1

2   DR GEORGE RICHARD THOMPSON (Orcid ID : 0000-0001-8518-5750)

3   DR MARISA H. MICELI (Orcid ID : 0000-0002-3175-0512)

4   DR DIMITRIOS KONTOYIANNIS (Orcid ID : 0000-0002-8051-2940)

5

6

8

9

10   **Systemic antifungal therapy with isavuconazonium sulfate or other agents in adults**

11   **with invasive mucormycosis or invasive aspergillosis (non-*fumigatus*): A multicentre,**

12   **non-interventional registry study**

13   **Running title:** Isavuconazole in mucormycosis/aspergillosis

14   George R. Thompson III*[1] (ORCID ID 0000-0001-8518-5750), Julia Garcia-Diaz[2], Marisa H.

15   Miceli[3], M. Hong Nguyen[4], Luis Ostrosky-Zeichner[5], Jo-Anne H. Young[6], Cynthia E.

16   Fisher[7], Nina M. Clark[8], Richard N. Greenberg[9], Andrej Spec[10], Laura Kovanda[11], Rodney

17   Croos-Dabrera[11], Dimitrios P. Kontoyiannis[12]

18

19   [1]UC Davis Health, Sacramento, California, USA; [2]Ochner Clinic Foundation, New Orleans,

20   Louisiana, USA; [3]University of Michigan, Ann Arbor, Michigan, USA; [4]University of

21   Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; [5]McGovern Medical School,

22   Houston, Texas, USA; [6]University of Minnesota, Minneapolis, Minnesota, USA; [7]University

23   of Washington, Seattle, Washington, USA; [8]Loyola Stritch School of Medicine, Maywood,

24   Illinois, USA; [9]University of Kentucky, Lexington, Kentucky, USA; [10]Washington

25   University in St. Louis School of Medicine, St. Louis, Missouri, USA; [11]Astellas Pharma

26   Global Development, Inc., Northbrook, Illinois, USA; [12]MD Anderson Cancer Center,

27   University of Texas, Houston, Texas, USA

28   ***Corresponding author:**

29   George R. Thompson III, MD

30   Associate Professor of Medicine

31   4150 V Street, Suite G500

32   Department of Internal Medicine, Division of Infectious Diseases

33   Department of Medical Microbiology and Immunology

34   University of California-Davis Health

35   grthompson@ucdavis.edu

36

37

38

76 **Ethics**

77 The Institutional Review Boards from each centre approved the study before it was
78 conducted. The study was conducted in accordance with Good Clinical Practice (GCP), the
79 International Council for Harmonisation (ICH) guidelines, applicable regulations and
80 guidelines governing clinical study conduct and the ethical principles of the Declaration of
81 Helsinki.

82

83 **Word count (max. 3500)**: 3585 (after peer-review revisions)

84   **ABSTRACT**

85   [248/250 words]

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

90   **Objectives**: To determine all-cause mortality and safety outcomes among adults with IM
91   and/or IA non-*fumigatus* (nf) treated with ISAVUSULF or other antifungal therapies (AFT).

92   **Patients and methods**: This multicentre, non-interventional registry enrolled patients aged
93   ≥18 years with IM or IA-nf who received systemic AFT January 2016–November 2018.
94   Patients received primary ISAVUSULF, non-primary ISAVUSULF, or other AFT, as
95   monotherapy or combination therapy. The primary endpoint was all-cause mortality at Days
96   42 and 84; safety outcomes were adverse drug reactions (ADRs) to ISAVUSULF.

97   **Results**: Of 204 patients enrolled, 74 received primary ISAVUSULF, 30 non-primary
98   ISAVUSULF and 100 other AFT. All-cause mortality through Day 42 was numerically lower
99   in the non-primary ISAVUSULF group than in the primary ISAVUSULF and other AFT
100   groups, for patients with IM (20% vs 33.3% and 41.3%, respectively) or IA-nf (0% vs 14.8%
101   and 17.8%). All-cause mortality tended to be lower with combination therapy than
102   monotherapy, except for patients with IM receiving primary ISAVUSULF. Of 111 patients
103   receiving ISAVUSULF, 14 (12.6%) reported ADRs, of whom 3 (2.7%) developed serious
104   ADRs. There were no drug-related deaths.

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

108   **Keywords:** antifungals, azoles, invasive aspergillosis, invasive mucormycosis,
109   isavuconazonium sulfate, non-*fumigatus Aspergillus*

110

111

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 (e.g. surgical intervention), influence clinical outcomes. The correlation between *in vitro* susceptibility and observed i*n 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 non-inferior 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 U.S. registry study (INQUIRE) of adults with IM or IA-nf who were treated with ISAVUSULF or other systemic AFT.

PATIENTS AND METHODS

Ethics

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

149   **Study design and participants**

150   This was a multicentre, non-interventional registry study. The aim was to assess data
151   from 33 U.S. centres for patients treated with systemic AFT for IM or IA-nf between January
152   2016 and November 2018. The study was to include patients aged ≥18 years at the time of
153   systemic AFT with proven or probable IM or IA-nf according to the 2008 European
154   Organisation for Research and Treatment of Cancer Invasive Fungal Infections Cooperative
155   Group/Mycoses Study Group (EORTC/MSG) criteria.[20] Those with multiple fungal
156   pathogens were eligible for inclusion into the study cohort; for these patients, the hierarchy
157   for categorisation was IM then IA if both were present. Patients were excluded from the study
158   if they received surgical treatment only for IM or IA-nf, had participated previously in this
159   registry, or had received an investigational drug for an invasive fungal disease (IFD) within
160   30 days of starting treatment with an approved AFT. There were no exclusions based on
161   liver/renal dysfunction. The study-defined data collection period began on the first date of
162   systemic AFT initiation through Day 84, or for 84 days after ISAVUSULF initiation,
163   whichever was longer. Data could be collected prospectively or retrospectively, provided that
164   the patient had a known vital status at Day 42.

165   **Treatment procedures**

166   Enrolled patients were treated by their physicians as per standard clinical practice. For
167   the analysis, participants were split into three groups according to systemic AFT use: primary
168   ISAVUSULF, non-primary ISAVUSULF, and other AFT. The 'primary ISAVUSULF' group
169   received ISAVUSULF as the primary AFT for IM or IA, either as monotherapy, or in
170   combination or sequentially with another systemic AFT. The 'non-primary ISAVUSULF'
171   group received primary therapy with a non-ISAVUSULF systemic AFT (as monotherapy, or

172 in combination or sequentially with another systemic AFT) and then received ≥1 dose of
173 ISAVUSULF due to refractory infection, AFT intolerance or oral step-down/maintenance
174 during treatment for the same IM or IA infection. The 'other AFT' group received non-
175 ISAVUSULF systemic AFT (as monotherapy, or in combination or sequentially with
176 additional AFT) as primary therapy and did not receive ISAVUSULF at a later date for their
177 infection. Individuals who received ISAVUSULF as prophylaxis or empirical therapy for <4
178 days, with no additional ISAVUSULF treatment administered, were included in the other
179 AFT group.

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

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

196 **Outcomes/endpoints**

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

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

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

211   **Statistical analyses**

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

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

225   **RESULTS**

226   **Patient disposition and baseline characteristics**

227   Patient disposition is shown in Fig. 1. In total, 204 patients were enrolled and
228   included in the FAS (104 ISAVUSULF and 100 other AFT). Of those receiving
229   ISAVUSULF, 74 (71.2%) patients received ISAVUSULF as primary AFT (24 monotherapy,
230   50 combination therapy) and 30 (28.8%) as non-primary AFT (11 monotherapy, 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 non-speciated *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 non-haematological malignancies, which was 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, neutropaenia, 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.

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

262 [26.7%]). Mixed fungal pathogens accounted for 27 (13.2%) of the IFD in the FAS. In the

263 primary ISAVUSULF group, mixed pathogens occurred only in patients with Mucorales spp.

264 (6/74 [8.1%]),and were more common than *Aspergillus* mixed infections in the other AFT

265 group (12.0% vs 5.0% of patients, respectively).

266 Mucorales species included *Cunninghamella* spp., *Lichtheimia corymbifera*, *Rhizopus*

267 spp., *Rhizomucor* spp., *Syncephalastrum* spp., *Apophysomyces elegans*, *Apophysomyces*

268 *variabilias* and Mucor spp. IA-nf species included *Aspergillus calidoustus*, *A. clavatus*, *A.*

269 *flavus*, *A. glaucus*, *A. lentulus*, *A. nidulans*, *A. niger*, *A. ochraceus*, *A. tamarii*, *A. terreus*, *A.*

270 *ustus* and *A. versicolor*. Susceptibility data were not available for the majority of organisms.

271 In the INQUIRE registry, 46.1% of patients had extrapulmonary IFD, 29.4% had

272 pulmonary IFD and 23.0% had disseminated IFD (defined as IFD in >1 non-contiguous site

273 or in the blood) (Table 4). Overall, the proportions of patients with pulmonary,

274 extrapulmonary, and disseminated IFD were similar across the primary ISAVUSULF, non-

275 primary ISAVUSULF, and other AFT groups. IM was more common than IA-nf in

276 extrapulmonary IFD (26.5% vs 11.8%) and IA-nf was more common than IM in pulmonary

277 IFD (19.1% vs 7.4%). IM and IA-nf accounted for similar proportions of disseminated IFD

278 (7.8% vs 8.3%).

279 **Treatment**

280 Of the 108 patients with single pathogen or mixed pathogen IM, 68 (63.0%)

281 underwent surgical treatment for IFD (primary ISAVUSULF n = 26, non-primary

282 ISAVUSULF n = 15 and other AFT n = 27). Of the 87 patients with single pathogen or

283 mixed pathogen IA-nf, 22 (25.3%) underwent surgical treatment for IFD (primary

284 ISAVUSULF n = 7, non-primary ISAVUSULF n = 2 and other AFT n = 13).

285 In patients with IM, the mean (SD) duration of systemic AFT was 66.0 (83.4) days

286 with primary ISAVUSULF, 77.6 (41.9) days with non-primary ISAVUSULF and 49.9 (32.9)

287 days with other AFT. In patients with IA (including patients with *A. fumigatus* only and

288 patients with non-speciated *Aspergillus*), the mean (SD) duration of systemic AFT was 65.1

289 (43.5) days with primary ISAVUSULF, 85.0 (28.6) days with non-primary ISAVUSULF and

290 57.0 (31.4) days with other AFT.

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 IFI (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).

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

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, 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 non-cardiac 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 resolved for this patient. In the non-primary ISAVUSULF group, one patient experienced leukopaenia of moderate intensity that 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.

DISCUSSION

This U.S. 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, neutropaenia, 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,

352   deaths during the first 6 weeks of treatment were considered to be the best indicator of AFT

353   efficacy, while deaths occurring after 6 weeks were presumed secondary to the patient's

354   underlying disease and its treatment rather than to IFD.[22] For patients enrolled in our registry,

355   we observed a lower all-cause mortality rate in the non-primary ISAVUSULF group (0–20%)

356   than in the primary ISAVUSULF group (15–33%) through Day 42. However, almost half of

357   the patients in this group were receiving ISAVUSULF as oral step-down or maintenance

358   therapy, while the remainder received ISAVUSULF to treat refractory infection or due to

359   intolerance to other AFT. Once the reason for non-primary treatment was accounted for, it

360   could be seen that mortality rates were lower among patients receiving oral step-

361   down/maintenance therapy and those who were intolerant to prior treatment, compared with

362   patients with refractory infection – in this last group, mortality rates were higher than rates

363   with primary ISAVUSULF or other AFT. Our results also concur with those of a previous

364   publication that showed that patients intolerant to prior AFT have a better prognosis than

365   patients with infections refractory to prior AFT.[23] Possible confounding factors in our study

366   may be the composition of the non-primary ISAVUSULF group in terms of underlying

367   conditions and the effect of combination therapy in this treatment group. However, without

368   randomization or case matching, it is difficult to control for these factors. Selection bias may

369   have also occurred in this registry study and may impact the generalizability of our findings

370   to other patients with the same mould infections.

371   ADR rates were low in our registry and no unexpected safety issues were identified.

372   There were no ISAVUSULF-related deaths, while serious ADRs were reported in 3 (2.7%)

373   patients receiving ISAVUSULF. Overall, 12.6% of patients in this study experienced ADRs

374   that were considered related to ISAVUSULF, versus 42% in SECURE, while ADRs leading

375   to permanent discontinuation affected 6.3% in this study and 8.0% in SECURE.[14] The

376   VITAL study reported treatment-emergent adverse events rather than ADR, so it is not

377   possible to compare those data with this study.[13]

378   Despite the similarities in the efficacy and safety of ISAVUSULF compared with

379   other studies, we would caution against uncritical comparisons between a registry study

380   focusing on IM and IA-nf, and the results of clinical studies in patients with IFD, such as the

381   SECURE study.[14] SECURE was a phase 3 non-inferiority study that assessed the efficacy and

382   safety of isavuconazole versus voriconazole in patients with IFD caused by *Aspergillus* spp.

383   or other filamentous fungi. In both SECURE and our registry study, IFD was diagnosed using

384   EORTC/MSG criteria; however, inclusion in our registry was restricted to those with known

385   causative *Aspergillus* spp, primarily focused on non-*fumigatus* spp. In contrast, most cases of

386   IA in the SECURE study were diagnosed based on cytology and serum galactomannan, with

387   very few patients having culture-documented IA and even fewer having IA-nf.[14]

388   Furthermore, unlike our study, patients with hepatic or renal dysfunction were excluded from

389   the SECURE study.

390   It is of interest that better outcomes were seen in patients in the combination therapy

391   treatment groups. Prior studies have similarly suggested improved outcomes from the

392   treatment of mould infections with more than one AFT.[24] However, definitive statements

393   regarding the potential superiority of combination therapy cannot be made due to the lack of

394   proven benefit in prospective clinical trials, and the limitations of prior observational studies

395   that have not been reproducible.[19,25,26]

396   As with any registry dataset, there are limitations that need to be taken into

397   consideration when interpreting the findings. In this registry, treatment decisions, sample

398   collection and laboratory testing were at the discretion of the treating clinical team. These

399   factors have the potential to introduce bias. Controlling for baseline factors that may

400   contribute to patient outcomes cannot be performed in a single-arm retrospective registry

401   study. For example, unresolved neutropaenia is associated with all-cause mortality and may

402   limit the effects of AFT, contributing to poor patient outcomes.[27] Only one-third of patients in

403   our study were reported to have neutropaenia, and the relatively low number may have

404   contributed to a higher rate of favourable outcomes. As these data are from a non-

405   interventional registry without any statistical testing, any hypotheses suggested by these data

406   would need to be tested in a clinical trial setting. Nevertheless, this study presents outcomes

407   from the largest registry of 'real-world' data to date.

408   In conclusion, our study demonstrates the efficacy and tolerability of ISAVUSULF in

409   clinical practice, supporting the results from clinical trials.[13,14] ISAVUSULF combination

410   therapy was generally associated with lower rates of all-cause mortality than ISAVUSULF

411   monotherapy; however, the number of events within these subgroups was relatively small,

412   and further studies are required to confirm the value of combination therapy in the setting of

413   IM and IA-nf. Additionally, in conjunction with data from other studies,[13,14] ISAVUSULF

414   demonstrated similar efficacy to other AFT and may be better tolerated compared with some

415   other AFT.

416

417

418

419 **DATA SHARING**

420 Researchers may request access to anonymized participant level data, trial level data and
421 protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com For
422 the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-
423 Sponsors/Study-Sponsors-Astellas.aspx.

424 **Author contributions**

425 Conception: G.R.T., M.H.N., L.O-Z., L.L.K.

426 Study design and conduct: G.R.T., M.H.N., L.O-Z., J-A.H.Y., N.M.C., L.L.K., D.P.K.

427 Data acquisition: G.R.T., J.G-D., M.H.M., M.H.N., L.O-Z., J-A.H.Y., C.E.F., N.M.C,
428 R.N.G., A.S., L.L.K., D.P.K.

429 Analysis and interpretation: G.R.T., M.H.N., L.O-Z., J-A.H.Y., C.E.F., N.M.C, A.S., L.L.K.,
430 R.C-D., D.P.K.

431 Writing: G.R.T., J.G-D., M.H.M., M.H.N., L.O-Z., J-A.H.Y., C.E.F., N.M.C, R.N.G., A.S.,
432 L.L.K., R.C-D., D.P.K.

433

REFERENCES

1. Latgé JP, Chamilos G. *Aspergillus fumigatus* and aspergillosis in 2019. *Clin Microbiol Rev* 2020; **33**. Available at: http://cmr.asm.org/. Accessed February 11, 2021.

2. Kontoyiannis DP, Marr KA, Park BJ, *et al.* Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) database. *Clin Infect Dis* 2010; **50**: 1091–100.

3. Neofytos D, Horn D, Anaissie E, *et al.* Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of multicenter Prospective Antifungal Therapy (PATH) alliance registry. *Clin Infect Dis* 2009; **48**: 265–73.

4. Friedman DZP, Schwartz IS. Emerging fungal infections: New patients, new patterns, and new pathogens. *J Fungi* 2019; **5**: 67.

5. Jenks JD, Hoenigl M. Treatment of aspergillosis. *J Fungi* 2018; **4**: 1–17.

6. Reid G, Lynch III JP, Fishbein MC, Clark NM. Mucormycosis. *Semin Respir Crit Care Med* 2020; **41**: 99–114.

7. Lamoth F, Kontoyiannis DP. Therapeutic challenges of non-*Aspergillus* invasive mold infections in immunosuppressed patients. *Antimicrob Agents Chemother* 2019; **63**: e01244-19.

8. Johnson G, Ferrini A, Dolan SK, *et al.* Biomarkers for invasive aspergillosis: the challenges continue. *Biomark Med* 2014; **8**: 429–51.

9. Dudakova A, Spiess B, Tangwattanachuleeporn M, *et al.* Molecular tools for the detection and deduction of azole antifungal drug resistance phenotypes in *Aspergillus* species. *Clin Microbiol Rev* 2017; **30**: 1065–91.

10. Cornely OA, Arikan-Akdagli S, Dannaoui E, *et al.* ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clin Microbiol Infect* 2014; **20**: 5–26.

11. Tortorano AM, Richardson M, Roilides E, *et al.* ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and

462 others. *Clin Microbiol Infect* 2014; **20**: 27–46.

12. Jenks JD, Salzer HJF, Prattes J, Krause R, Buchheidt D, Hoenigl M. Spotlight on
isavuconazole in the treatment of invasive aspergillosis and mucormycosis: design,
development, and place in therapy. *Drug Des Devel Ther* 2018; **12**: 1033–44.

13. Marty FM, Ostrosky-Zeichner L, Cornely OA, *et al.* Isavuconazole treatment for
mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis*
2016; **16**: 828–37.

14. Maertens JA, Raad II, Marr KA, *et al.* Isavuconazole versus voriconazole for primary
treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi
(SECURE): A phase 3, randomised-controlled, non-inferiority trial. *Lancet* 2016; **387**: 760–9.

15. European Medicines Agency. *Cresemba (isavuconazole) product information*. 2019.
Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/cresemba#product-
information-section. Accessed February 19, 2021.

16. US Food and Drug Administration. *Cresemba (isavuconazonium sulfate) prescribing
information*. 2015. Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207500orig1s000lbl.pdf.
Accessed February 19, 2021.

17. Stern A, Su Y, Lee YJ, *et al.* A single-center, open-label trial of isavuconazole
prophylaxis against invasive fungal infection in patients undergoing allogeneic hematopoietic
cell transplantation: isavuconazole for antifungal prophylaxis following HCT. *Biol Blood
Marrow Transplant* 2020; **26**: 1195–202.

18. Seyedmousavi S, Lionakis MS, Parta M, Peterson SW, Kwon-Chung KJ. Emerging
Aspergillus species almost exclusively associated with primary immunodeficiencies. *Open
Forum Infect Dis* 2018; **5**: ofy213.

19. Abidi MZ, Sohail MR, Cummins N, *et al.* Stability in the cumulative incidence, severity
and mortality of 101 cases of invasive mucormycosis in high-risk patients from 1995 to 2011:
a comparison of eras immediately before and after the availability of voriconazole and
echinocandin-amphotericin c. *Mycoses* 2014; **57**: 687–98.

20. De Pauw B, Walsh TJ, Donnelly JP, *et al.* Revised definitions of invasive fungal disease

491   from the European Organization for Research and Treatment of Cancer/Invasive Fungal

492   Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases

493   Mycoses Study Group (EORTC/MSG) c. *Clin Infect Dis* 2008; **46**: 1813–21.

494   **21**. Cornely OA, Hoenigl M, Lass-Flörl C, *et al.* Defining breakthrough invasive fungal

495   infection–Position paper of the mycoses study group education and research consortium and

496   the European Confederation of Medical Mycology. *Mycoses* 2019; **62**: 716–29.

497   **22**. Wingard JR, Ribaud P, Schlamm HT, Herbrecht R. Changes in causes of death over time

498   after treatment for invasive aspergillosis. *Cancer* 2008; **112**: 2309–12.

499   **23**. Perfect JR, Marr KA, Walsh TJ, *et al.* Voriconazole treatment for less-common,

500   emerging, or refractory fungal infections. *Clin Infect Dis* 2003; **36**: 1122–31.

501   **24**. Marr KA, Schlamm HT, Herbrecht R, *et al.* Combination antifungal therapy for invasive

502   aspergillosis: a randomized trial. *Ann Intern Med* 2015; **162**: 81–9.

503   **25**. Reed C, Bryant R, Ibrahim AS, *et al.* Combination polyene-caspofungin treatment of

504   rhino-orbital-cerebral mucormycosis. *Clin Infect Dis* 2008; **47**: 364–71.

505   **26**. Kyvernitakis A, Torres HA, Jiang Y, Chamilos G, Lewis RE, Kontoyiannis DP. Initial

506   use of combination treatment does not impact survival of 106 patients with haematologic

507   malignancies and mucormycosis: a propensity score analysis. *Clin Microbiol Infect* 2016; **22**:

508   811.e1-811.e8.

509   **27**. Kontoyiannis DP, Selleslag D, Mullane K, *et al.* Impact of unresolved neutropenia in

510   patients with neutropenia and invasive aspergillosis: A post hoc analysis of the SECURE

511   trial. *J Antimicrob Chemother* 2018; **73**: 757–63.

512

TABLES

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)†	10 (90.9) †	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[‡]	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)[†]	8 (100)[†]	2 (5.3)[§]
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[¶]
Amphotericin B			
Liposomal (AmBisome)	0	0	1 (100.0)
Posaconazole	0	0	1 (100.0)

AFT, antifungal therapy, 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. 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 (%). †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. ‡Includes two patients with non-speciated IA; excludes patients with only *Aspergillus fumigatus* as the causative organism. §Two patients with IA in the 'Other AFT' group received ISAVUSULF as empirical therapy. ¶One patient with an unknown pathogen received other AFT as combination therapy.

Table 2. Patient baseline characteristics (FAS)

Characteristic	IM				IA†				Unknown pathogen
	Primary ISAVUSULF‡ (n = 42)	Non-primary ISAVUSULF§ (n = 20)	Other AFT¶ (n = 46)	Overall (n = 108)	Primary ISAVUSULF‡ (n = 32)	Non-primary ISAVUSULF§ (n = 10)	Other AFT¶ (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 m^2, 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
Neutropaenia, 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

| Characteristic | IM | | | | IA[†] | | | | Unknown pathogen |
	Primary ISAVUSULF[‡] (n = 42)	Non-primary ISAVUSULF[§] (n = 20)	Other AFT[¶] (n = 46)	Overall (n = 108)	Primary ISAVUSULF[‡] (n = 32)	Non-primary ISAVUSULF[§] (n = 10)	Other AFT[¶] (n = 53)	Overall (n = 95)	Other AFT (n = 1)
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

AFT, antifungal therapy; 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; ISAVUSULF, isavuconazonium sulfate; IM, invasive mucormycosis; SD, standard deviation. [†]Includes three patients with only *Aspergillus fumigatus* as the causative organism plus five patients with non-speciated IA. [‡]Patients received ISAVUSULF as primary therapy against IM or IA. [§]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. [¶]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.

Table 3. Pathogens causing invasive fungal disease (FAS)

Pathogen causing IFD, n (%)	Primary ISAVUSULF[†] (n = 74)	Non-primary ISAVUSULF[‡] (n = 30)	Other AFT[§] (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[¶]	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)

AFT, antifungal therapy; IA, invasive aspergillosis; FAS, full analysis set (all patients who received ≥1 dose of systemic AFT for IM or IA); IFD, invasive fungal disease; IM, invasive mucormycosis; ISAVUSULF, isavuconazonium sulfate. For mixed pathogens, the hierarchy for categorisation was IM then IA if both were present. [†]Patients received ISAVUSULF as primary therapy against IM or IA. [‡]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. [§]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. [¶]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.

Table 4. Site of infection (FAS)

Site/pathogen causing IFD, n (%)	Primary ISAVUSULF[†] (n = 74)	Non-primary ISAVUSULF[‡] (n = 30)	Other AFT[§] (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[¶]	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)

AFT, antifungal therapy; 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. Data include three patients with only *Aspergillus fumigatus* as the causative organism. [†]Patients received ISAVUSULF as primary

therapy against IM or IA. ‡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. §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. ¶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.

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

	Primary ISAVUSULF[†] (n = 74)	Non-primary ISAVUSULF[‡] (n = 30)				Other AFT[§] (n = 100)
		Refractory infection (n = 12)	Intolerance (n = 5)	Oral step-down/ maintenance (n = 13)	Total (n = 30)	
Day 42[¶,#], 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[††]	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[¶, #] 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)

	Primary ISAVUSULF† (n = 74)	Non-primary ISAVUSULF‡ (n = 30)				Other AFT§ (n = 100)
		Refractory infection (n = 12)	Intolerance (n = 5)	Oral step-down/ maintenance (n = 13)	Total (n = 30)	
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††	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)

AFT, antifungal therapy; 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; ISAVUSULF, isavuconazonium sulfate; IM, invasive mucormycosis

†Patients received ISAVUSULF as primary therapy against IM or IA. ‡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. §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. ¶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. #Includes patients whose survival status was unknown. ††Includes three patients with only *Aspergillus fumigatus* as the causative organism, plus five patients with non-speciated IA.

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

	Primary ISAVUSULF[†] monotherapy (n = 24)	Primary ISAVUSULF[†] combination therapy (n = 50)	Primary difference[‡]	Other AFT[§] monotherapy (n = 30)	Other AFT[§] combination therapy (n = 70)	Other AFT difference[‡]
Day 42[¶, #], 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[††]	6/15 (40.0%)	2/17 (11.8)	28.2%	4/15 (26.7)	6/38 (15.8)	10.9%
Day 84[¶, #], 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[††]	6/15 (40.0)	6/17 (35.3)	4.7%	6/15 (40.0)	11/38 (28.9)	11.1%

AFT, antifungal therapy; 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. [†]ISAVUSULF as primary monotherapy or combination therapy against IM or IA. [‡]Monotherapy (%) – Combination therapy (%). [§]Patients

received non-ISAVUSULF systemic AFT as primary mono- 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. ¶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. #Includes patients whose survival status was unknown. ††Includes three patients who had only *Aspergillus fumigatus* as the causative organism, plus five patients who had non-speciated IA.

**Table 7. Adverse drug reactions to ISAVUSULF (SAF)**

ADR, number of patients (%)	Primary ISAVUSULF[†] (n = 74)	Non-primary ISAVUSULF[‡] (n = 30)	Other AFT[§] (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)

ADR, adverse drug reaction; AFT, antifungal therapy; ISAVUSULF, isavuconazonium sulfate; SAF, safety analysis set (all patients who received ≥1 dose of ISAVUSULF).
[†]Patients received ISAVUSULF as primary therapy against IM or IA. Includes one patient who had only *Aspergillus fumigatus* as the causative organism. [‡]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. [§]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.

FIGURES

Figure 1. Patient disposition
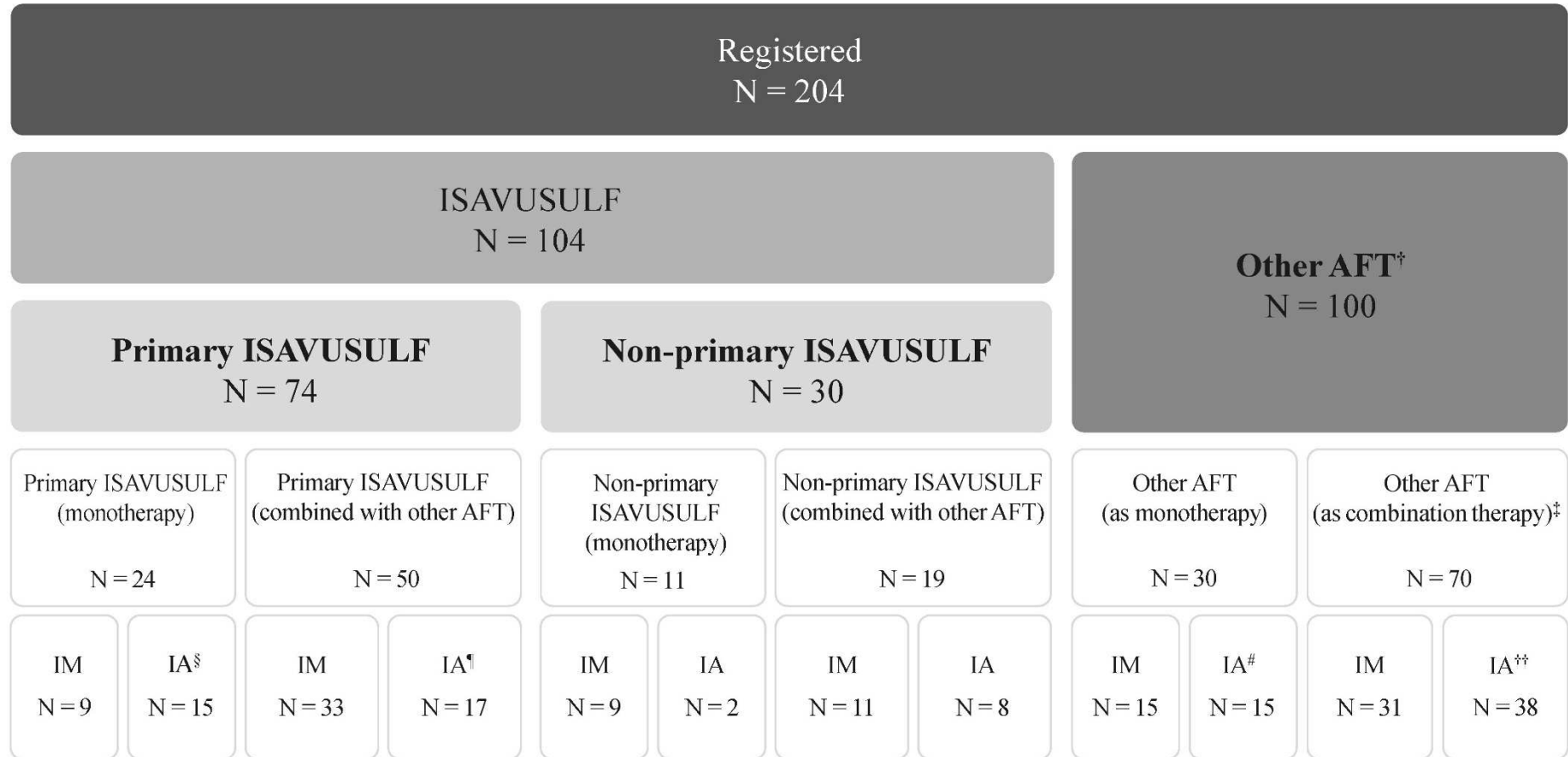
AFT, antifungal therapy; IA, invasive aspergillosis; ISAVUSULF, isavuconazonium sulfate; IM, invasive mucormycosis. Bold text indicates treatment groups. †Includes seven patients who received ISAVUSULF for prophylaxis or empirical therapy for <4 days. ‡Includes one patient with an unknown pathogen. §Includes one patient with only *Aspergillus fumigatus* as the causative organism, and two patients with non-speciated IA. ¶Includes two patients with non-speciated IA. #Includes one patient with non-speciated IA. ††Includes two patients with only *Aspergillus fumigatus* as the causative organism.

Registered
N = 204

ISAVUSULF
N = 104

Other AFT†
N = 100

Primary ISAVUSULF
N = 74

Non-primary ISAVUSULF
N = 30

Primary ISAVUSULF
(monotherapy)

N = 24

Primary ISAVUSULF
(combined with other AFT)

N = 50

Non-primary
ISAVUSULF
(monotherapy)
N = 11

Non-primary ISAVUSULF
(combined with other AFT)

N = 19

Other AFT
(as monotherapy)

N = 30

Other AFT
(as combination therapy)‡

N = 70

IM	IA§	IM	IA¶	IM	IA	IM	IA	IM	IA#	IM	IA††
N = 9	N = 15	N = 33	N = 17	N = 9	N = 2	N = 11	N = 8	N = 15	N = 15	N = 31	N = 38