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Systemic antifungal therapy with isavuconazonium sulfate or other agents in adults with invasive mucormycosis or invasive aspergillosis (non-*fumigatus*): A multicentre, non-interventional registry study

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Abstract

Background: Isavuconazole, administered as isavuconazonium sulfate (ISAVUSULF), is a broad-spectrum triazole agent for the treatment of invasive fungal disease. In phase 3 studies, ISAVUSULF showed comparable efficacy to voriconazole and amphotericin B for the treatment of invasive aspergillosis (IA) and invasive mucormycosis (IM), respectively.

Objectives: The objective of this study is to determine all-cause mortality and safety outcomes among adults with IM and/or IA non-*fumigatus* (nf) treated with ISAVUSULF or other antifungal therapies (AFT).

Patients and methods: This multicentre, non-interventional registry enrolled patients aged ≥18 years with IM or IA-nf who received systemic AFT from January 2016 to November 2018. Patients received primary ISAVUSULF, non-primary ISAVUSULF, or other AFT, as monotherapy or combination therapy. The primary end point was all-cause mortality at Days 42 and 84; safety outcomes were adverse drug reactions (ADRs) to ISAVUSULF.

Results: Of 204 patients enrolled, 74 received primary ISAVUSULF, 30 non-primary ISAVUSULF, and 100 other AFT. All-cause mortality through Day 42 was numerically lower in the non-primary ISAVUSULF group than in the primary ISAVUSULF and other AFT groups, for patients with IM (20.0% vs. 33.3% and 41.3%, respectively) or IA-nf (0% vs. 14.8% and 17.8%, respectively). All-cause mortality tended to be lower with combination therapy than with monotherapy, except for patients with IM receiving primary ISAVUSULF. Of 111 patients receiving ISAVUSULF, 14 (12.6%) reported ADRs, of whom three (2.7%) developed serious ADRs. There were no drug-related deaths.

Conclusions: This study supports the effectiveness and tolerability of ISAVUSULF in clinical practice. Further research is required to confirm the value of ISAVUSULF combination therapy over monotherapy.

KEYWORDS

antifungals, azoles, invasive aspergillosis, invasive mucormycosis, isavuconazonium sulfate, non-*fumigatus Aspergillus*

1 | INTRODUCTION

Aspergillus fumigatus is the most common cause of invasive mould infections[1]; however, other opportunistic moulds including *Aspergillus* non-*fumigatus* spp. and the Mucorales have emerged as significant causes of human infection.[2-4] These organisms can potentially lead to severe disease, including dissemination or invasion of contiguous sites.[5,6] Limited biomarkers are available for the diagnosis of non-*Aspergillus* moulds, and these organisms may exhibit resistance to multiple antifungal therapies (AFT).[4,7-9]

The evaluation of antifungal efficacy in the treatment of these less common opportunistic mould infections is challenging. A number of factors, including the degree of host immunosuppression, time to diagnosis, penetration of AFT at the site of infection, and availability of adjunctive therapy (eg, surgical intervention), influence clinical outcomes. The correlation between in vitro susceptibility and observed in vivo responses to AFT is thus difficult to demonstrate,[7] and robust evidence on their clinical efficacy is scarce in patients with these less common infections.[7,10,11]

Isavuconazonium sulfate (ISAVUSULF) is the prodrug of isavuconazole, a broad-spectrum mould-active triazole AFT.[12] ISAVUSULF has shown similar activity to amphotericin B in adults with invasive mucormycosis (IM) in a single-arm, open-label trial (VITAL study) with a case–control analysis.[13] ISAVUSULF was also noninferior to voriconazole in a phase 3, double-blind study of adults with proven, probable, or possible invasive aspergillosis (IA) and other mould infections (the SECURE study).[14] On the basis of these data, oral or intravenous ISAVUSULF has been approved for the treatment of adults with IM or IA.[15,16] However, the use of ISAVUSULF for prophylaxis is considered off label for high-risk patients and is supported by minimal data.[17]

Despite the increasing incidence of IM and non-*fumigatus* IA (IA-nf), the availability of clinical outcomes data remains limited.[18,19] We report the all-cause mortality and safety outcomes from a US registry study (INQUIRE) of adults with IM or IA-nf who were treated with ISAVUSULF or other systemic AFT.

2 | PATIENTS AND METHODS

2.1 | Ethics

The Institutional Review Board (IRB) from each centre approved the study before it was conducted. The study was conducted in accordance with Good Clinical Practice, the International Council for Harmonisation guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles of the Declaration of Helsinki. Patients, or their guardian/legal representative, signed informed consent forms (ICFs) prior to participation, unless consent requirements were waived by the local ethics committee (EC). For the majority of cases of retrospective data collection (from patients who had already completed treatment), IRB/EC waivers to ICFs were granted.

2.2 | Study design and participants

This was a multicentre, non-interventional registry study. The aim was to assess data from 33 US centres for patients treated with systemic AFT for IM or IA-nf between January 2016 and November 2018. The study was to include patients aged ≥18 years at the time of systemic AFT with proven or probable IM or IA-nf according to the 2008 European Organisation for Research and Treatment of Cancer Invasive Fungal Infections Cooperative Group/Mycoses Study Group (EORTC/MSG) criteria.[20] Those with multiple fungal pathogens were eligible for inclusion into the study cohort; for

these patients, the hierarchy for categorisation was IM then IA if both were present. Patients were excluded from the study if they received surgical treatment only for IM or IA-nf, had participated previously in this registry, or had received an investigational drug for an invasive fungal disease (IFD) within 30 days of starting treatment with an approved AFT. There were no exclusions based on liver/renal dysfunction. The study-defined data collection period began on the first date of systemic AFT initiation through Day 84 or for 84 days after ISAVUSULF initiation, whichever was longer. Data could be collected prospectively or retrospectively, provided that the patient had a known vital status at Day 42.

2.3 | Treatment procedures

Enrolled patients were treated by their physicians as per standard clinical practice. For the analysis, participants were split into three groups according to systemic AFT use: primary ISAVUSULF, non-primary ISAVUSULF, and other AFT. The 'primary ISAVUSULF' group received ISAVUSULF as the primary AFT for IM or IA, either as monotherapy or in combination or sequentially with another systemic AFT. The 'non-primary ISAVUSULF' group received primary therapy with a non-ISAVUSULF systemic AFT (as monotherapy or in combination or sequentially with another systemic AFT) and then received ≥1 dose of ISAVUSULF due to refractory infection, AFT intolerance, or oral step-down/maintenance during treatment for the same IM or IA infection. The 'other AFT' group received non-ISAVUSULF systemic AFT (as monotherapy or in combination or sequentially with additional AFT) as primary therapy and did not receive ISAVUSULF at a later date for their infection. Individuals who received ISAVUSULF as prophylaxis or empirical therapy for <4 days, with no additional ISAVUSULF treatment administered, were included in the other AFT group.

Primary therapy was defined as the initial AFT administered to treat IFD. Therapy was considered 'primary' if the patient received ≤4 cumulative days of alternative mould-active therapy within 7 days prior to initiation of the systemic AFT. If a patient received only one mould-active therapy and died within 7 days of initiating treatment, that therapy was considered primary. Patients could receive multiple non-primary therapies concomitantly or sequentially.

Non-primary therapy was classified according to the reason for treatment as refractory infection, AFT intolerance, or oral step-down/maintenance. Refractory infection was defined as the need for additional or alternative systemic AFT as a result of disease progression (ie, worsening or new clinical signs or symptoms or radiological findings attributable to IFD as a result of non-response to primary mould-active therapy).[21] Intolerance was defined as switching to an alternative systemic AFT due to a patient's inability to tolerate previous mould-active therapy. Oral step-down/maintenance was defined as oral systemic AFT received after a patient had received >4 cumulative days of mould-active systemic intravenous AFT, unless the reason for oral step-down was classified as refractory infection or intolerance.

2.4 | Outcomes/end points

The primary end point was all-cause mortality at Days 42 and 84 (Day 84 rates were cumulative). For patients who received ≥1 dose of ISAVUSULF, Day 1 was the first day of dosing of ISAVUSULF as primary, refractory, intolerant, or oral step-down/maintenance treatment. For patients who did not receive ISAVUSULF, Day 1 was the first day of dosing of non-ISAVUSULF primary systemic AFT.

Adverse events suspected by the investigator to be possibly or probably causally related to ISAVUSULF were summarised by group as all adverse drug reactions (ADRs); serious ADRs (defined as an ADR that resulted in death, was life threatening, caused persistent or significant disability/incapacity, a congenital abnormality or a birth defect, led to hospitalisation or prolongation of hospitalisation, or was another medically important event); or ADRs leading to permanent treatment discontinuation.

Due to the retrospective nature of this study, the location of IFD was determined on clinical grounds only, as there was no autopsy or systemic imaging to document the site of disease in these registry participants.

2.5 | Statistical analyses

A sample size calculation was not performed as this was a non-interventional study for rare diseases that was not designed to make statistical inference. The planned minimum enrolment for ISAVUSULF-treated patients was 35 patients with IM and 30 patients with IA-nf, with ≥50% for each infection type expected to receive ISAVUSULF as primary therapy. To achieve this and based on the assumption that approximately one third of the patients enrolled would have received ISAVUSULF, it was estimated that up to 195 patients would need to participate.

The full analysis set (FAS) comprised all patients who received ≥1 dose of systemic AFT for IM or IA. All-cause mortality and demographic and baseline characteristics were assessed in the FAS. The safety analysis set (SAF) comprised all patients who received ≥1 dose of ISAVUSULF and was used to describe safety findings. Continuous variables were summarised by group as means with standard deviation (SD). Categorical data were summarised by group as frequencies with percentages.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Patient disposition is shown in Figure 1. In total, 204 patients were enrolled and included in the FAS (104 ISAVUSULF and 100 other AFT). Of those receiving ISAVUSULF, 74 (71.2%) patients received ISAVUSULF as primary AFT (24 monotherapy and 50 combination therapy) and 30 (28.8%) as non-primary AFT (11 monotherapy and
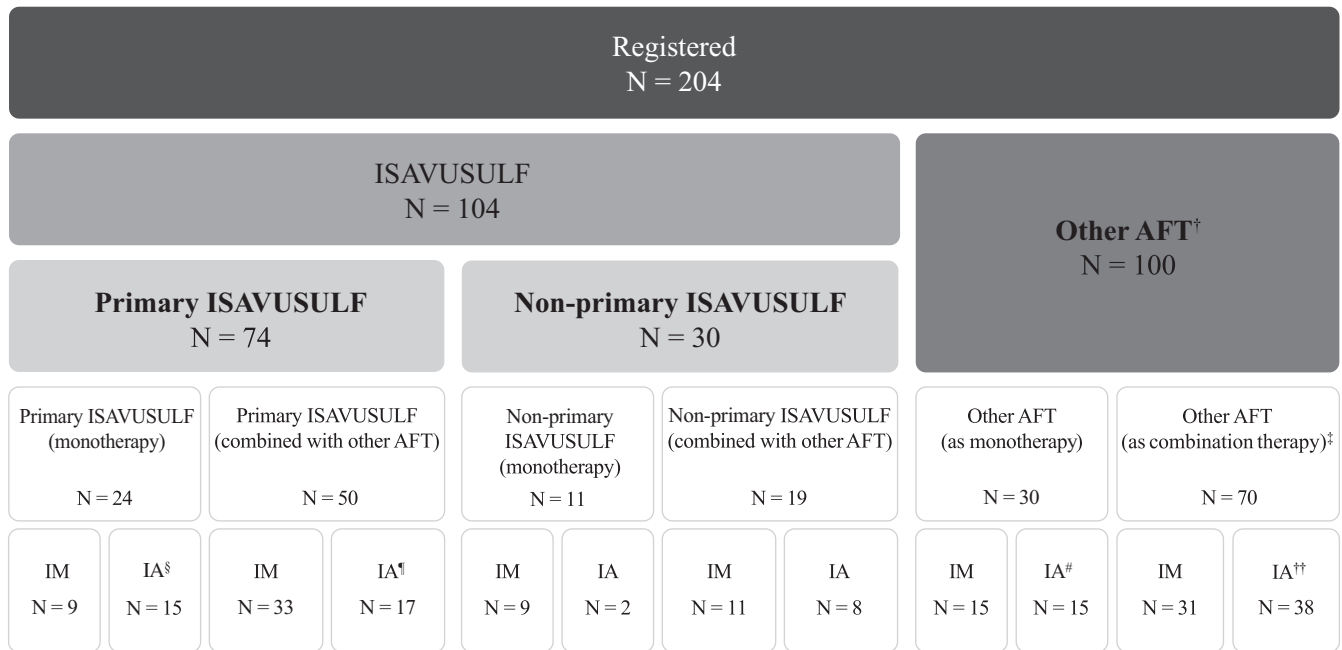
FIGURE 1 Patient disposition. Bold text indicates treatment groups. [†]Includes seven patients who received ISAVUSULF for prophylaxis or empirical therapy for <4 days. [‡]Includes one patient with an unknown pathogen. [§]Includes one patient with only *Aspergillus fumigatus* as the causative organism and two patients with nonspeciated IA. [¶]Includes two patients with nonspeciated IA. [#]Includes one patient with nonspeciated IA. [††]Includes two patients with only *Aspergillus fumigatus* as the causative organism. AFT, antifungal therapies; IA, invasive aspergillosis; IM, invasive mucormycosis; ISAVUSULF, isavuconazonium sulfate

19 combination therapy). Of the 30 patients receiving non-primary AFT, five were intolerant to prior therapy, 12 were refractory to prior therapy, and 13 received ISAVUSULF as oral step-down/maintenance therapy. A list of any concurrent AFT is provided in Table 1. The SAF included all the enrolled patients in the primary and non-primary ISAVUSULF groups (n = 104) and those from the other AFT group who received ISAVUSULF as prophylaxis, empirical therapy, or for <4 days (n = 7). One patient with an unknown pathogen was included in the overall study data; this patient was not included in the IM or IA subgroups. Three patients with only *Aspergillus fumigatus* as the causative organism were enrolled and included in the IA group, despite not meeting the entry criteria for the study; the IA group also included five patients with nonspeciated *Aspergillus*. The IA-nf group included only patients with *Aspergillus* non-*fumigatus* species.

There were 108 patients with IM in the FAS. The mean age (±SD) of these patients was 54.0 (±15.3) years, and 63 (58.3%) were male (Table 2). Baseline characteristics were similar across the primary ISAVUSULF, non-primary ISAVUSULF, and other AFT groups with the exception of incidence of nonhaematological malignancies, which was the highest in the primary ISAVUSULF group. Four patients with IM had diabetic ketoacidosis at baseline: two in the non-primary ISAVUSULF group and two in the other AFT group.

There were 95 patients with IA in the FAS. The mean age (±SD) of these patients was 58.3 (±14.6) years, and 52 (54.7%) were male (Table 2). The primary ISAVUSULF group had a higher proportion of patients with allogeneic bone marrow transplant, neutropenia,

and haematological malignancy, compared with the non-primary ISAVUSULF or other AFT groups.

This study included a high proportion of significantly immunosuppressed patients (Table 2). Overall, 56.5% and 67.4% of patients in the IM and IA groups, respectively, received corticosteroids, and 37.0% of IM and 52.6% of IA patients received T-cell immunosuppressive agents.

3.2 | Pathogens causing IFD and sites of infection

Overall, 176 of 204 (86.3%) patients in the FAS had a single pathogen causing IFD (Table 3). The proportions of patients with only a Mucorales species (88/204 [43.1%]) or only an IA-nf species (80/204 [39.2%]) were similar. IM caused by a single pathogen was more common than IA-nf in the non-primary ISAVUSULF group (18/30 [60.0%] vs. 8/30 [26.7%]). Mixed fungal pathogens accounted for 27 (13.2%) of the IFD in the FAS. In the primary ISAVUSULF group, mixed pathogens occurred only in patients with Mucorales spp. (6/74 [8.1%]) and were more common than *Aspergillus* mixed infections in the other AFT group (12.0% vs. 5.0% of patients, respectively).

Mucorales species included *Cunninghamella* spp., *Lichtheimia corymbifera*, *Rhizopus* spp., *Rhizomucor* spp., *Syncephalastrum* spp., *Apophysomyces elegans*, *Apophysomyces variabilias*, and Mucor spp. IA-nf species included *Aspergillus calidoustus*, *A clavatus*, *A flavus*, *A glaucus*, *A lentulus*, *A nidulans*, *A niger*, *A ochraceus*, *A tamarii*, *A terreus*, *A ustus*, and *A versicolor*. Susceptibility data were not available for the majority of organisms.

TABLE 1 Second systemic AFT received by patients on combined treatment (FAS)

	Primary ISAVUSULF with other AFT	Non-primary ISAVUSULF with other AFT	Other AFT as combination therapy
IM	**N = 33**	**N = 11**	**N = 31**
Amphotericin B			
Conventional	2 (6.1)	2 (18.2)	4 (12.9)
Lipid complex (Abelcet®)	1 (3.0)	0	0
Liposomal (AmBisome®)	9 (27.3)	3 (27.3)	7 (22.6)
Anidulafungin	1 (3.0)	0	0
Caspofungin	0	0	2 (6.5)
Isavuconazonium sulfate	13 (39.4)[a]	10 (90.9) [a]	0
Micafungin	2 (6.1)	4 (36.4)	5 (16.1)
Posaconazole	8 (24.2)	6 (54.5)	14 (45.2)
Terbinafine	0	0	1 (3.2)
Voriconazole	4 (12.1)	2 (18.2)	4 (12.9)
IA[b]	**N = 17**	**N = 8**	**N = 38**
Amphotericin B			
Conventional	1 (5.9)	2 (25.0)	2 (5.3)
Lipid complex (Abelcet)	0	0	1 (2.6)
Liposomal (AmBisome)	3 (17.6)	3 (37.5)	4 (10.5)
Anidulafungin	2 (11.8)	0	1 (2.6)
Caspofungin	1 (5.9)	0	4 (10.5)
Isavuconazonium sulfate	4 (23.5)[a]	8 (100)[a]	2 (5.3)[c]
Itraconazole	0	0	2 (5.3)
Micafungin	2 (11.8)	5 (62.5)	5 (13.2)
Posaconazole	4 (23.5)	3 (37.5)	3 (7.9)
Voriconazole	0	3 (37.5)	7 (18.4)
Unknown pathogen	**N = 0**	**N = 0**	**N = 1[d]**
Amphotericin B			
Liposomal (AmBisome)	0	0	1 (100.0)
Posaconazole	0	0	1 (100.0)

Note: Patients taking multiple non-primary therapies are counted once for each non-primary therapy. Other systemic AFT may have been taken either concomitantly or sequentially with the initial primary therapy. Values are *n* (%).

Abbreviations: AFT, antifungal therapies, FAS, full analysis set (all patients who received ≥1 dose of systemic AFT for IM or IA); IA, invasive aspergillosis; IM, invasive mucormycosis; ISAVUSULF, isavuconazonium sulfate.

[a]Patients in the primary ISAVUSULF and non-primary ISAVUSULF groups could receive ISAVUSULF as empirical therapy, oral step-down/maintenance therapy, or to treat infection refractory to prior AFT, in addition to their primary ISAVUSULF course.

[b]Includes two patients with nonspeciated IA and excludes patients with only *Aspergillus fumigatus* as the causative organism.

[c]Two patients with IA in the 'Other AFT' group received ISAVUSULF as empirical therapy.

[d]One patient with an unknown pathogen received other AFT as combination therapy.

In the INQUIRE registry, 46.1% of patients had extrapulmonary IFD, 29.4% had pulmonary IFD, and 23.0% had disseminated IFD (defined as IFD in >1 noncontiguous site or in the blood) (Table 4). Overall, the proportions of patients with pulmonary, extrapulmonary, and disseminated IFD were similar across the primary ISAVUSULF, non-primary ISAVUSULF, and other AFT groups. IM was more common than IA-nf in extrapulmonary IFD (26.5% vs. 11.8%), and IA-nf was more common than IM in pulmonary IFD (19.1% vs. 7.4%). IM and IA-nf accounted for similar proportions of disseminated IFD (7.8% vs. 8.3%).

3.3 | Treatment

Of the 108 patients with single pathogen or mixed pathogen IM, 68 (63.0%) underwent surgical treatment for IFD (primary ISAVUSULF *n* = 26, non-primary ISAVUSULF *n* = 15, and other AFT *n* = 27). Of the 87 patients with single pathogen or mixed pathogen IA-nf, 22 (25.3%) underwent surgical treatment for IFD (primary ISAVUSULF *n* = 7, non-primary ISAVUSULF *n* = 2, and other AFT *n* = 13).

In patients with IM, the mean (SD) duration of systemic AFT was 66.0 (83.4) days with primary ISAVUSULF, 77.6 (41.9) days

TABLE 2 Patient baseline characteristics (FAS)

Characteristic	IM				IA[a]				Unknown pathogen
	Primary ISAVUSULF[b] (n = 42)	Non-primary ISAVUSULF[c] (n = 20)	Other AFT[d] (n = 46)	Overall (n = 108)	Primary ISAVUSULF[b] (n = 32)	Non-primary ISAVUSULF[c] (n = 10)	Other AFT[d] (n = 53)	Overall (n = 95)	Other AFT (n = 1)
Mean age (SD), years	55.8 (14.8)	54.4 (15.9)	52.3 (15.6)	54.0 (15.3)	54.6 (14.7)	62.8 (10.1)	59.8 (15.0)	58.3 (14.6)	71.0 (−)
Male, n (%)	26 (61.9)	14 (70.0)	23 (50.0)	63 (58.3)	18 (56.3)	5 (50.0)	29 (54.7)	52 (54.7)	1 (100.0)
eGFR <60 ml/min/1.73 m², n (%)	16 (38.1)	4 (20.0)	14 (30.4)	34 (31.5)	15 (46.9)	6 (60.0)	17 (32.1)	38 (40.0)	1 (100.0)
Allogeneic BMT recipient, n (%)	8 (19.0)	4 (20.0)	9 (19.6)	21 (19.4)	6 (18.8)	0	5 (9.4)	11 (11.6)	0
Neutropenia, n (%)	15 (35.7)	7 (35.0)	19 (41.3)	41 (38.0)	16 (50.0)	1 (10.0)	15 (28.3)	32 (33.7)	0
Haematological malignancy, n (%)	18 (42.9)	9 (45.0)	23 (50.0)	50 (46.3)	17 (53.1)	2 (20.0)	16 (30.2)	35 (36.8)	0
Other malignancy, n (%)	8 (19.0)	2 (10.0)	4 (8.7)	14 (13.0)	5 (15.6)	2 (20.0)	11 (20.8)	18 (18.9)	0
Use of corticosteroids, n (%)	25 (59.5)	12 (60.0)	24 (52.2)	61 (56.5)	23 (71.9)	6 (60.0)	35 (66.0)	64 (67.4)	1 (100.0)
Use of T-cell immunosuppressants, n (%)	19 (45.2)	7 (35.0)	14 (30.4)	40 (37.0)	18 (56.3)	3 (30.0)	29 (54.7)	50 (52.6)	1 (100.0)
Diabetic ketoacidosis, n (%)	0	2 (10.0)	2 (4.3)	4 (3.7)	0	0	0	0	0

Abbreviations: AFT, antifungal therapies; BMT, bone marrow transplant; eGFR, estimated glomerular filtration rate; FAS, full analysis set (all patients who received ≥1 dose of systemic AFT for IM or IA); IA, invasive aspergillosis; IM, invasive mucormycosis; ISAVUSULF, isavuconazonium sulfate; SD, standard deviation.

[a]Includes three patients with only *Aspergillus fumigatus* as the causative organism plus five patients with nonspeciated IA.

[b]Patients received ISAVUSULF as primary therapy against IM or IA.

[c]Patients received non-ISAVUSULF systemic AFT as primary therapy and received ≥1 dose of ISAVUSULF against IM or IA after primary AFT due to refractory infection, AFT intolerance, or oral step-down/maintenance.

[d]Patients received non-ISAVUSULF systemic AFT as primary therapy and received no ISAVUSULF against IM or IA after primary AFT due to refractory infection, AFT intolerance, or oral step-down/maintenance; patients who received ISAVUSULF as prophylaxis or empirical therapy for <4 days were included in this group.

Pathogen causing IFD, n (%)	Primary ISAVUSULF[a] (n = 74)	Non-primary ISAVUSULF[b] (n = 30)	Other AFT[c] (n = 100)	Overall (n = 204)
Single pathogen	68 (91.9)	26 (86.7)	82 (82.0)	176 (86.3)
Mucorales spp. only	36 (48.6)	18 (60.0)	34 (34.0)	88 (43.1)
Aspergillus non-*fumigatus* spp. only	27 (36.5)	8 (26.7)	45 (45.0)	80 (39.2)
Aspergillus fumigatus only[d]	1 (1.4)	0	2 (2.0)	3 (1.5)
Aspergillus non-speciated	4 (5.4)	0	1 (1.0)	5 (2.5)
Mixed pathogens	6 (8.1)	4 (13.3)	17 (17.0)	27 (13.2)
Mucorales with *Aspergillus* non-*fumigatus*	6 (8.1)	2 (6.7)	12 (12.0)	20 (9.8)
Aspergillus non-*fumigatus* with another organism	0	2 (6.7)	5 (5.0)	7 (3.4)
Unknown pathogen	0	0	1 (1.0)	1 (0.5)

TABLE 3 Pathogens causing invasive fungal disease (FAS)

Note: For mixed pathogens, the hierarchy for categorisation was IM then IA if both were present.

Abbreviations: AFT, antifungal therapies; FAS, full analysis set (all patients who received ≥1 dose of systemic AFT for IM or IA); IA, invasive aspergillosis; IFD, invasive fungal disease; IM, invasive mucormycosis; ISAVUSULF, isavuconazonium sulfate.

[a]Patients received ISAVUSULF as primary therapy against IM or IA.

[b]Patients received non-ISAVUSULF systemic AFT as primary therapy and received ≥1 dose of ISAVUSULF against IM or IA after primary AFT due to refractory infection, AFT intolerance, or oral step-down/maintenance.

[c]Patients received non-ISAVUSULF systemic AFT as primary therapy and received no ISAVUSULF against IM or IA after primary AFT due to refractory infection, AFT intolerance, or oral step-down/maintenance; patients who received ISAVUSULF as prophylaxis or empirical therapy for <4 days were included in this group.

[d]Three patients with only *Aspergillus fumigatus* as the causative organism were enrolled and included in the registry, despite not meeting the entry criteria for the study.

with non-primary ISAVUSULF, and 49.9 (32.9) days with other AFT. In patients with IA (including patients with *A fumigatus* only and patients with nonspeciated *Aspergillus*), the mean (SD) duration of systemic AFT was 65.1 (43.5) days with primary ISAVUSULF, 85.0 (28.6) days with non-primary ISAVUSULF, and 57.0 (31.4) days with other AFT.

3.4 | All-cause mortality

All-cause mortality rates through Day 42 for patients with IM in the primary ISAVUSULF, non-primary ISAVUSULF, and other AFT groups were 33.3%, 20.0%, and 41.3%, respectively (Table 5). All-cause mortality rates through Day 42 for patients with IA-nf in the primary ISAVUSULF, non-primary ISAVUSULF, and other AFT groups were 14.8%, 0%, and 17.8%, respectively (Table 5). For patients with either IM and/or IA receiving non-primary ISAVUSULF, the mortality rate was higher among patients with refractory IFD (5/12, 41.7%) than those who were intolerant to previous treatment

(0/5, 0%) or who were receiving oral step-down or maintenance therapy (1/13, 7.7%) (Table 5).

Cumulative all-cause mortality rates through Day 84 for patients with IM were 40.5% in the primary ISAVUSULF group, 25.0% in the non-primary ISAVUSULF group, and 50.0% in the other AFT group (Table 5). Cumulative all-cause mortality rates through Day 84 for patients with IA-nf were similar in the primary ISAVUSULF and other AFT groups (29.6% and 28.9%, respectively) and lower in the non-primary ISAVUSULF group (12.5%) (Table 5). However, patients with either IM or IA in the non-primary ISAVUSULF group who were receiving ISAVSULF as oral step-down or maintenance therapy had lower mortality rates (1/13, 7.7%) than those who were refractory (6/12, 50.0%) or intolerant (1/5, 20.0%) to prior treatment (Table 5).

For patients with IM, all-cause mortality rates through Day 42 were similar between primary ISAVUSULF monotherapy and primary ISAVUSULF combination therapy (Table 6); however, for the other AFT groups, all-cause mortality through Day 42 was 8% lower among patients receiving combination therapy versus monotherapy (Table 6).

TABLE 4 Site of infection (FAS)

Site/pathogen causing IFD, n (%)	Primary ISAVUSULF[a] (n = 74)	Non-primary ISAVUSULF[b] (n = 30)	Other AFT[c] (n = 100)	Overall (n = 204)
Pulmonary	27 (36.5)	6 (20.0)	27 (27.0)	60 (29.4)
Single pathogen				
Mucorales spp. only	9 (12.2)	3 (10.0)	3 (3.0)	15 (7.4)
Aspergillus non-*fumigatus* spp. only	14 (18.9)	3 (10.0)	22 (22.0)	39 (19.1)
Mixed fungal pathogens	2 (2.7)	0	2 (2.0)	4 (2.0)
Disseminated[d]	19 (25.7)	5 (16.7)	23 (23.0)	47 (23.0)
Single pathogen				
Mucorales spp. only	5 (6.8)	1 (3.3)	10 (10.0)	16 (7.8)
Aspergillus non-*fumigatus* spp. only	7 (9.5)	2 (6.7)	8 (8.0)	17 (8.3)
Mixed fungal pathogens	4 (5.4)	2 (6.7)	4 (4.0)	10 (4.9)
Unknown pathogen	0	0	1 (1.0)	1 (0.5)
Extrapulmonary	27 (36.5)	17 (56.7)	50 (50.0)	94 (46.1)
Single pathogen				
Mucorales spp. only	21 (28.4)	12 (40.0)	21 (21.0)	54 (26.5)
Aspergillus non-*fumigatus* spp. only	6 (8.1)	3 (10.0)	15 (15.0)	24 (11.8)
Mixed fungal pathogens	0	2 (6.7)	11 (11.0)	13 (6.4)
Site unknown	1 (1.4)	2 (6.7)	0	3 (1.5)

Note: Data include three patients with only *Aspergillus fumigatus* as the causative organism.

Abbreviations: AFT, antifungal therapies; FAS, full analysis set (all patients who received ≥1 dose of systemic AFT for IM or IA); IA, invasive aspergillosis; IFD, invasive fungal disease; IM, invasive mucormycosis; ISAVUSULF, isavuconazonium sulfate.

[a]Patients received ISAVUSULF as primary therapy against IM or IA.

[b]Patients received non-ISAVUSULF systemic AFT as primary therapy and received ≥1 dose of ISAVUSULF against IM or IA after primary AFT due to refractory infection, AFT intolerance, or oral step-down/maintenance.

[c]Patients received non-ISAVUSULF systemic AFT as primary therapy and received no ISAVUSULF against IM or IA after primary AFT due to refractory infection, AFT intolerance, or oral step-down/maintenance; patients who received ISAVUSULF as prophylaxis or empirical therapy for <4 days were included in this group.

[d]One additional patient in the primary ISAVUSULF group had a possible central nervous system infection (based on magnetic resonance imaging finding of septic emboli), with probable pulmonary infection caused by *Lichtheimia corymbifera* and *A fumigatus*; the patient was treated with combination therapy with ISAVUSULF and liposomal amphotericin B (AmBisome) and later died of septic shock after 14 days.

For patients with IA, those receiving primary ISAVUSULF combination therapy had a 28.2% lower rate of all-cause mortality through Day 42 than those receiving primary ISAVUSULF monotherapy, and those receiving other AFT combination therapy had a 10.9% lower mortality rate than those receiving other AFT monotherapy (Table 6).

By Day 84, the differences in all-cause mortality between monotherapy and combination therapy among patients with IM were 5.0% and 4.9% for the primary ISAVUSULF and other AFT groups, respectively (Table 6). For patients with IA, differences in all-cause mortality between monotherapy and combination therapy were

TABLE 5 All-cause mortality by invasive fungal disease categories (FAS)

	Primary ISAVUSULF[a] (n = 74)	Non-primary ISAVUSULF[b] (n = 30)				Other AFT[c] (n = 100)
		Refractory infection (n = 12)	Intolerance (n = 5)	Oral step-down/ maintenance (n = 13)	Total (n = 30)	
Day 42[d,e], no. deaths/ group total (%)	22/74 (29.7)	5/12 (41.7)	0/5 (0.0)	1/13 (7.7)	6/30 (20.0)	30/100 (30.0)
IM	14/42 (33.3)	3/7 (42.9)	0/3 (0.0)	1/10 (10.0)	4/20 (20.0)	19/46 (41.3)
IA[f]	8/32 (25.0)	2/5 (40.0)	0/2 (0.0)	0/3 (0.0)	2/10 (20.0)	10/53 (18.9)
IA-nf only	4/27 (14.8)	0/3 (0.0)	0/2 (0.0)	0/3 (0.0)	0/8 (0.0)	8/45 (17.8)
Unknown pathogen	0/0	0/0	0/0	0/0	0/0	1/1 (100.0)
Day 84[d,e] no. deaths / group total (%)	29/74 (39.2)	6/12 (50.0)	1/5 (20.0)	1/13 (7.7)	8/30 (26.7)	41/100 (41.0)
IM	17/42 (40.5)	3/7 (42.9)	1/3 (33.3)	1/10 (10.0)	5/20 (25.0)	23/46 (50.0)
IA[f]	12/32 (37.5)	3/5 (60.0)	0/2 (0)	0/3 (0.0)	3/10 (30.0)	17/53 (32.1)
IA-nf only	8/27 (29.6)	1/3 (33.3)	0/2 (0)	0/3 (0.0)	1/8 (12.5)	13/45 (28.9)
Unknown pathogen	0/0	0/0	0/0	0/0	0/0	1/1 (100.0)

Abbreviations: AFT, antifungal therapies; FAS, full analysis set (all patients who received ≥1 dose of systemic AFT for IM or IA); IA, invasive aspergillosis; IA-nf, invasive aspergillosis caused by a non-*fumigatus* species; IM, invasive mucormycosis; ISAVUSULF, isavuconazonium sulfate.

[a]Patients received ISAVUSULF as primary therapy against IM or IA.

[b]Patients received non-ISAVUSULF systemic AFT as primary therapy and received ≥1 dose of ISAVUSULF against IM or IA after primary AFT due to refractory infection, AFT intolerance, or oral step-down/maintenance.

[c]Patients received non-ISAVUSULF systemic AFT as primary therapy and received no ISAVUSULF against IM or IA after primary AFT due to refractory infection, AFT intolerance, or oral step-down/maintenance; patients who received ISAVUSULF as prophylaxis or empirical therapy for <4 days were included in this group.

[d]For the ISAVUSULF and other AFT groups, the day number is relative to the first day of dosing of ISAVUSULF or the primary AFT; Day 84 mortality rates are cumulative.

[e]Includes patients whose survival status was unknown.

[f]Includes three patients with only *Aspergillus fumigatus* as the causative organism, plus five patients with nonspeciated IA.

4.7% and 11.1% for the primary ISAVUSULF and other AFT groups, respectively (Table 6).

3.5 | Adverse events

Fourteen of 111 ISAVUSULF-treated patients experienced ADRs (primary ISAVUSULF: 7/74 [9.5%]; non-primary ISAVUSULF: 7/30 [23.3%]; and ISAVUSULF for prophylaxis, empirical therapy, or for <4 days: 0/7 [0%]) (Table 7). Most ADRs were reported by one patient per group. ADRs reported by >1 patient per group were nausea and vomiting (primary ISAVUSULF 2/74 [2.7%] and non-primary ISAVUSULF 1/30 [3.3%] patients for each ADR), and liver function test increased (primary ISAVUSULF 2/74 [2.7%]). There were no drug-related deaths. ADRs leading to ISAVUSULF discontinuation were experienced by 4/74 (5.4%) patients in the primary ISAVUSULF group and 3/30 (10.0%) patients in the non-primary ISAVUSULF group.

Three (2.7%) patients developed serious ADRs. In the primary ISAVUSULF group, one patient experienced noncardiac chest pain and increases in aspartate aminotransferase and alanine aminotransferase, which were all moderate in severity and considered probably related to ISAVUSULF. Treatment with ISAVUSULF was permanently discontinued based on the chest pain. All serious ADRs were resolved for this patient. In the non-primary ISAVUSULF group, one patient experienced leukopenia of moderate intensity that was resolved, and one patient experienced hypoaesthesia and paraesthesia of severe intensity that did not resolve; all three events were considered to be probably related to ISAVUSULF and led to permanent discontinuation of ISAVUSULF treatment.

4 | DISCUSSION

This US registry study analyses outcomes following the use of currently available AFT to treat IM or IA-nf in clinical practice. Our data expand the experience of ISAVUSULF for IM or IA-nf based on the VITAL and SECURE trials[13,14] and is the largest assessment of treatment and outcomes for these uncommon infections. The registry included seriously ill patients with high rates of renal impairment, haematological malignancies, neutropenia, and disseminated infections.

The outcomes of this study were all-cause mortality and the frequency of ADRs. All-cause mortality is an objective outcome, but effects of AFT on mortality rates are difficult to assess in seriously ill patients with comorbid conditions. In a prior study of patients with haematological malignancies, solid organ transplantation, or underlying immunosuppression, deaths during the first

TABLE 6 All-cause mortality invasive fungal disease categories for monotherapy versus combination therapy (FAS)

	Primary ISAVUSULF[a] monotherapy (n = 24)	Primary ISAVUSULF[a] combination therapy (n = 50)	Primary difference[b]	Other AFT[c] monotherapy (n = 30)	Other AFT[c] combination therapy (n = 70)	Other AFT difference[b]
Day 42[d,e], no. deaths/group total (%)	9/24 (37.5)	13/50 (26.0)	11.5%	11/30 (36.7)	19/70 (27.1)	9.6%
IM	3/9 (33.3)	11/33 (33.3)	0.0%	7/15 (46.7)	12/31 (38.7)	8.0%
IA[f]	6/15 (40.0)	2/17 (11.8)	28.2%	4/15 (26.7)	6/38 (15.8)	10.9%
Day 84[d,e], no. deaths/group total (%)	10/24 (41.7)	19/50 (38.0)	3.7%	14/30 (46.7)	27/70 (38.6)	8.1%
IM	4/9 (44.4)	13/33 (39.4)	5.0%	8/15 (53.3)	15/31 (48.4)	4.9%
IA[f]	6/15 (40.0)	6/17 (35.3)	4.7%	6/15 (40.0)	11/38 (28.9)	11.1%

Abbreviations: AFT, antifungal therapies; FAS, full analysis set (all patients who received ≥1 dose of systemic AFT for IM or IA); IA, invasive aspergillosis; IA-nf, invasive aspergillosis caused by a non-*fumigatus* species; IM, invasive mucormycosis; ISAVUSULF, isavuconazonium sulfate.

[a]ISAVUSULF as primary monotherapy or combination therapy against IM or IA.

[b]Monotherapy (%)–combination therapy (%).

[c]Patients received non-ISAVUSULF systemic AFT as primary monotherapy or combination therapy and received no ISAVUSULF against IM or IA after primary AFT due to refractory infection, AFT intolerance, or oral step-down/maintenance; patients who received ISAVUSULF as prophylaxis or empirical therapy for <4 days were included in this group.

[d]For the ISAVUSULF and other AFT groups, the day number is relative to the first day of dosing of ISAVUSULF or the primary AFT; Day 84 mortality rates are cumulative.

[e]Includes patients whose survival status was unknown.

[f]Includes three patients who had only *Aspergillus fumigatus* as the causative organism, plus five patients who had nonspeciated IA.

ADR, number of patients (%)	Primary ISAVUSULF[a] (n = 74)	Non-primary ISAVUSULF[b] (n = 30)	Other AFT[c] (n = 7)	Overall (n = 111)
ADRs	7 (9.5)	7 (23.3)	0	14 (12.6)
Fatal drug reaction	0	0	0	0
Serious ADR	1 (1.4)	2 (6.7)	0	3 (2.7)
ADR leading to permanent discontinuation of study drug	4 (5.4)	3 (10.0)	0	7 (6.3)

Abbreviations: ADR, adverse drug reaction; AFT, antifungal therapies; ISAVUSULF, isavuconazonium sulfate; SAF, safety analysis set (all patients who received ≥1 dose of ISAVUSULF).

[a]Patients received ISAVUSULF as primary therapy against IM or IA. Includes one patient who had only *Aspergillus fumigatus* as the causative organism.

[b]Patients received non-ISAVUSULF systemic AFT as primary therapy and received ≥1 dose of ISAVUSULF against IM or IA after primary AFT due to refractory infection, AFT intolerance, or oral step-down/maintenance.

[c]Only patients who received ISAVUSULF were included in the SAF, so only those who received ISAVUSULF as prophylaxis or empirical therapy for <4 days were included in this group.

6 weeks of treatment were considered to be the best indicator of AFT efficacy, whereas deaths occurring after 6 weeks were presumed secondary to the patient's underlying disease and its treatment rather than to IFD.[22] For patients enrolled in our registry, we observed a lower all-cause mortality rate in the non-primary ISAVUSULF group (0%–20%) than in the primary ISAVUSULF group (15%–33%) through Day 42. However, almost half of the patients in this group were receiving ISAVUSULF as oral step-down or maintenance therapy, and the remainder received ISAVUSULF to treat refractory infection or due to intolerance to other AFT. Once the reason for non-primary treatment was accounted for, it could be seen that mortality rates were lower among patients receiving oral step-down/maintenance therapy and those who were intolerant to prior treatment, compared with patients with refractory infection—in this last group, mortality rates were higher than rates with primary ISAVUSULF or other AFT. Our results also concur with those of a previous publication that showed that patients intolerant to prior AFT have a better prognosis than patients with infections refractory to prior AFT.[23] Possible confounding factors in our study may be the composition of the non-primary ISAVUSULF group in terms of underlying conditions and the effect of combination therapy in this treatment group. However, without randomisation or case matching, it is difficult to control for these factors. Selection bias may have also occurred in this registry study and may impact the generalisability of our findings to other patients with the same mould infections.

Adverse drug reaction rates were low in our registry, and no unexpected safety issues were identified. There were no ISAVUSULF-related deaths, and serious ADRs were reported in three (2.7%) patients receiving ISAVUSULF. Overall, 12.6% of patients in this study experienced ADRs that were considered related to ISAVUSULF, versus 42% in SECURE, and ADRs leading to permanent discontinuation affected 6.3% in this study and 8.0% in SECURE.[14] The VITAL study

reported treatment-emergent adverse events rather than ADR, so it is not possible to compare those data with this study.[13]

Despite the similarities in the efficacy and safety of ISAVUSULF compared with other studies, we would caution against uncritical comparisons between a registry study focusing on IM and IA-nf and the results of clinical studies in patients with IFD, such as the SECURE study.[14] SECURE was a phase 3 noninferiority study that assessed the efficacy and safety of isavuconazole versus voriconazole in patients with IFD caused by *Aspergillus* spp. or other filamentous fungi. In both SECURE and our registry study, IFD was diagnosed using EORTC/MSG criteria; however, inclusion in our registry was restricted to those with known causative *Aspergillus* spp., primarily focused on non-*fumigatus* spp. In contrast, most cases of IA in the SECURE study were diagnosed based on cytology and serum galactomannan, with very few patients having culture-documented IA and even fewer having IA-nf.[14] Furthermore, unlike our study, patients with hepatic or renal dysfunction were excluded from the SECURE study.

It is of interest that better outcomes were seen in patients in the combination therapy treatment groups. Prior studies have similarly suggested improved outcomes from the treatment of mould infections with more than one AFT.[24] However, definitive statements regarding the potential superiority of combination therapy cannot be made due to the lack of proven benefit in prospective clinical trials and the limitations of prior observational studies that have not been reproducible.[19,25,26]

As with any registry dataset, there are limitations that need to be taken into consideration when interpreting the findings. In this registry, treatment decisions, sample collection, and laboratory testing were at the discretion of the treating clinical team. These factors have the potential to introduce bias. Controlling for baseline factors that may contribute to patient outcomes cannot be performed in a single-arm retrospective registry study. For example, unresolved

neutropenia is associated with all-cause mortality and may limit the effects of AFT, contributing to poor patient outcomes.[27] Only one third of patients in our study were reported to have neutropenia, and the relatively low number may have contributed to a higher rate of favourable outcomes. As these data are from a non-interventional registry without any statistical testing, any hypotheses suggested by these data would need to be tested in a clinical trial setting. Nevertheless, this study presents outcomes from the largest registry of 'real-world' data to date.

In conclusion, our study demonstrates the efficacy and tolerability of ISAVUSULF in clinical practice, supporting the results from clinical trials.[13,14] ISAVUSULF combination therapy was generally associated with lower rates of all-cause mortality than ISAVUSULF monotherapy; however, the number of events within these subgroups was relatively small, and further studies are required to confirm the value of combination therapy in the setting of IM and IA-nf. Additionally, in conjunction with data from other studies,[13,14] ISAVUSULF demonstrated similar efficacy to other AFT and may be better tolerated compared with some other AFT.

CONFLICTS OF INTEREST

G. R. T. has received research grants and consultancy fees from Astellas, Amplyx, Cidara, and Mayne and was on the Data Review Committee (DRC) for Pfizer. M. H. M. has received investigator-initiated research grants and consultancy fees from Astellas and Scynexis. M. H. N. has received research grants from the National Institutes of Health, grants for investigator-initiated research from Astellas, Scynexis, Mayne, Pulmocide, T2Biosystems, and Cidara, and consulting fees from Scynexis, Mayne, and Pulmocide. L. O-Z. has received grants from Astellas, Cidara, Scynexis, and Amplyx and personal fees from Astellas, Pfizer, Therapeutics Inc, Viracor, Octapharma, Mayne, F2G, Gilead, and Cidara. J-A. H. Y. has received research support for the University of Minnesota from Cidara and Scynexis and grants from Astellas and Mayne. C. F. has received research support from Karius. N. M. C. has received a research grant from Astellas Pharma. A. S. has received a grant from Astellas Pharma Global Development, Inc, and personal fees from Scynexis. L. K. and R. C-D. are employees of Astellas Pharma Global Development, Inc. D. P. K. has received research support from Astellas and honoraria from Merck, Astellas, Gilead, Cidaras, Pulmocide, and Mayne Pharmaceuticals. D. P. K. is a member of the Data Review Committee of Cidaras, Inc, and AbbVie, Inc. He acknowledges the Robert C Hickey Chair endowment. J. G-D. and R. N. G. have none to declare.

AUTHOR CONTRIBUTION

George R. Thompson: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – review & editing (equal). Julia Garcia-Diaz: Data curation (equal); Writing – review & editing (equal). Marisa H. Miceli: Data curation (equal); Writing – review & editing (equal). M. Hong Nguyen: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – review & editing (equal). Luis Ostrosky-Zeichner: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – review & editing (equal). Jo-Anne H. Young: Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – review & editing (equal). Cynthia E. Fisher: Data curation (equal); Formal analysis (equal); Writing – review & editing (equal). Nina M. Clark: Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – review & editing (equal). Richard N. Greenberg: Data curation (equal); Writing – review & editing (equal). Andrej Spec: Data curation (equal); Formal analysis (equal); Writing – review & editing (equal). Laura Kovanda: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – review & editing (equal). Rodney Croos-Dabrera: Formal analysis (equal); Writing – review & editing (equal). Dimitrios P. Kontoyiannis: Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – review & editing (equal).

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