maria Jiminez. Data interpretation: Dionysios Neofytos, Katherine Houghton, Maria Jimenez, Oliver Cornely, Antonio Pagliuca, Edward Broughton, Maria Lavinea Novis de Figueiredo Valente, Maria Fernandez. Manuscript development: all authors.

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Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. Upon request, and subject to review, Pfizer will provide the data that support the findings of this non-interventional study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Declarations

Conflict of Interest. Carolina Garcia-Vidal has received grants and honoraria for talks from MSD, Gilead Sciences Inc., Pfizer Inc., Janssen, Novartis, Eli Lilly, Mundipharma, and Shionogi. Carolina Garcia-Vidal has also received a national research grant from the Instituto de Salud Carlos III. David A Enoch has participated in advisory boards for Mundipharma/Napp, Pfizer Inc., and MSD and has received honoraria for consulting services to Tillots Pharmaceuticals and Pfizer Inc. Dionysios Neofytos has received research support from MSD and Pfizer Inc. and consulting fees from MSD, Pfizer Inc., Basilea, Takeda, and Gilead Sciences Inc. Katherine Houghton and Maria Jiminez are salaried employees of RTI Health Solutions. RTI Health Solutions received funding from Pfizer Inc. for the conduct of this research and medical writing services. Oliver Cornely has received consulting fees and payment or honoraria from Abbott, AbbVie, Akademie für Infektionsmedizin, Al-Jazeera Pharmaceuticals/Hikma, Amedes, AstraZeneca, Aicuris, Basilia, Biocon, Cidara, Seqirus, Deutscher Ärzteverlag, Gilead Sciences Inc., GSK, IQVIA, Janssen, Grupo Biotoscana/United Medical/Knight, Ipsen Pharma, Medscape/WebMD, MedUpdate, MSD, Moderna, Mundipharma, Matinas, MedPace, Menarini, Molecular Partners, MSG-ERC, Munipharma, Noscendo, Noxxon, Octopharma, Paul-Martini-Stiftung, Pardes, Partner Therapeutics, Pfizer Inc., PSI, Sandoz, Scynexis, Seres, Shionogi, streamedup!, Touch Independent, and Vitis. OC has also participated on advisory boards for Boston Strategic Partners, Cidara, IQVIA, Janssen, MedPace, PSI, Pulmocide, Shionogi, and The Prime Meridian Group. Edward Broughton, Lili Jiang, Maria Lavinea Novis de Figueiredo Valente, and Maria Fernandez are shareholders in Pfizer Inc. Tobias Lahmer has received travel grants and lecture fees from Pfizer Inc., Gilead Sciences Inc., and MSD. Antonio Pagliuca, Beate Gruener, Raoul Herbrecht, Olivier Lortholary, and Cléa Melenotte have no conflicts of interest to declare.

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