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CADTH COMMON DRUG REVIEW

Clinical Review Report

ISAVUCONAZOLE (CRESEMBA)

(AVIR Pharma Inc.)

Indication: Invasive aspergillosis and invasive mucormycosis.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AmB	amphotericin B
AmB-D	amphotericin B deoxycholate
CI	confidence interval
IA	invasive aspergillosis
IFD	invasive fungal disease
IFI	invasive fungal infection
IM	invasive mucormycosis
ISA	isavuconazole
ITT	intention-to-treat
IV	intravenous
L-AmB	liposomal amphotericin B
mITT	modified intention-to-treat
myITT	mycological intention-to-treat
NMA	network meta-analysis
RCT	randomized controlled trial
SAS	safety analysis set
TEAE	treatment-emergent adverse event
VRC	voriconazole
WDAE	withdrawal due to adverse event

Drug	Isavuconazole (Cresemba)
Indication	Cresemba (isavuconazole, as isavuconazonium sulfate) is an azole antifungal indicated for use in adults for the treatment of: • invasive aspergillosis • invasive mucormycosis
Reimbursement Request	Per Health Canada indications: in adults for the treatment of: • invasive aspergillosis • invasive mucormycosis
Dosage Form(s)	Oral capsules, 100 mg IV infusion: Powder for solution for intravenous infusion, 200 mg
NOC Date	December 19, 2018
Manufacturer	AVIR Pharma Inc.

Executive Summary

Introduction

Fungal diseases are opportunistic infections caused by fungi. Fungal disease may become invasive (i.e., invasive fungal disease [IFD]) and life-threatening in a high-risk population, such as patients with bone marrow transplant, patients with HIV infection, and immunosuppressed patients, especially those with neutropenia.[1,2] In Canada, it was estimated that the incidence of IFDs was 1.6 per 100,000 people.[2,3] In Canada, *Candida* accounts for 85.0% of all fungal disease in the high-risk population, *Aspergillus* for 14.4%, *Cryptococcus* for 2.0% and *Mucorales* for 0.9%.[4] *Aspergillus* causes aspergillosis with three main clinical forms: invasive aspergillosis (IA), chronic aspergillosis, and allergic aspergillosis.[5] *Rhizopus*, (*Mucor*, *Cunninghamella bertholletiae*, *Apophysomyces*, and *Lichtheimia*) cause invasive mucormycosis (IM).[1] No Canadian prevalence and incidence data were available for IM.[6] The systems most commonly affected by IFDs are the respiratory (e.g., lungs), skin, and digestive systems (especially for IM). The common clinical symptoms of IA are fever, chest pain, cough, and shortness of breath.[6] IM presents with similar clinical features, with the brain as the most common site of dissemination.[6] In current clinical practice, establishing a definitive diagnosis of IA or IM remains a challenge.[7] Clinically, IA and IM are life-threatening infections with a mortality rate approaching 100% if untreated or if treatment is delayed.[8]

Prior to the approval of isavuconazole (ISA), systemic antifungal drugs approved by Health Canada for the treatment of IA included voriconazole (VRC), posaconazole, itraconazole, amphotericin B (AmB), and caspofungin; posaconazole and caspofungin specifically have Health Canada indications for patients whose IA is refractory or who are intolerant of other antifungals.[9-15] Of the aforementioned antifungal drugs, only AmB is approved by Health Canada for the treatment of IM. Three formulations of AmB are available in Canada: AmB deoxycholate (AmB-D; Fungizone),[16] liposomal AmB (L-AmB; AmBisome),[14] and AmB lipid complex (Abelcet).[15] Due to its renal toxicity, Fungizone is no longer commonly used in Canada. The clinical expert consulted for this review indicated that AmBisome is the most commonly used formulation of AmB in Canada. The CADTH Common Drug Review (CDR)

clinical expert indicated that VRC, itraconazole, and caspofungin are empirically used for the treatment of IA, while posaconazole and AmB are empirically used for IM or IA.

The optimal strategy for managing IFDs (e.g., IA and IM) includes prevention and early treatment aimed at eradicating the fungal infection. Empirical treatment with AmB, which can only be used intravenously, has been used for both IA and IM. However, several factors — such as the inconvenience of long-term intravenous (IV) infusion, infusion-related adverse events, and renal toxicity — have limited the use of AmB. VRC is more commonly used to treat suspected IA in high-risk patients with fever. However, patients with suspected IA may actually have IM caused by *Mucorales*, as clinical manifestations of IM are similar to IA. Since VRC has no effect on IM, its use may delay and compromise the future successful treatment of IM.[1,6] Antifungal drugs that treat both IA and IM would expand the options for the empirical treatment of IFDs and minimize the risk of delaying treatment of potentially late-diagnosed IM.[6,17]

ISA belongs to the azole antifungal drug class. It is approved by Health Canada as an antifungal drug for use in adults for the treatment of both IA and IM. It is available as an oral (100 mg capsules) and IV drug (200 mg powder for IV infusion solution). The Health Canada–recommended dose in the treatment IA or IM is 200 mg (IV or oral) every eight hours for 48 hours (six doses), followed by a maintenance dose of 200 mg (IV or oral) once daily.[10]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of ISA compared with the other available antifungal drugs marketed in Canada for the treatment of IA or IM.

Results and Interpretation

Included Studies

The evidence for this CDR submission was obtained from two clinical trials: the SECURE and VITAL studies. The SECURE study was a double-blind, multi-centre, noninferiority randomized controlled trial (RCT), while the VITAL study was an open-label single-arm trial. Both trials were conducted in multiple regions, including Canada, North and South America, Europe, Africa, Asia, and Pacific. The SECURE study (N = 527) enrolled adults with proven, probable, or possible IFD caused by *Aspergillus* or other filamentous fungi. Patients were randomized (1:1) to ISA (200 mg IV three times a day on days 1 and 2, then either IV or oral administration once daily), or VRC (6 mg/kg IV twice daily on day 1, 4 mg/kg IV twice daily on day 2, then 4 mg/kg IV twice daily or 200 mg orally twice daily from day 3 onward). The maximum treatment duration was 84 days.

The SECURE study identified several efficacy analysis sets based on diagnostic certainty and causative organism:

- The intention-to-treat (ITT) population consisted of all randomized patients who received at least one dose of the study drug (i.e., all patients with proven, probable, or possible IFD).
- The modified intention-to-treat (mITT) population consisted of ITT patients who had proven or probable IFD.

- The mycological intention-to-treat (myITT) population consisted of mITT patients with proven or probable IA based on cytology, histology, culture, or galactomannan criteria assessed by the data review committee.

The primary outcome was all-cause mortality through day 42 in the ITT population (i.e., all patients with proven, probable, or possible IFD). The pre-specified noninferiority margin for the primary efficacy outcome (all-cause mortality in the ITT population through day 42) was that the upper limit of the 95% confidence interval (CI) for a treatment difference was 10% or less. The key secondary outcome was overall response at end of treatment in the mITT (i.e., patients who had proven or probable IFD) population; overall response was a composite of clinical, mycological, and radiological responses. Other secondary outcomes included all-cause mortality through day 84, treatment response (overall, clinical, mycological, and radiological responses) at the end of treatment, and on day 42 and day 84. Limitations of the study include the high percentage of patients who discontinued treatment; 54.3% and 53.5% in the ISA and VRC treatment groups, respectively. While patients appeared to be adequately followed up for the primary outcome (survival) and those with unknown survival status were presumed to have died, it is unclear how the high discontinuation rate affected the validity of the overall response or its components (clinical mycological and radiological response).

The VITAL study (N = 146) assessed the efficacy and safety of IV and oral formulations of ISA (the same dose used as in the SECURE study) in the treatment of proven, probable, or possible IM (N = 37), IA (N = 24), or other rare fungal infection. The maximum treatment duration was 180 days. From the VITAL study, only information on IM or IA was reported for the purpose of this review.

Efficacy

For Invasive Aspergillosis

In the SECURE study, all-cause mortality through day 42 in patients with proven, probable, or possible IFDs was reported in 18.6% and 20.2% of the ISA and VRC treatment groups, respectively. The adjusted treatment difference was −1.0% (95% CI: −7.8 to 5.7). Given that the upper bound of the 95% CI was less than the pre-specified noninferiority margin, ISA was considered noninferior to VRC. Results for the per-protocol population through day 42 were consistent with the primary analysis. All-cause mortality through day 84 in the ITT population was reported in 29.1% and 31.0% of patients in the ISA and VRC treatment groups, respectively; the adjusted treatment difference was −1.4% (95% CI: −9.2 to 6.3).

All-cause mortality through day 42 in subpopulations defined by the certainty of diagnosis and causative organism was similar to that for the full (ITT) population. All-cause mortality through day 42 in the subpopulation of proven or probable IFDs (mITT), was 19.6% and 23.3% in the ISA and VRC treatment groups, respectively (adjusted treatment difference of −2.6; 95% CI: −12.2 to 6.9) and 18.7% and 22.2% for ISA and VRC, respectively, in the subpopulation of proven or probable IA (myITT) (adjusted treatment difference of −2.7; 95% CI: −12.9 to 7.5). All-cause mortality through day 84 in both the mITT and myITT subpopulations was consistently lower in the ISA groups compared with the VRC groups.

Overall treatment response in the mITT population at end of treatment (key secondary outcome) was reported in 35.0% and 36.4% of patients in the ISA and VRC groups, respectively (adjusted treatment difference of 1.6%; 95% CI: −9.3 to 12.6). Overall treatment response at end of treatment in the ITT population was reported in 39.4% and

41.4% of patients in the ISA and VRC treatment groups, respectively. Overall response was consistently lower in the ISA groups compared with the VRC groups at both day 42 and day 84 for the ITT population: 38.5% versus 40.1% and 30.7% versus 34.2%, respectively.

Theoretically, the most relevant population for the indication of IA would be the myITT subpopulation, (patients with proven or probable IA). However, the CDR clinical expert consulted for this review indicated that due to the nature of the difficulties in confirming the diagnosis of IFDs such as IA or IM, the clinically suspected IFDs population (i.e., the ITT population, those with proven, probable, or possible IFD) reflects the most relevant patient population in real-world clinical practice. However, the results were consistent across the various analysis populations for both all-cause mortality and overall response, thereby increasing confidence in the findings.

For the ITT population, health care resource utilization, reported as the days in hospital, was reportedly similar in both the ISA and VRC treatment groups. Comparative clinical efficacy (in terms of all-cause mortality or overall response) between ISA and VRC when examining subgroups based on underlying medical conditions was similar to that in the main analyses. The SECURE trial did not report the need for salvage therapy or changes in health-related quality of life (HRQoL), nor did it provide evidence relevant to patients whose treatment had failed prior antifungal therapy.

The VITAL trial included a small number of patients with IA; however, the lack of a control group is a major limitation. VRC in the SECURE trial is a highly relevant comparator, given that clinical practice guidelines recommend it as first-line treatment for IA. However, this CDR review did not identify clinical trials comparing ISA with other potentially relevant comparators for first-line treatment of IFDs or IA, such as itraconazole or AmB. The indirect treatment comparison (network meta-analysis [NMA]) suggests that the efficacy of ISA in terms of all-cause mortality and overall response in the treatment of the patients with IA is similar to VRC and L-AmB. However, due to the various limitations, particularly the potential methodological and clinical heterogeneity and sparsity of trials, no conclusion on the comparative efficacy of ISA and other available therapies could be credibly drawn from the NMA. No NMA evidence was identified to compare ISA with posaconazole, itraconazole, or caspofungin for the treatment of IA.

For Invasive Mucormycosis

Evidence for the use of ISA in patients with IM is restricted to one open-label, single-arm study (VITAL) that enrolled 37 patients with proven or probable IM, including primary-therapy patients, excluding those who had received more than four days of itraconazole, VRC, or posaconazole for any reason in the seven days prior to the administration of the study drug (N = 21), patients with refractory disease (N = 11), and patients who were intolerant of the study drug (N = 5). For all IM patients, all-cause mortality through day 42 and day 84 were 37.8% and 43.2%, respectively. The lack of a control group in the VITAL study is a major limitation. The manufacturer conducted an additional analysis that compared all-cause mortality in patients receiving ISA as primary therapy in the VITAL study[18] (7/21, 33%) with that of patients who received AmB therapy for IM as recorded in the FungiScope registry database (13/33, 39%).[19] The manufacturer reported there was no statistically significant difference between the two cohorts (P = 0.775).[18] However, the extent to which these two patient cohorts are similar is not clear. While the rarity of IM is understood to make conducting an RCT challenging, the lack of direct evidence with other relevant comparators for the treatment of IM (e.g., AmB) means that the comparative

efficacy is uncertain. The VITAL study included only a very limited number of patients whose IM was refractory to previous treatment and did not report the need for salvage therapy among IM patients receiving primary treatment with ISA, or changes in HRQoL.

Harms

In the treatment of IAs, the overall frequency of adverse events in patients treated with ISA versus VRC appeared to be similar (96.1% in the ISA and 98.5% in the VRC group, respectively). ISA seemed to have a numerically lower risk than VRC in terms of vomiting, nausea, constipation, and decreased appetite, while patients treated with ISA appeared to have a higher risk of experiencing headache, dyspnea, fatigue, and back pain. Compared with VRC, fewer patients in the ISA group reported adverse events of special interest, including hepatic impairment (1.6% versus 3.5%, respectively); cardiovascular harms (tachycardia: 4.7% versus 8.7%, respectively) and visual disturbances (1.6% versus 7.3%, respectively). The proportion of patients who discontinued the study drug due to adverse events appeared lower in the ISA group than in the VRC group. Furthermore, the overall frequency of patients with serious adverse events also appeared similar in both groups, despite being numerically lower in the ISA group versus the VRC group (52.1% and 57.5%, respectively). It is noted that a numerically higher percentage of patients in the ISA group reported serious adverse events such as febrile neutropenia, respiratory failure, and septic shock, while patients in the VRC group more often reported serious adverse events such as pyrexia, sepsis, acute renal failure, pneumonia, and acute myeloid leukemia.

Potential Place in Therapy[1]

ISA is designed for the treatment of invasive fungal infections (IFIs) specifically. It covers *Candida* infection (which may be covered by other azoles, echinocandins, or polyene antifungals), but the appeal of this drug is the expanded coverage for IA (covered by VRC, posaconazole, echinocandins, and polyenes) and IM (covered by posaconazole and polyenes).[20,21]

These severe, life-threatening infections typically present in patients with significant underlying immune suppression, such as from solid organ transplant or human stem cell transplant. The difficulty with managing these infections lies with the lack of readily available, economical, expedited testing to make a diagnosis. Patients are often critically ill at the time of presentation of these IFIs; thus, the preferred diagnostic test — tissue biopsy for culture and pathologic examination — is not usually practical.[20,21]

This drug does provide an additional less toxic option, compared with AmBisome and other polyenes, for treatment of IFI in high-risk immune-compromised populations. ISA would not necessarily be first-line therapy, given currently available, less expensive therapies. This drug could certainly be an alternative therapy for IA in those unable to tolerate VRC and when the benefit of, for example, posaconazole, is unsure. In addition, for patients on initial therapy with polyenes for proven or probable IA, the oral option with ISA makes it a potential option for follow-on therapy. Many patients at high risk for IFI are not at as high a risk for IM and, thus, their disease can be managed with VRC, posaconazole, or echinocandins. For these patients, there is not a clear need for ISA as first-line therapy; hence, this drug would be an alternative for those with IA, whether proven or probable. As for higher-risk patients where IM is of concern, ISA would be a first-line choice along with the existing recommended first-line therapies, polyenes[22] or posaconazole, when AmB

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

formulations are absolutely contraindicated.[22] Of course, polyenes are more difficult to administer and associated with more adverse drug reactions.

For IM, there are fewer options for therapy. Based on the VITAL study, ISA is similar to polyenes, and the SECURE study showed noninferiority for VRC, though the latter drug is not generally considered as primary therapy for IM. Neither of these studies compared ISA with posaconazole, an azole with recognized activity for treating mucormycosis. For that grave infection, ISA could be used in conjunction with surgical debridement.

In summary, the major role for this drug would be when IM is a possible cause for an IFI for which polyenes are currently first-line therapy but their use is often limited by toxicity. There is additional benefit to the oral follow-on therapy with the same drug; thus, this drug would be an alternative to posaconazole. This drug is not as critical for IA, since VRC and posaconazole are other azole options with oral as well as parenteral therapy available. However, it could be an alternative, since data suggest less visual toxicity than VRC.

Conclusions

For the treatment of patients with IA, ISA appears to have a treatment effect similar to VRC in terms of overall response and all-cause mortality over a nearly three-month period. For the treatment of patients with IM, based on a small single-arm trial that includes comparison with a historical control, similar clinical efficacy (overall response and all-cause mortality) of ISA compared with AmB was suggested; however, uncertainty remained. No direct evidence was identified that compared ISA with other drugs used in the treatment of IA or IM. The NMA did not provide credible evidence for ISA versus AmB in the treatment of IA. No notable difference in adverse events or serious adverse events was observed between ISA and VRC. However, more patients reported adverse events of special interest (hepatic impairment, cardiovascular harms, and visual impairments) in the VRC group than in the ISA group.

Table 1: Summary of Key Results

	SECURE					VITAL	
	ISA (N = 258)		VRC (N = 258)		Adjusted Treatment Difference[a] (ISA Minus VRC)	ISA	
						IM (N = 37)	IA (N = 24)
	N	n(%)	N	n(%)	% (95% CI)	n (%)	n (%)
All-Cause Mortality							
Through day 42							
ITT	258	48 (18.6)	258	52 (20.2)	−1.0 (−7.8 to 5.7)	NA	NA
PP	172	26 (15.1)	175	31 (17.7)	−2.6 (−10.3 to 5.1)	NA	NA
mITT	143	28 (19.6)	129	30 (23.3)	−2.6 (−12.2 to 6.9)	14 (37.8)	3 (12.5)
myITT	123	23 (18.7)	108	24 (22.2)	−2.7 (−13.6 to 8.2)	NA	NA
Through Day 84							
ITT	258	75 (29.1)	258	80 (31.0)	−1.4 (−9.2 to 6.3)	NA	NA
PP	172	43 (25.0)	175	48 (27.4)	−2.8 (−11.9 to 6.2)	NA	NA
mITT	143	43 (30.1)	129	48 (37.2)	−5.5 (−16.1 to 5.1)	16 (43.2)	6 (25.0)
myITT	123	35 (28.5)	108	39 (36.1)	−5.7 (−17.1 to 5.6)	NA	NA
Overall response (EOT, mITT)	143	50 (35.0)	129	47 (36.4)	1.6 (−9.3 to 12.6)	11/35 (31.4)	8/23 (34.8)
Overall response (EOT, ITT)	231	91(39.4)	237	98 (41.4)	NR	NA	
Patients with ≥ 1 TEAE	257	247 (96.1)	259	255 (98.5)	NR	139 (95.2)[b]	
Patients with ≥ 1 SAE	257	134 (52.1)	259	149 (57.5)	NR	89 (61.0)[b]	
WDAE	257	37 (14.4)	259	59 (22.8)	NR	19 (13.0)[b]	
Death	257	81(31.5)	259	87 (33.6)	NR	47 (32.2)[b]	

AE = adverse event; CI = confidence interval; EOT = end of treatment; IA = invasive aspergillosis; IM = invasive mucormycosis; ISA = isavuconazole; ITT = intention-to-treat; mITT = modified intention-to-treat; myITT = mycological intention-to-treat; NA = not applicable; NR = not reported; PP = per-protocol; RCT = randomized controlled trial; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VRC = voriconazole; WDAE = withdrawal due to adverse event.

Note: mITT population consisted of ITT patients who had proven or probable invasive fungal disease. The myITT population consisted of mITT patients with proven or probable IA based on cytology, histology, culture, or galactomannan criteria.

[a] The adjusted treatment difference was calculated using a stratified Cochran–Mantel–Haenszel method with the strata of geographical region, allogeneic bone marrow transplant status, and uncontrolled malignancy status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

[b] In the VITAL study, the AE outcome was reported only for total patients (N = 146), not specifically for patients with IM (N = 24) or IA (N = 37).

Source: Clinical Study Reports.[23,24]

Introduction

Disease Prevalence and Incidence

Fungal diseases are opportunistic infections caused by fungi. Fungal disease may become invasive (i.e., invasive fungal disease, [IFD]) and life-threatening in a high-risk population, such as patients with bone marrow transplant, patients with HIV, and immunosuppressed patients, especially those with neutropenia.[1,2] In Canada, it was estimated that the incidence of IFDs was 1.6 per 100,000 people.[2,3] In Canada, *Candida* accounts for 85.0% of all fungal disease in the high-risk population, *Aspergillus* for 14.4%, *Cryptococcus* for 2.0%, and *Mucorales* for 0.9%.[4] *Aspergillus* causes aspergillosis with three main clinical forms: invasive aspergillosis (IA), chronic aspergillosis, and allergic aspergillosis.[5] *Rhizopus*, *Mucor*, *Cunninghamella bertholletiae*, *Apophysomyces*, and *Lichtheimia*) cause invasive mucormycosis (IM).[1] No Canadian prevalence and incidence data were available for IM.[6] In the US, a surveillance study from 2001 to 2006 found that IM accounts for 8% of all invasive fungal infections (IFIs) in high-risk patients.[1]

Clinical Symptoms, Diagnosis, and Prognosis

The systems most commonly affected by IFDs are the respiratory (e.g., lungs), skin, and digestive systems (especially for IM). IFDs will spread rapidly through the bloodstream, causing sepsis.[1] The common clinical symptoms of IA are fever, chest pain, cough, and shortness of breath.[6] IM presents similar clinical features, with the brain as the most common site of dissemination.[6] In current clinical practice, establishing a definitive diagnosis of IA or IM remains a challenge.[7] Several diagnostic tests are available, but histologic/cytologic testing and fungal culture examination are the current standard.[21] Culture assays, typically using Sabouraud dextrose agar, can reveal fungal viability and identity. However, a delay of one to three weeks is expected to obtain culture results. Histologic testing has been crucial to confirm the diagnosis of *Aspergillus* in growing culture, but diagnostic accuracy is suboptimal. Fluorescent stains, blood molecular biology, and antigen detection can also be used to diagnose IA.[21] Due to the limitations in culture, cytological, and histological testing discussed previously, surrogate markers, such as serological tests of galactomannan and beta-D-glycan as well as a thoracic CT scan, are often useful.[7] Galactomannan detection is more sensitive and faster than histologic testing or culture assays for diagnosis of IA, especially for patients not treated with prophylaxis or empirical therapy. Diagnosis of IM is similar to IA, but a biopsy with histologic examination is the most sensitive and specific diagnosis technique.[21] In addition, specific staining methods such as periodic acid–Schiff or methenamine silver can effectively support the diagnosis.[6]

Clinically, IA and IM are life-threatening infections with a mortality rate approaching 100% if untreated or if treatment is delayed.[8] The global mortality rate for IA ranges from 30% to 80%, depending on the affected system.[17] In Canada, one study has estimated a 66% probability of survival 90 days following diagnosis of IA.[4] As for IM, estimated mortality in the US varies according to the underlying condition (44% in patients with diabetes and 66% in patients with a malignancy) and site of infection (76% for pulmonary infections, 85% for gastrointestinal infections and 96% for disseminated infections).[25] When affecting the brain, the IM mortality rate approaches 100%.[6]

Standards of Therapy

In Canada, systemic antifungal drugs for IFDs, including IA and IM, include isavuconazole (ISA), voriconazole (VRC) and posaconazole, itraconazole, amphotericin B (AmB) and caspofungin[9-15] (Table 2). Approved by Health Canada, VRC and itraconazole are indicated for the treatment of IA. Three formulations of AmB are available in Canada. The indications for the three formulations of AmB are as follows:

- AmBisome (liposomal AmB [L-AmB] for injection), the most common formulation used in Canada, is indicated for empirical therapy for presumed fungal infection in febrile, neutropenic patients and for the treatment of cryptococcal meningitis in HIV-infected patients. AmBisome is also indicated for the treatment of systemic or disseminated infections due to *Candida*, *Aspergillus*, or *Cryptococcus* in patients with disease that is refractory to or who are intolerant of conventional AmB therapy or who are renal-impaired.[14]
- Abelcet (AmB lipid complex injection) is indicated for the treatment of IFIs in patients whose disease is refractory to or who are intolerant of Fungizone (also known as conventional AmB or AmB deoxycholate [AmB-D]) therapy.[15]
- Fungizone is specifically intended for the treatment of disseminated mycotic infections, including coccidioidomycosis; cryptococcosis (torulosis); disseminated candidiasis, histoplasmosis, South American leishmaniasis, North and South American blastomycosis; mucormycosis (phycomycosis) caused by of the genera *Mucor*, *Rhizopus*, *Absidia*, *Entomophthora*, and *Basidiobolus*, sporotrichosis (*Sporotrichum schenckii*), and aspergillosis (*Aspergillus fumigatus*).[16] The CADTH Common Drug Review (CDR) clinical expert indicated that, due to its renal toxicity, Fungizone is no longer used in Canada. Posaconazole is indicated for the treatment of IA in patients with disease that is refractory to AmB or itraconazole, or in patients who are intolerant of these medicinal products. Caspofungin is indicated for the treatment of IA in patients who are refractory to or intolerant of other therapies. The CDR clinical expert indicated that voriconazole, itraconazole, and caspofungin are empirically used for the treatment of IA, while posaconazole and AmB are empirically used for IM or IA.

ISA, VRC, itraconazole, and posaconazole are triazoles inhibiting 14-alpha-sterol demethylase. This prevents ergosterol synthesis, leading to the accumulation of toxic 14-alpha-methylsterols and resulting in the inhibition of fungal growth.[9-12] Caspofungin is echinocandin inhibiting the synthesis of glucan, a polysaccharide in the cell wall of fungi, via non-competitive inhibition of the 1,3-beta-glucan synthase, which disturbs the strength, shape, and osmotic integrity of the fungal cell.[13] The AmB binds to the ergosterol component in the cell membrane of susceptible fungi and results in a change in membrane permeability, allowing leakage of cell components.

The optimal strategy for managing IFDs (e.g., IA and IM) includes prevention and early treatment aimed at eradicating the fungal infection. Empirical treatment with AmB, which can only be used intravenously, has been used for both IA and IM. However, several factors — such as the inconvenience of long-term intravenous (IV) infusion, infusion-related adverse events, and renal toxicity — have limited the use of AmB. VRC is more commonly used to treat suspected IA in high-risk patients with fever. Without a confirmed diagnosis, those patients with suspected IA may actually have IM caused by *Mucorales*, as clinical manifestations of IM are similar to IA. Since VRC has no effect on IM, its use may delay and compromise the future successful treatment of IM.[1,6] Antifungal drugs that treat

both IA and IM would expand the options for the empirical treatment of IFDs and minimize the risk of delaying treatment of potentially late-diagnosed IM.[6,17]

Based on the findings reported in the SECURE study and the VITAL study, the European Society for Clinical Microbiology and Infectious Diseases, the European Confederation of Medical Mycology and the European Respiratory Society Joint Clinical Guidelines, as well as the European Conference on Infections in Leukemia (ECIL), have recommended ISA and VRC as the preferred drugs for first-line treatment of pulmonary IA.[26]

Table 2: Key Characteristics of Anti-Invasive Aspergillosis or Anti-Invasive Mucormycosis Drugs

	ISA[10]	VRC[9,27]	AmB[14]	POS[11]	ITRA[12]	CAS[13]
Mechanism of Action	Inhibition of cytochrome P450-dependent enzyme lanosterol 14-alpha-demethylase	Inhibition of cytochrome P450–mediated 14-alpha-sterol demethylation	AmBisome, binding to the ergosterol component in the cell membrane of susceptible fungi	Blocks the synthesis of ergosterol, a key component of the fungal cell membrane	Inhibits the cytochrome P450–dependent synthesis of ergosterol	Inhibits the synthesis of 1,3-beta-D-glucan, an integral component of the fungal cell wall
Indication[a]	Use in adults for the treatment of IA or IM	Treatment of IA	AmBisome (L-AmB for injection) is indicated for empirical therapy for presumed fungal infection in febrile, neutropenic patients and for treatment of cryptococcal meningitis in HIV-infected patients AmBisome is also indicated for the treatment of systemic or disseminated infections due to *Candida*, *Aspergillus,* or *Cryptococcus* in patients who are refractory to or intolerant to conventional AmB therapy or are renal-impaired	Treatment of IA in patients with disease that is refractory to AmB or ITRA, or in patients who are intolerant of these medicinal products	Treatment of IA	Treatment of IA in patients who are refractory to or intolerant of other therapies
	Oral, IV	Oral, IV	IV	Oral, IV	Oral	IV
Recommended Dose	**Oral for IA or IM** • Loading dose: 200 mg orally every 8 hours for six doses (48 hours) • Maintenance dose: 200 mg orally once daily **IV for IA or IM** • Loading dose: 1 reconstituted and diluted vial (200 mg) by IV every 8 hours for six doses (48 hours) • Maintenance dose: 1 reconstituted and diluted vial (200 mg) by IV once daily	Oral — loading dose: • patients ≥ 40 kg: 400 mg b.i.d. • patients < 40 kg: 200 mg b.i.d. Oral — maintenance dose: • patients ≥ 40 kg: 200 mg b.i.d. • patients < 40 kg: 100 mg b.i.d. IV: • loading dose (first 24 hours): 6 mg/kg, b.i.d. • maintenance dose (after first 24 hours): 4 mg/kg b.i.d.	• The recommended concentration for IV infusion is 0.5 mg/mL to 2.0 mg/mL • The daily dose and duration of therapy of AmBisome should be based on the infecting organism, the patient's condition, and the response to therapy Treatment should be continued until clinical parameters and laboratory tests indicate that an active fungal infection has been cured or subsided	• IV loading dose of 300 mg b.i.d. on the first day, then 300 mg once a day thereafter. • Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response	For invasive pulmonary aspergillosis: 200 mg, b.i.d. Median duration: 3 to 4 months for both	IA: A single 70 mg loading dose on day 1 followed by 50 mg daily thereafter. Duration of treatment should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response
Serious Side Effects / Safety Issues	Contraindications: • co-administration with	Voriconazole is contraindicated with drugs	Contraindications for AmBisome (L-AmB for	Contraindications: • hypersensitive to this	Contraindications: • should not be	Contraindications: • patients with

	ISA[10]	VRC[9,27]	AmB[14]	POS[11]	ITRA[12]	CAS[13]
	strong CYP3A4 inhibitor ketoconazole • co-administration with strong CYP3A4 inducers, such as rifampin, rifabutin, etc. • co-administration with moderate CYP3A4/5 inducers such as efavirenz and etravirine, etc. • patients with familial short QT syndrome Warnings or precautions: • embryo-fetal toxicity: should not be used during pregnancy unless the potential benefit to the patient outweighs the risk to the fetus • not recommended for women of childbearing potential who are not using contraception	that: • are highly dependent on cytochrome P450 isozymes CYP2C19, CYP2C9, and CYP3A4 • significantly decrease voriconazole plasma concentrations due to induction of cytochrome P450 isozymes CYP2C19, CYP2C9, and CYP3A4; • are CYP450 substrates and for which elevated plasma levels may result in serious and/or life-threatening events Warnings or precautions: • cardiovascular effects: QT interval prolongation, cardiac arrests, and sudden deaths • caution should be exercised if voriconazole is used in patients taking other drugs that may prolong the QT interval • visual disturbances • hepatic toxicity	injection): • patients who have demonstrated or have known hypersensitivity to conventional AmB or any other constituents of AmBisome • should not be used to treat the common apparent forms of fungal diseases that show only positive skin or serologic tests. Warnings or precautions: • anaphylaxis • AmBisome should be administered primarily to patients with progressive, potentially fatal infections This drug should not be used to treat the common apparent forms of fungal diseases; in particular, caution should be exercised when prolonged therapy is required.	drug • co-administration of posaconazole with ergot alkaloids or with certain medicinal products metabolized through the CYP3A4 system • with CYP3A4 substrates • with HMG-CoA reductase inhibitors (statins) • with sirolimus Warnings or precautions: • cardiovascular effects • QT interval prolongation • hepatic toxicity	administered to patients with evidence of ventricular dysfunction such as congestive heart failure • co-administration with a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor • should not be administered for the treatment of onychomycosis or dermatomycoses to pregnant patients or to women contemplating pregnancy Warnings or precautions: • cardiovascular (use in patients with underlying cardiac disease) • liver toxicity	hypersensitivity to any component of this product Warnings or precautions: • concomitant use with cyclosporine • hepatic effects • pregnant women

AmB = amphotericin B; b.i.d. = twice a day; CAS = caspofungin; CHF = congestive heart failure; IA = invasive aspergillosis; IM = invasive mucormycosis; ISA = isavuconazole; ITRA = itraconazole; IV = intravenous infusion; L-AmB = liposomal amphotericin B; LD = loading dose; POS = posaconazole; VRC = voriconazole.

Note: For this review, only relevant information (treatment for IA and IM) is presented. Three AmB formulations are available in Canada (i.e., AmBisome,[14] Abelcet,[15] and Fungizone[16]). The indications for these are presented as follows:

- AmBisome (L-AmB for injection) is indicated for empirical therapy for presumed fungal infection in febrile, neutropenic patients and for treatment of cryptococcal meningitis in HIV-infected patients. AmBisome is also indicated for the treatment of systemic or disseminated infections due to *Candida*, *Aspergillus*, or *Cryptococcus* in patients whose disease is refractory to or who are intolerant of conventional AmB therapy or who are renal-impaired.[14]
- Abelcet (AmB lipid complex injection) is indicated for the treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional AmB therapy.[15]
- Fungizone (AmB) is intended specifically for the treatment of disseminated mycotic infections, including coccidioidomycosis; cryptococcosis (torulosis); disseminated candidiasis, histoplasmosis, South American leishmaniasis, and North and South American blastomycosis; and mucormycosis (phycomycosis) caused by species of the genera *Mucor*, *Rhizopus*, *Absidia*, *Entomophthora,* and *Basidiobolus*; sporotrichosis (*Sporotrichum schenckii*); and aspergillosis (*Aspergillus fumigatus*).[16]

[a] Health Canada indication.

Source: Product monographs.[9-14]

Drug

ISA belongs to the azole antifungal drug class. ISA demonstrates a fungicidal effect by blocking the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of the cytochrome P450–dependent enzyme lanosterol 14-alpha-demethylase, which is responsible for converting lanosterol to ergosterol. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane, thus weakening the structure and function of the fungal cell membrane. It is approved by Health Canada as an antifungal drug for use in adults for the treatment of IA or IM. It is available as both an oral drug (100 mg capsules) and IV drug (200 mg powder for solution for IV infusion). The Health Canada–recommended dose for ISA in the treatment IA or IM is 200 mg (IV or oral) every eight hours for 48 hours (six doses), followed by a maintenance dose of 200 mg (IV or oral) once daily.[10]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of ISA (as isavuconazonium sulfate [100 mg capsules for oral use and 200 mg powder for solution for IV infusion]) for use in adults for the treatment of IA and IM.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients with IA or IM. Subgroups: • diagnosis (e.g., IA versus IM versus other IFDs; proven versus probable versus possible IFD) • underlying medical conditions (e.g., neutropenia, AIDs, organ/tissue transplant) • prior antifungal treatment (e.g., treatment-experienced versus treatment-naive; prior treatment failure)
Intervention	Isavuconazole as per Health Canada–recommended dose[a]
Comparators	(Used alone or in combination)[b] • Voriconazole • Amphotericin B • Posaconazole • Itraconazole • Caspofungin
Outcomes	**Efficacy outcomes:** • survival • response (e.g., overall, clinical, mycological, radiological) • need for salvage therapy • HRQoL • health care resource utilization (e.g., days in hospital, days in ICU, readmission) **Harms outcomes:** • AEs • SAEs • WDAEs • mortality • notable harms: hepatic impairment, cardiovascular harms, and visual disturbances
Study Design	Published and unpublished phase III or IV RCTs

AE = adverse event; HRQoL = health-related quality of life; IA = invasive aspergillosis; ICU = intensive care unit; IFD = invasive fungal disease; IM = invasive mucormycosis; IV = intravenous; L-AmB = liposomal amphotericin B; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Cresemba, ISA, and isavuconazonium sulfate.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on December 05, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on April 7, 2019. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trial Registries, Databases (free), Internet Search, and Background. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4 and Table 5. The excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of two studies (the SECURE study for IA[23,28-30] and the VITAL study for IM and IA[18,24,31-33]) were identified from the literature or considered as the pivotal study by the manufacturer and Health Canada for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and Table 5. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

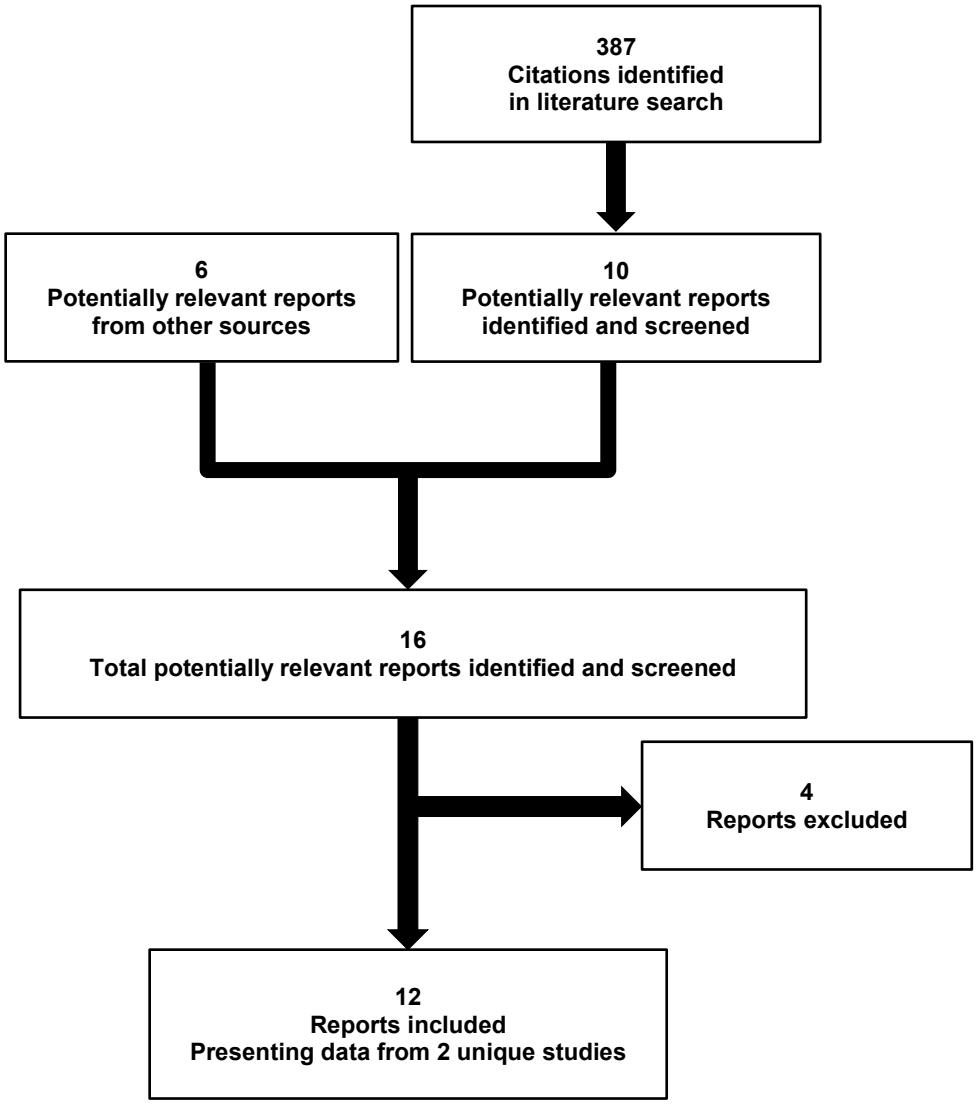


Table 4: Details of Included Study for Invasive Aspergillosis (SECURE Study)

		SECURE
Designs and Populations	**Study Design**	DB RCT (phase III, noninferiority study of ISA versus VRC)
	Locations	102 centres in Canada, North and South America, Europe, the Middle East, Africa, Southeast Asia, the Far East, and Pacific regions
	Randomized (N)	527
	Inclusion Criteria	• Male and female patients aged ≥ 18 years • Patients with proven, probable, or possible IFD caused by *Aspergillus* or other filamentous fungi
	Exclusion Criteria	• Patients with any other invasive fungal infection other than *Aspergillus* or other filamentous fungi • Patients with zygomycosis/mucormycosis or *Scedosporium* prolificans infection not expected to respond to voriconazole treatment • Women who were pregnant or breastfeeding • Allergy, hypersensitivity to, or any serious reaction to the azole class of antifungals or to the study medication • Patients with evidence of hepatic dysfunction at the time of randomization • Patients who had been administered more than four cumulative days of itraconazole, VRC, or posaconazole, for any reason, within the 7 days prior to the first administration of study medication • Concomitant use of sirolimus, efavirenz, ritonavir, astemizole, cisapride, rifampin/rifampicin, rifabutin, ergot alkaloids, long-acting barbiturates, carbamazepine, pimozide, quinidine, neostigmine, terfenadine, ketoconazole, valproic acid, or St. John's wort in the 5 days prior to the first administration of the study medication • Advanced HIV infection with CD4 count < 200 or AIDS-defining condition • Patients with evidence of moderate-to-severe renal dysfunction (CrCl < 50 mL/min)
Drugs	**Intervention**	ISA, 200 mg IV three times a day on days 1 and 2, then either IV or orally once daily
	Comparator(s)	VRC (6 mg/kg IV twice daily on day 1, 4 mg/kg IV twice daily on day 2, then 4 mg/kg IV twice daily or 200 mg orally twice daily from day 3 onward)
Duration	**Phase**	
	Screening / dose stabilization	Screening, 96 hours prior to randomization
	Treatment	Maximum 84 days (ISA: Day 1 to EOT; VRC: Day 1 to EOT)
	Follow-up	EOT plus 4 weeks
Outcomes	**Primary End Point**	All-cause mortality through day 42 for ITT population
	Other End Points	• Treatment response (overall response,[a] clinical response,[b] mycological response,[c] and radiological response[d]) • Safety outcomes
Notes	**Publications**	• Maertens, J. A. et al., 2016[29] • Maertens, J. et al., 2018[28]

CDR = CADTH Common Drug Review; CrCl = creatinine clearance; CSR = clinical study report; DB = double-blind; EOT = end of treatment; IFD = invasive fungal disease; ISA = isavuconazole; ITT = intention-to-treat; IV = intravenously; mITT = modified intention-to-treat; RCT = randomized controlled trial; VRC = voriconazole.

Note: Six additional reports were included (three FDA medical and statistical reports,[34,35] Health Canada Reviewer Report,[30] CDR submission,[6] CSR).[23,24]

[a] The overall response at the end of treatment for the mITT population was the key secondary outcome.[23] The overall response (success) was a composite of the clinical, mycological, and radiological responses based on the pre-specified criteria (see Table 36 in Appendix 5).

[b] Clinical response (success) criteria: Resolution of all attributable clinical symptoms and physical findings; partial resolution of attributable clinical symptoms and physical findings.

[c] Mycological response (success): Eradication or presumed eradication.

[d] Radiological response (success): ≥ 25% improvement from baseline if EOT occurs prior to day 42, or ≥ 50% improvement from baseline if EOT occurs after day 42.

Source: Clinical Study Report.[23]

Table 5: Details of Included Study for Invasive Mucormycosis or Invasive Aspergillosis (VITAL Study)

		VITAL
Designs and Populations	**Study Design**	Single-arm, open-label, multi-centre
	Locations	US, European Union, South America, Asia, and the Middle East
	Randomized (N)	Not an RCT (Total N = 146, N = 37 for IM, N = 24 for IA)
	Inclusion Criteria	Male and female patients aged ≥ 18 years with one of the following: • proven, probable, or possible IA plus renal impairment (CrCl < 50 mL/min) • meet EORTC/MSG definition of proven or culture-positive probable IFD by rare moulds, yeast, dimorphic fungi • proven or probable IM and requiring therapy • meet EORTC/MSG definition of proven or culture-positive probable IFD by rare moulds, yeast, dimorphic fungi, and refractory to current treatment • proven or culture-positive probable IFD and intolerant of current treatment
	Exclusion Criteria	• Women who were pregnant or breastfeeding • Allergy, hypersensitivity to, or any serious reaction to the azole class of antifungals or to the study medication • Patients at high risk for QT prolongation • Patients with evidence of hepatic dysfunction at the time of enrolment • Concomitant use of astemizole, cisapride, rifampin/rifampicin, rifabutin, ergot alkaloids, long-acting barbiturates, ritonavir, efavirenz, carbamazepine, pimozide, quinidine, neostigmine, terfenadine, ketoconazole, valproic acid, or St. John's wort in the 5 days prior to the first administration of study drug • Patients with chronic IA, aspergilloma, or allergic bronchopulmonary IA • Microbiological findings or other potential conditions that may suggest a different etiology for clinical features in the absence of systemic fungal infection • Advanced HIV infection with CD4 count < 50 or uncontrolled AIDS-defining condition • Patients unlikely to survive 30 days • Patients who need primary therapy for IA who have been administered more than four cumulative days of itraconazole, voriconazole, or posaconazole
Drugs	**Intervention**	• Loading dose (for 2 days): 200 mg ISA, IV or oral, three times daily • Maintenance dose: 200 mg ISA IV or oral, once daily
	Comparator(s)	NA
Duration	**Phase**	
	Screening	5 days
	Loading dose	2 days
	Maintenance dose	Day 3 to end of treatment (maximum 180 days)
	Follow-up	4 weeks after EOT
Outcomes	**Primary End Point**	• Overall response at day 42
	Other End Points	• Overall response at day 84 and end of treatment • Clinical, radiological, and mycological responses at day 42 and day 84 • All-cause mortality through day 42 and day 84 • Safety outcomes
Notes	**Publications**	Marty et al., 2016[18] Marty et al., 2018[32] Comely et al., 2018[31] Perfect et al., 2018[33]

CrCl = creatinine clearance; EORTC/MSG = European Organization for the Research and Treatment of Cancer/Mycoses Study Group; EOT = end of treatment; IA = invasive aspergillosis; IFD = invasive fungal disease; IM = invasive mucormycosis; ISA = isavuconazole; ITT = intention-to-treat; IV = intravenously; NA = not applicable; VRC = voriconazole.

Source: Clinical Study Report and the publications.[18,24,31-33]

Included Studies

Description of Studies

Two studies (one randomized controlled study [RCT] [the SECURE study][23] and one single-arm study [the VITAL study][24]) were included for this review. The SECURE study was a phase III, randomized, multi-centre, double-blind, noninferiority study that compared ISA with VRC in the treatment of patients with IFDs (especially IA). The VITAL study was a phase III, single-arm, open-label, multi-centre study of ISA in the treatment of IA in patients with renal impairment, patients with IM, or patients with an IFD caused by other rare moulds, yeasts, or dimorphic fungi. Health Canada considered the VITAL study to be pivotal. For the purpose of this review, only the information on the subpopulation of patients with IM or IA reported in the VITAL study is presented in this report. Both trials were conducted in multiple centres in Canada, North and South America, Europe, Africa, Asia, and Pacific regions (Table 4 and Table 5).

Populations

Inclusion and Exclusion Criteria

Patients enrolled in the SECURE study were adults (≥ 18 years of age) with proven, probable, or possible IFD caused by *Aspergillus* or other filamentous fungi. Patients enrolled in the VITAL study included a subpopulation of 37 patients with proven or probable IM and a subpopulation of 24 patients with IA. In both studies, the IFD diagnoses were based on European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2008 diagnostic criteria and the use of the galactomannan assay to provide evidence of IA[36] (see Table 35 in Appendix 5).

The main exclusion criteria in the SECURE study were hepatic dysfunction (bilirubin ≥ 3 times the upper limit of normal [ULN], alanine transaminase or aspartate transaminase ≥ 5 times the ULN, cirrhosis, or chronic hepatic failure), or moderate-to-severe renal dysfunction (calculated creatinine clearance < 50 mL/min). Patients with any IFI other than *Aspergillus* or other filamentous fungi and patients with zygomycosis/mucormycosis or *Scedosporium* prolificans infection not expected to respond to VRC treatment.[23] The main exclusion criteria in the VITAL study were patients with severe liver injury or evidence of hepatic impairment at baseline (total bilirubin ≥ 3 times ULN, alanine aminotransferase or aspartate aminotransferase ≥ 5 times the ULN, or known cirrhosis or chronic hepatic failure), known allergy, hypersensitivity, or serious reaction to triazole antifungal drugs or any component of the study drug[24,32] (Table 4 and Table 5).

Baseline Characteristics

The baseline characteristics in the intention-to-treat (ITT) population for the SECURE study are presented in Table 6. Overall, the mean age of patients was 51 years and the majority of patients were white (78.1%). There were fewer male patients in the ISA than in the VRC treatment group (56.2% and 63.2%, respectively). The most common underlying medical condition was hematological malignant disease (84%).

A total of 105 (20%) patients were recipients of allogeneic hematopoietic stem cell transplantation, and 338 (66%) had neutropenia. The stratification factors included: geographic region, allogeneic bone marrow transplant status and uncontrolled malignancy status. Allogeneic bone marrow transplant status was defined as “Yes” for patients having a bone marrow transplant, hematopoietic stem cell transplant, or other progenitor cell

transplant with the type of transplant identified as allogeneic. Uncontrolled malignancy was defined as patients with active malignancy. The stratification factors were generally balanced across the two treatment groups in the ITT population (Table 6). IFDs caused by *Aspergillus* comprised only 33.3% of the ISA group and 30.2% of the VRC group, respectively. No pathogen was identified (i.e., mycology based on galactomannan test only) in 50.3% of the ISA group and 52.7% of the VRC group, respectively (Table 17 in Appendix 4). The location of IFDs was mainly in the low respiratory tract only, which was reported in 81.1% of the ISA group and 82.9% of the VRC group, respectively (Table 18 in Appendix 4). The percentage of patients in the ISA group diagnosed with a proven IFD, probable IFD, possible IFD, or no IFD was 11.2%, 44.2%, 34.1%, and 10.5%, respectively. The percentage of patients in the VRC group diagnosed with a proven IFD, probable IFD, possible IFD, or no IFD was 14.0%, 36.0%, 41.9%, and 8.1%, respectively (see Table 19 in Appendix 4). The diagnostic criteria for proven, probable, or possible IFD are presented in Table 35 in Appendix 5.

The baseline characteristics in the VITAL study for the mucormycosis and aspergillosis subpopulations are presented in Table 7. For the mucormycosis subpopulation, the three patient groups of interest were pre-specified based on prior antifungal therapy: patients with primary therapy (defined as four or fewer days of treatment with previous systemic antifungals), patients whose disease was refractory to, and patients who were intolerant of, previous other antifungal therapy. For the mucormycosis subpopulation, the mean age of patients was 48.5 years and the majority of patients were white (67.6%) and male (81%). The most common underlying medical conditions were hematological malignant disease (59.5%), uncontrolled malignancy status (48.6), and allogeneic bone marrow transplant (25.1%). T-cell immunosuppressants were used by 48.6% of patients (Table 7). The percentage of patients diagnosed as proven mucormycosis, probable mucormycosis, and possible mucormycosis were 84.2%, 13.2%, and 2.6%, respectively (see Table 20 in Appendix 4). There were 21 patients receiving ISA as primary therapy (56.8%), 11 patients whose disease was refractory to prior antifungal therapy (29.7%), and five patients who were intolerant of prior antifungal therapy (13.5%) (Table 7). For the aspergillosis subpopulation, the mean age of patients was 55.3 years and the majority of patients were white (87.5%) and male (62.5%). The most common underlying medical conditions were T-cell immunosuppressant use (75%) hematological malignant disease (58.3%), allogeneic bone marrow transplant (37.5%), neutropenia (33.3%), and uncontrolled malignancy status (29.2) (Table 7). The percentage of patients diagnosed with proven or probable aspergillosis was 37.5% and 62.5%, respectively. The percentage of patients with renal impairment or no renal impairment was 83.3% and 16.7%, respectively (see Table 20 in Appendix 4).

Table 6: Demographics and Baseline Characteristics (SECURE: Intention-to-Treat)

	SECURE (ITT)	
	ISA (N = 258)	VRC (N = 258)
Age (Years)		
Mean	51.1	51.2
Range	17 to 82	18 to 87
Sex, n (%)		
Male	145 (56.2)	163 (63.2)
Female	113 (43.8)	95 (36.8)
Race, n (%)		

	SECURE (ITT)	
	ISA (N = 258)	VRC (N = 258)
White	211 (81.8)	191 (74.3)
Black or African American	1 (0.4)	1 (0.4)
Asian	45 (17.4)	64 (24.9)
Other	1 (0.4)	1 (0.4)
Geographical Region n (%)		
North America	30 (11.6)	28 (10.9)
Western Europe, Australia, and New Zealand	105 (40.7)	107 (41.5)
Other regions	123 (47.7)	123 (47.7)
Underlying Medical Conditions n (%)		
Hematologic malignancy	211 (81.8)	222 (86.0)
Prior allogeneic BMT/HSCT	54 (20.9)	51 (19.8)
Uncontrolled malignancy at baseline	173 (67.1)	187 (72.5)
Neutropenia[a]	163 (63.2)	175 (67.8)
Diabetes mellitus	4 (1.6)	0
eGFR-MDRD (mL/min/1.73 m^2), n (%)		
< 60	20 (8.0)	33 (13.2)
≥ 60	231 (92.0)	217 (86.8)
Corticosteroid use	48 (18.6)	39 (15.1)
T-cell immunosuppressant use	111 (43.0)	109 (42.2)

ANC = absolute neutrophil count; BMT = bone marrow transplant; eGFR-MDRD = estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; EOT = end of treatment; HSCT = hematopoietic stem cell transplant; ISA = isavuconazole; ITT = intention-to-treat; VRC = voriconazole.

[a] The presence or absence of neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3).

Source: FDA report,[34] Clinical Study Report,[23] and Maertens (2016).[29]

Table 7: Demographics and Baseline Characteristics (VITAL: Invasive Mucormycosis or Invasive Aspergillosis)

	ISA						
	IM				IA		
	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (N = 37)	RI (n = 20)	NRI (n = 4)	Total (n = 24)
Age (years), mean (SD)	51.7 (14.72)	46.4 (16.55)	39.6 (15.22)	48.5 (15.51)	55.7 (20.65)	41.5 (25.72)	55.3 (21.63)
Gender, n (%)							
Male	17 (81.0)	8 (72.7)	5 (100.0)	30 (81.1)	12 (60.0)	3 (75.0)	15 (62.5)
Female	4 (19.0)	3 (27.3)	0	7 (18.9)	8 (40.0)	1 (25.0)	9 (37.5)
Race, n (%)							
White	12 (57.1)	10 (90.9)	3 (60.0)	25 (67.6)	17 (85.0)	4 (100.0)	21 (87.5)
Black or African American	1 (4.8)	1 (9.1)	2 (40.0)	4 (10.8)	0	0	0
Asian	8 (38.1)	0	0	8 (21.6)	3 (15.0)	0	3 (12.5)
eGFR-MDRD category (< 60 mL/min/1.73m^2), n (%)	6 (28.6)	3 (27.3)	2 (40.0)	11 (29.7)	20 (100.0)	0	20 (83.3)
Geographic Region, n (%)							
North America	7 (33.3)	4 (36.4)	5 (100.0)	16 (43.2)	11 (55.0)	1 (25.0)	12 (50.0)
Western Europe	1 (4.8)	4 (36.4)	0	5 (13.5)	4 (20.0)	0	4 (16.7)
Other regions[a]	13 (61.9)	3 (27.3)	0	16 (43.2)	5 (25.0)	3 (75.0)	8 (33.3)

	ISA						
	IM				IA		
	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (N = 37)	RI (n = 20)	NRI (n = 4)	Total (n = 24)
Underlying Medical Conditions, n (%)[b]							
Neutropenic	4 (19.0)	5 (45.5)	1 (20.0)	10 (27.0)	5 (25.0)	3 (75.0)	8 (33.3)
Allogeneic BMT status	4 (19.0)	4 (36.4)	5 (100.0)	13 (35.1)	7 (35.0)	2 (50.0)	9 (37.5)
Uncontrolled malignancy status	11 (52.4)	6 (54.5)	1 (20.0)	18 (48.6)	5 (25.0)	2 (50.0)	7 (29.2)
Hematologic malignancy status	11 (52.4)	7 (63.6)	4 (80.0)	22 (59.5)	11 (55.0)	3 (75.0)	14 (58.3)
T-cell immunosuppressant use	7 (33.3)	6 (54.5)	5 (100.0)	18 (48.6)	15 (75.0)	3 (75.0)	18 (75.0)
Corticosteroid use	5 (23.8)	3 (27.3)	2 (40.0)	10 (27.0)	12 (60.0)	1 (25.0)	13 (54.2)
Renal impairment	6 (28.6)	3 (27.3)	2 (40.0)	11 (29.7)	20 (100)	0	20 (83.3)
Therapy Status							
Primary therapy	21/37	–	–	21/37	15 (75.0)	1 (25.0)	16 (66.7)
Refractory	–	11/37	–	11/37	4 (20.0)	3 (75.0)	7 (29.2)
Intolerant	–	–	5/37	5/37	1 (50.0)	0	1 (4.2)

BMT = bone marrow transplant; eGFR-MDRD = estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; EOT = end of treatment; HSCT = hematopoietic stem cell transplant; IA = invasive aspergillosis; IM = invasive mucormycosis; ISA = isavuconazole; ITT = intention-to-treat; NRI = no renal impairment; RI = renal impairment; SD = standard deviation.

[a] Other regions included Russia, Mexico, Brazil, Thailand, South Korea, India, Lebanon, and Israel.

[b] An eGFR-MDRD rate of < 60 mL/min suggests kidney damage.

Source: Clinical Study Report.[24]

Interventions

In the SECURE study, patients were randomized 1:1 to receive either ISA or VRC. For ISA, the loading dose was 200 mg (IV) three times a day for day 1 and day 2, and the maintenance dose was 200 mg daily (IV or oral) from day 3 to the end of treatment. For VRC, the loading dose was 6 mg/kg (IV) twice a day on day 1. The maintenance dose for VRC was 4 mg/kg (IV) twice daily on day 2, and either IV (4 mg/kg twice daily) or orally (200 mg twice daily) from day 3 to the end of treatment. The maximum treatment duration was 84 days. The sponsor, investigators, and patients were blinded to the randomization of the study drug.[23]

In the VITAL study, the ISA dose regimen was the same as that used in the SECURE study. The maximum treatment duration was 180 days.[24] As this was a single-arm trial, there was no control group.

Outcomes

In the SECURE study, the primary outcome was all-cause mortality through day 42 in the ITT population. The manufacturer's rationale for using the ITT population (i.e., all patients with proven, probable, or possible IFD, regardless of certainty of diagnosis of IFD and causative organism) is that this reflects the population of patients requiring antifungal therapy in a real clinical setting. The key secondary outcome was overall response (as assessed by the data review committee) at end of treatment in patients who had proven or probable IFD (i.e., modified intention-to-treat [mITT] population). Other secondary outcomes included all-cause mortality through day 84, treatment response (overall, clinical, mycological, and radiological responses) assessed by the data review committee at the end of treatment and on day 42 and day 84. Other outcomes included safety. Treatment-

emergent adverse events (TEAEs) were defined as an adverse event starting after administration of the first study drug until 28 days after the last dose.

In the VITAL study, the primary outcome was the overall response to treatment at day 42.[18] The secondary outcomes included the treatment response (overall, clinical, radiological, and mycological responses) at the end of treatment and on day 42 and day 84, as well as all-cause mortality through day 84).[18]

In both studies, the overall response included treatment success (defined as complete or partial responses) or treatment failure (defined as stable or progressive disease). The overall response was a composite of the clinical, mycological, and radiological responses based on the pre-specified criteria (see Table 36 in Appendix 5). Briefly, success required resolution (complete or partial) of clinical symptoms and physical findings associated with IFD; resolution (complete) or improvement (partial) of radiological abnormalities (where relevant); and presumed or documented eradication.

In both trials, safety data are presented as adverse events, serious adverse events, and death. All data on adverse events presented in this review report are for TEAEs, defined as an adverse event starting after administration of the first study drug until 28 days after the last dose of the study drug.

Statistical Analysis

In the SECURE study, the pre-specified noninferiority margin for the primary efficacy outcome (all-cause mortality in the ITT population through day 42) was that the upper limit of the 95% confidence interval [CI] for a treatment difference was 10% or less. The sample size calculation was based on the primary efficacy outcome. It was suggested that about 255 patients in each group were required for an 80% power to demonstrate that the upper limit of the 95% CI for a treatment difference was 10% or less. This calculation was based on a one-sided, normal-approximation, and noninferiority test at a 2.5% significance level. A 20% mortality rate was assumed for both drugs in the primary efficacy population. The manufacturer indicated that the FDA, Infectious Diseases Society of America, the American Thoracic Society, the Society of Critical Care Medicine, and the American College of Chest Physicians proposed that a 10% noninferiority margin for all-cause mortality in serious infections would be clinically acceptable.[37] For the primary outcome, the adjusted treatment difference was calculated using a stratified Cochran–Mantel–Haenszel method with the randomization strata of geographical region, allogeneic hemopoietic stem cell transplantation status, and active malignancy status. The 95% CI for the adjusted treatment difference was calculated on the basis of a normal approximation. Treatment-by-subgroup interaction (baseline neutropenic status, glomerular filtration rate, etc.) was evaluated using a logistic regression according to the pre-specified statistical significance value of $P < 0.15$. Categorical data were summarized by number and percentage of patients within each category. Any missing data were presented as part of a missing category. To calculate crude mortality, unknown survival status was counted as dead, while the Kaplan–Meier method censored them. For treatment response, only patients with both a baseline and at least one post-baseline value were included in the calculation. Patients with missing data were considered to have experienced treatment failure.

The VITAL study was an open-label trial without a comparator group and its analyses were descriptive. No formal statistical analyses were performed.[24] However, for the IM subpopulation, IM cases treated with ISA as primary treatment were matched with controls

from the FungiScope registry,[19] which recruited from 17 centres worldwide; patients with proven or probable IM received primary AmB-based treatment and were analyzed for day 42 all-cause mortality.[18] Matching was based on three dichotomous covariates: severe disease (defined as central nervous system or disseminated involvement), hematological malignancy, and surgical treatment within seven days of antifungal treatment initiation. Investigators, sponsors, and statisticians were blinded to patient outcomes. The case matching and the comparative analysis were conducted blindly.[18]

Analysis Populations

In the SECURE study, the following population analysis sets were used:

ITT: The ITT population consisted of all randomized patients who received at least one dose of the study drug. For this population, data were analyzed by the treatment group that patients were randomized to, even though they might not be compliant with the protocol or assigned treatment.

mITT: The mITT population consisted of ITT patients who had a proven or probable IFD. The diagnosis criteria for IFDs are presented in Table 35 in Appendix 5.

Mycological intention-to-treat (myITT): The myITT population consisted of mITT patients with proven or probable IA based on cytology, histology, culture, or galactomannan criteria assessed by the data review committee.

Per-protocol set: The per-protocol population was a subset of ITT patients who did not deviate from protocol.

Safety analysis set (SAS): The SAS population consisted of all randomized patients who received at least one dose of the study drug. For the SAS, data were analyzed according to the study drug that patients received as the first dose, even if it was different from what they were randomized to.

In the VITAL study (for the IM and IA subpopulation), the mITT population included patients with proven or probable IM or IA only. The IM population was presented by therapy status (i.e., primary, refractory, or intolerant). The IA population was presented by renal function status (renal impairment or no renal impairment). The SAS was based on all enrolled patients (N = 146) who received at least one dose of the study drug.

Patient Disposition

Patient dispositions for the SECURE study and the VITAL study are presented in Table 8 and Table 9, respectively. In the SECURE study, a total of 527 patients were randomized. Of these, 516 (97.9%) patients (258 in each treatment group) received at least one dose of the treatment (i.e., the ITT population). Of the ITT population, 46.1% completed the study and 53.9% of patients discontinued the study drug. A patient was considered to have completed the study if they received 84 days of treatment or had a successful outcome and received a minimum of seven days of treatment. The most common reasons for stopping the study drug were adverse events (12.0% versus 20.5% in the ISA and VRC groups, respectively), Insufficient response (15.1% versus 8.9%), death (6.6% versus 8.1%), violation of selection at entry (6.6% versus 3.9%), and administration reason (6.6% versus 3.9) (Table 8).

In the VITAL study, for the IM subpopulation (N = 37), 30% had completed treatment, 65% had discontinued, and 5% were ongoing. The most common reasons for treatment discontinuation were death (30%), adverse events / intercurrent illness (16%), and patient did not cooperate (11%). For the IA subpopulation (N = 24), 37.5% had completed, 58.3% had discontinued, and 4.2% were ongoing. The most common reasons for treatment discontinuation were adverse events / intercurrent illness (20.8%), death (16.7%), insufficient therapeutic response (8.3%), and protocol violation (8.3%) (Table 9).

Table 8: Patient Disposition (SECURE)

	SECURE	
	ISA	VRC
	(N = 263)	(N = 264)
Patient with informed consent	532	
Randomized, n (%)	263 (100)	264 (100)
Did not receive the drug n (%)	5 (1.9)	6 (2.3)
Intention-to-treat, n (%)	258 (98.1)	258 (97.7)
Completed	118 (45.7)	120 (46.5)
Discontinued	140 (54.3)	138 (53.5)
Adverse event / intercurrent illness	31 (12.0)	53 (20.5)
Death	17 (6.6)	21 (8.1)
Insufficient therapeutic response	39 (15.1)	23 (8.9)
Failure to return / lost to follow-up	2 (0.8)	1 (0.4)
Violation of selection at entry	17 (6.6)	10 (3.9)
Other protocol violation	10 (3.9)	6 (2.3)
Did not cooperate	12 (4.7)	9 (3.5)
Refused treatment	7 (2.7)	5 (1.9)
Withdrew consent	5 (1.9)	4 (1.6)
Administrative/other	12 (4.7)	15 (5.8)
Modified intention-to-treat, n (%)	143 (54.4)	129 (48.9)
Mycological intention-to-treat, n (%)	123 (46.8)	108 (40.9)
Probable *Aspergillus* by serum GM only, n (%)	71 (27.0)	68 (25.8)
Aspergillus only or *Aspergillus* plus other mould pathogens, n (%)	52 (19.8)	40 (15.2)
Per-protocol, n (%)	172 (65.4)	175 (66.3)
Safety analysis set, n (%)	257 (97.7)	259 (98.1)

GM = galactomannan; ISA = isavuconazole; VRC = voriconazole.

Source: Clinical Study Report, pages 174 to 175.[23]

Table 9: Patient Disposition (VITAL: Overall, Invasive Mucormycosis, or Invasive Aspergillosis)

	VITAL (ITT)		
	RI	**NRI**	**Total**
Signed informed consent, N			149
Enrolled, N	59	90	149
Randomized, N (%)	NA	NA	NA
ITT, N (%)	59 (100.0)	87 (96.7)	146 (98.0)
mITT, N (%)	54 (91.5)	86 (95.6)	140 (94.0)
mITT-*Aspergillus*	20 (33.9)	4 (4.4)	24 (16.1)
mITT-*Mucorales*	11 (18.6)	26 (28.9)	37 (24.8)
Safety, N	59 (100.0)	87 (96.7)	146 (98.0)

	IM				IA		
n (%)	**Primary Therapy (N = 21)**	**Refractory (N = 11)**	**Intolerant (N = 5)**	**Total (N = 37)**	**RI (N = 20)**	**NRI (N = 4)**	**Total (N = 24)**
Treatment period							
Completed	6 (28.6)	2 (18.2)	3 (60.0)	11 (29.7)	8 (40.0)	1 (25.0)	9 (37.5)
Discontinued	13 (61.9)	9 (81.8)	2 (40.0)	24 (64.9)	12 (60.0)	2 (50.0)	14 (58.3)
Death	6 (28.6)	3 (27.3)	2 (40.0)	11 (29.7)	3 (15.0)	1 (25.0)	4 (16.7)
AE / intercurrent illness	2 (9.5)	4 (36.4)	0	6 (16.2)	4 (20.0)	1 (25.0)	5 (20.8)
Did not cooperate	3 (14.3)	1 (9.1)	0	4 (10.8)	–	–	–
Insufficient therapeutic response	1 (4.8)	1 (9.1)	0	2 (5.4)	2 (10.0)	0	2 (8.3)
Administrative/other	1 (4.8)	0	0	1 (2.7)	1 (5.0)	0	1 (4.2)
Other protocol violation	–	–	–	–	2 (10.0)	0	2 (8.3)
Failure to return/LTFU	–	–	–	–	1 (5.0)	0	1 (4.2)
Ongoing	2 (9.5)	0	0	2 (5.4)	0	1 (25.0)	1 (4.2)

AE = adverse event; IA = invasive aspergillosis; IM = invasive mucormycosis; ISA = isavuconazole; ITT = intention-to-treat; LTFU = lost to follow-up; mITT = modified intention-to-treat; NA = not applicable; NRI = no renal impairment; RI = renal impairment.

Source: Clinical Study Report.[24]

Exposure to Study Treatments

In the SECURE study, the total study drug duration was similar between the ISA and VRC treatment groups (see Table 21 in Appendix 4). The mean treatment duration was 46.7 days and ranged from 1 day to 102 days. The median IV- or oral-dosing days were 5 days (range: 1 to 84) or 55.8 days (range: 0.5 to 99.5), respectively.

In the VITAL study for the IM subpopulation, the mean treatment duration was 132.5 days and ranged from 2 days to 882 days. The median IV- or oral-dosing days were 10 days (range: 2 to 77) or 80 days (range: 7 to 882), respectively. For the IA subpopulation, the mean treatment duration was 91.2 days and ranged from 4 days to 343 days. The median IV- or oral-dosing days were 9.5 days (range: 2.5 to 35) or 77.5 days (range: 4 to 321), respectively (see Table 22 in Appendix 4).

Critical Appraisal

Internal Validity

The SECURE study was a phase III double-blind, noninferiority active-controlled randomized trial with appropriate randomization and allocation-concealment procedures. These methods included an interactive response computer system to randomize (1:1 ratio) patients to receive ISA or VRC. Randomization was conducted using a block size of four and was stratified by geographical region, allogeneic hematopoietic stem cell transplantation, and active malignancy at study entry. Baseline characteristics were generally similar across treatment groups, although some minor numerical differences between treatment groups existed in terms of proportion of patients by sex or race. However, based on the clinical expert CDR consulted for this review, it is not expected that there would be a difference in treatment effect for antifungal drugs between males and females or among different races. The SECURE study was designed to test the noninferiority of ISA versus VRC for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi, based on a 10% noninferiority margin of the upper limit of the 95% CI of the treatment group difference for the all-cause mortality through day 42 for ITT population. The justification for the 10% noninferiority margin was provided and was accepted by the FDA and Health Canada.[30,34] The primary analysis was based on the ITT population, which could potentially bias the results in favour of a finding of noninferiority. However, secondary analyses using the per-protocol analysis set was conducted to corroborate the primary findings, thus providing reassurance of the results. Analyses for subgroups with greater diagnostic certainty were also performed, including for patients with a proven or probable IFD (i.e., mITT analysis) or patients with proven or probable IA (i.e., myITT analysis) to support the results from the ITT population. However, results for these subgroups may be subject to bias, given that the benefit of randomization (equal distribution of prognostic factors) may not have been achieved in these subgroups. The clinical expert consulted for this review indicated that while the ITT population represents a patient population with the greatest diagnostic uncertainty, given the nature of the difficulties in diagnosing IFDs and the common use of empiric treatment, the ITT population reflects a patient population that would be treated for IFDs in real-world clinical settings.

All-cause mortality (the primary outcome) is an objective measure and was assessed with well accepted standard methodologies; patients with unknown survival status were counted as dead. The key secondary outcome, the overall response for the mITT population, was assessed in a blind manner. The overall response was a composite outcome, which could potentially affect the interpretation of the results, although the individual components (clinical, mycological, and radiological responses) were also reported. Overall, the major concern was the high discontinuation rate in both groups (54.3% and 53.5 in the ISA and VRC groups, respectively). It was uncertain how the high discontinuation rate affected the validity of the outcomes reported in the SECURE study. Overall, the appropriate design features as described previously minimize the risk of selection bias, performance bias, detection bias, and attrition bias.

The VITAL study was an open-label, single-arm study. In theory, due to the nature of the open-label and single-arm study, as well as the relatively small sample size for the IM subpopulation (N = 37) and IA subpopulation (total: N = 24, including renal impairment [N = 20] and no renal impairment [N = 4]), the lack of a comparator group limits interpretation. However, since IM is a rare disease, the manufacturer provided a historical

cohort control analysis for the subpopulation of IM[18] and compared the all-cause mortality for ISA treatment reported in the VITAL study with that for AmB treatment obtained from the FungiScope registry.[19] While it showed similar all-cause mortality in the ISA group compared with the AmB group in the treatment of IM, various limitations of the matched analysis need to be pointed out: the findings could be biased by several of the following confounding factors. There was some imbalance in some of the important characteristics at baseline between the two groups (i.e., cases from the VITAL study versus the controls from the FungiScope registry), such as the proportion of patients with hematological malignancy (ISA versus AmB [45% versus 39%]), severity of disease (50% versus 62%), and surgical treatment (44% versus 23%).[18] Furthermore, the median ISA treatment duration was 102 days in the VITAL study, but the AmB treatment from the FungiScope registry was for a median of 18 days (see Table 25 in Appendix 4).[18]

Both trials conducted pre-planned subgroup analyses for the primary outcome. The *P* values for subgroup interactions were reported; no *P* values were reported as statistically significant.

Both studies featured an appropriate approach for analyzing safety data, including all adverse events after first dose of the treatment medication until four weeks after end of treatment.

External Validity

Eleven per cent of the enrolled patients in the SECURE study, 40% of patients in the IM subpopulation, and 50% of patients in the IA subpopulation in the VITAL study were from North American (US and Canada). The CDR clinical experts consulted for this review indicated there is no treatment difference expected between geographic regions. Other baseline and demographic characteristics, including age, gender, underlying medical conditions, and renal impairment, were similar to the patients observed in Canadian settings. No comparative efficacy data were available for patients with prior treatment failure. Whether the comparative efficacy of ISA versus VRC observed in the SECURE study can be generalized to those patients with prior treatment failure is uncertain. The generalizability of the findings from the SECURE study could also be limited because of the exclusion of patients with AIDS, abnormal liver function, and those receiving antifungal prophylaxis with a mould-active azole. In addition, in the SECURE study, 11% of patients with rare disorders for invasive mould disease other than *Aspergillus* or other filamentous fungi were enrolled. In 51.5% of patients, the mycological diagnosis was based on the galactomannan test with no pathogen identified. So, the population was not strictly limited to IA. However, the clinical expert consulted by CDR indicated that the mycological confirmation of the diagnosis for IM or IA is very difficult in clinical practice; the antifungal treatment usually starts based on the host factors, clinical manifestations, radiological signs, and the mycological evidence. Therefore, the populations included in both studies are reflective of and similar to Canadian settings; there should be no concern regarding generalization.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported subsequently. (See Appendix 4 for additional efficacy data.) Limited data were reported for health care resource utilization (e.g., hospitalizations). No data were reported in either trial regarding the need for salvage therapy or health-related quality of life.

Survival Status

In the SECURE study, all-cause mortality through day 42 in the ITT population was reported in 18.6% and 20.2% of the ISA and VRC treatment groups, respectively. The adjusted treatment difference was −1.0% (95% CI: −7.8 to 5.7) (Table 10). This demonstrated that ISA was noninferior to VRC based on a prior specified noninferiority margin (the upper limit of the 95% CI for a treatment difference was ≤ 10%). The per-protocol analysis for all-cause mortality was 15.1% and 17.7% in the ISA and VRC treatment groups, respectively. The adjusted treatment difference was −2.6 (95% CI: −10.3 to 5.1) (Table 10). The more detailed information on the subgroup analysis based on the certainty of the diagnosis analysis is also presented in Table 23 in Appendix 4. For the subgroups based on the underlying medical condition, the adjusted treatment differences (ISA minus VRC) ranged from −3.3% in patients with no neutropenia to 4.6% in patients with bone marrow transplant. The upper limit of the 95% CIs around the adjusted treatment differences ranged from 5.0% in patients without bone marrow transplant to 21.9% in patients with bone marrow transplant (see Table 23 in Appendix 4). The all-cause mortality through day 84 in the ITT population and other population analysis sets and in various subgroups is presented In Table 24). The adjusted treatment differences ranged from −10.5 % to 2.6%. The upper limit of the 95% CIs around the adjusted treatment differences ranged from 4.1% to 21.7% (see Table 24 in Appendix 4). There were no analysis results reported on subgroups by prior antifungal treatments.

For the IM subpopulation in the VITAL study, the all-cause mortality through day 42 and day 84 was 37.8% and 43.2%, respectively (Table 11). The all-cause mortality for the patients with renal impairment was 15% and 25% through day 42 and day 84, respectively (Table 11). The manufacturer provided an additional analysis that compared the all-cause mortality for ISA treatment as primary therapy for IM (N = 21) in the VITAL study with that for AmB therapy for IM reported in the FungiScope registry database (N = 33). It was reported that all-cause mortality from the FungiScope registry database was 13 out of 33 (39%; 95% CI: 22.9% to 57.9%). All-cause mortality from the VITAL study was 7 out of 21 (33%; 95% CI: 14.6% to 57.0%). No statistically significant difference was identified between the two groups (P = 0.775).[18] For the IA subpopulation, all-cause mortality through day 42 and day 84 was reported in 12.5% and 25% of patients, respectively.)

The results of the Kaplan–Meier survival analysis in the SECURE study are presented in Figure 2 and Figure 3 in Appendix 4 for the ITT population and proven and probable IFDs subpopulation, respectively. Patients on ISA showed a consistently higher survival than patients on VRC through 84 days. A similar pattern was observed for patients with “proven or probable” IFDs. However, no statistical testing results are available on those differences in survival between the two treatment arms. The Kaplan–Meier survival analysis in the VITAL study is presented in Figure 4 and Figure 5 in Appendix 4 for IM and IA, respectively.

Table 10: All-Cause Mortality (SECURE)

	SECURE				
	ISA (N = 258)		VRC (N = 258)		Adjusted Treatment Difference[a] (ISA Minus VRC) (%) 95% CI (%)
	N	n (%)	N	n (%)	
Through Day 42					
ITT	258	48 (18.6)	258	52 (20.2)	−1.0 (−7.8 to 5.7)
PP	172	26 (15.1)	175	31 (17.7)	−2.6 (−10.3 to 5.1)
mITT	143	28 (19.6)	129	30 (23.3)	−2.6 (−12.2 to 6.9)
myITT	123	23 (18.7)	108	24 (22.2)	−2.7 (−12.9 to 7.5)
Through Day 84					
ITT	258	75 (29.1)	258	80 (31.0)	−1.4 (−9.2 to 6.3)
PP	172	43 (25.0)	175	48 (27.4)	−2.8 (−11.9 to 6.2)
mITT	143	43 (30.1)	129	48 (37.2)	−5.5 (−16.1 to 5.1)
myITT	123	35 (28.5)	108	39 (36.1)	−5.7 (−17.1 to 5.6)

CI = confidence interval; GM = galactomannan; ISA = isavuconazole; ITT = intention-to-treat; mITT = modified intention-to-treat; myITT = mycological intention-to-treat; PP = per-protocol; VRC = voriconazole.

[a] The adjusted treatment difference (ISA minus VRC) was calculated using a stratified Cochran–Mantel–Haenszel method with the strata of geographical region, allogeneic bone marrow transplant status and uncontrolled malignancy status. The 95% confidence interval for the adjusted treatment difference was calculated based on a normal approximation.

Note: The ITT population consisted of all randomized patients with proven, probable, or possible IFD who received at least one dose of the study drug. The mITT population consisted of ITT patients who had proven or probable IFD. The myITT population consisted of mITT patients with proven or probable IA based on cytology, histology, culture, or GM criteria.

Source: Clinical Study Report.[23]

Table 11: All-Cause Crude Mortality (VITAL: For Invasive Mucormycosis or Invasive Aspergillosis)

All-Cause Mortality	VITAL (ISA)						
	IM				IA		
	Primary Therapy (N = 21)	Refractory (N = 11)	Intolerant (N = 5)	Total (N = 37)	RI (N = 20)	NRI (N = 4)	Total (N = 24)
Through day 42, n (%)	7 (33.3)	5 (45.5)	2 (40.0)	14 (37.8)	3 (15.0)	0	3 (12.5)
Through day 84, n (%)	9 (42.9)	5 (45.5)	2 (40.0)	16 (43.2)	5 (25.0)	1 (25.0)	6 (25.0)

IA = invasive aspergillosis; IM = invasive mucormycosis; ISA = isavuconazole; ITT = intention-to-treat; LTFU = lost to follow-up; NRI = no renal impairment; RI = renal impairment.

Source: Clinical Study Report.[24]

Treatment Response

In the SECURE study, as a key secondary efficacy, the overall response in patients with proven or probable IFD (mITT population) at the end of treatment was similar for the ISA and VRC groups (35.0% and 36.4%, respectively [Table 12]). The adjusted treatment-group difference (VRC minus ISA) was 1.6% (95% CI: −9.3%, 12.6% [Table 12]). The overall response at end of treatment for various subgroups in patients with proven or probable IFDs is presented in Table 28 in Appendix 4. In general, results were consistent with those for the aforementioned mITT population. The overall response at end of treatment for patients with proven, probable, or possible (ITT population) is presented in Table 13. It was demonstrated that overall response at the end of treatment was 39.4% and 41.4% in the ISA group and VRC group, respectively. The overall response for patients with proven or probable IA (myITT population) at the end of treatment is presented

in Table 27 in Appendix 4, which showed a similar response to that observed in the patients with proven or probable IFDs (mITT population).

The overall response at day 84 for the patients with proven or probable IFD (mITT population) is presented in Table 26 in Appendix 4. The percentage of patients with overall response at day 84 was numerically higher in the VRC group compared with the ISA group (32.6% versus 25.2%). Clinical, mycological, and radiological responses between ISA and VRC treatment groups at end of treatment, and at day 42 and day 84 are presented in Table 29. In the VITAL study, the overall response at the end of treatment was 31.4% for the IM subpopulation and 34.8% for the IA subpopulation, respectively (Table 12). The overall response at end of treatment based on the treatment type for IM and renal function status for IA is presented in Table 30 in Appendix 4. The response by IM patients to the primary therapy was 31.6% (see Table 30 in Appendix 4). The overall response for the IM subpopulation at day 42 and day 84 were 10.8% and 18.9%, respectively (Table 31). The overall response for the IA subpopulation at day 42 and day 84 were 29.2% and 29.2%, respectively (Table 31). The clinical, mycological, and radiological response at end of treatment as well as at day 42 and day 84 are presented in Table 32 and Table 33 in Appendix 4, respectively.

Table 12: Overall Response (End of Treatment, Modified Intention-to-Treat)

Outcome	SECURE		VITAL	
	ISA	VRC	ISA	
			IM	IA
Response	(N = 143)	(N = 129)	Total (N = 37)	Total (N = 24)
Success, n (%)	50 (35.0)	47 (36.4)	11/35 (31.4)	8/23 (34.8)
Adjusted difference (%, 95% CI %)	1.6 (−9.4 to 12.6)		NA	NA
Complete	17 (11.9)	13 (10.1)	5/35 (14.3)	4/23 (17.4)
Partial	33 (23.1)	34 (26.4)	6/35 (17.1)	4/23 (17.4)
Failure, n (%)	93 (65.0)	82 (63.6)	24/35 (68.6)	15/23 (65.2)
Stable	42 (29.4)	33 (25.6)	10/35 (28.6)	4/23 (17.4)
Progression	51 (35.7)	49 (38.0)	14/35 (40.0)	11/23 (47.8)

CI = confidence interval; IA = invasive aspergillosis; IFD = invasive fungal disease; IM = invasive mucormycosis; ISA = isavuconazole; ITT = intention-to-treat; mITT = modified intention-to-treat; NA = not applicable; VRC = voriconazole.

Note: mITT population consisted of ITT patients who had proven or probable IFD.

Source: Clinical Study Report.[23,24]

Table 13: Overall Response (SECURE, Intention-to-Treat)

	SECURE		
	IFD Category	ISA	VRC
		n/N (%)	n/N (%)
End of treatment	**Total**	91/231 (39.4)	98/237 (41.4)
	Proven	7/29 (24.1)	11/36 (30.6)
	Probable	43/114 (37.7)	36/93 (38.7)
	Possible	41/88 (46.6)	51/108 (47.2)
Day 42	**Total**	89/231 (38.5)	95/237 (40.1)
	Proven	7/29 (24.1)	13/36 (36.1)
	Probable	45/114 (39.5)	33/93 (35.5)
	Possible	37/88 (42.0)	49/108 (45.4)
Day 84	**Total**	71/231 (30.7)	81/237 (34.2)
	Proven	7/29 (24.1)	8/36 (22.2)
	Probable	30/114 (26.3)	35/93 (37.6)
	Possible	34/88 (38.6)	38/108 (35.2)

IFD = invasive fungal disease; ISA = isavuconazole; VRC = voriconazole.

Note: Overall response by IFD category without imputation of death; patients having no IFD were excluded by the data review committee.

Source: Clinical Study Report.[23]

Need for Salvage Therapy

The need for salvage therapy was not reported in the SECURE study. In the VITAL study, for the IM subpopulation (N = 37), 11 out of 37 patients (29.7%) had disease that was refractory and 5 out of 37 patients (13.5%) were intolerant of other antifungals at baseline; thus, ISA could be considered as salvage treatment for IM. No comparative information (ISA versus VRC) on the need for salvage therapy for either IM or IA was available in this submission.

Health-Related Quality of Life

Not evidence was reported.

Health Care Resource Utilization

For the patients with proven, probable, or possible IFDs in the SECURE study, the days in hospital are presented in Table 14. It was observed that the mean days in hospital for the ITT population were similar in both the ISA (19.7 days) and VRC (19.4 day) groups.

No information on health care resource utilization was reported for IM or IA in the VITAL study.

Table 14: Days in Hospital (SECURE Study)

		SECURE	
		ISA	VRC
Intention-to-treat	N of patients	245	250
	Mean days (SD)	19.7 (28.4)	19.4 (18.3)
	Median	13.0	14.0
	Range	1 to 371	2 to 118
Modified intention-to-treat	N of patients	134	124
	Mean days (SD)	18.8 (18.5)	20.5 (19.6)
	Median	12.0	14.0
	Range	1 to 106	3 to 118

ISA = isavuconazole; SD = standard deviation; VRC = voriconazole.

Source: Clinical Study Report.[23]

Harms

Adverse Events

In the SECURE study, overall adverse events (TEAEs) were reported by 96.1% and 98.5% of patients in the ISA and VRC groups, respectively (Table 15). The most common TEAEs in the respective ISA and VRC treatment groups were nausea (27.6% versus 30.1%), vomiting (24.9% versus 28.2%), diarrhea (23.7% versus 23.2%), pyrexia (22.2% versus 30.1%), constipation (14.0% versus 20.8%) and hypokalemia (17.5% versus 21.6%). In the VITAL study, safety outcomes was reported for all patients (N = 146). One or more TEAEs were reported by 95.2% of patients (Table 15). The most common TEAEs were vomiting (24.7%) and nausea (23.3%).

Serious Adverse Events

In the SECURE study, overall serious adverse events were reported by 52.1% and 57.5% of patients in the ISA and VRC groups, respectively (Table 15 and Table 34 in Appendix 4). Serious TEAEs that occurred in 5% or more of the patients in either the ISA or VRC treatment group were respiratory failure (5.4% versus 4.6%), septic shock (5.4% versus 3.9%), febrile neutropenia (5.4% versus 1.9%) (see Table 34 in Appendix 4). In the VITAL study, a total of 61.1% of patients reported one or more serious adverse event (see Table 34 in Appendix 4). The most common serious TEAE was acute renal failure (5.5%) (see Table 34 in Appendix 4).

Withdrawals Due to Adverse Events

In the SECURE study, the proportion of patients who stopped treatment due to adverse events was 14.4% and 22.8% in the ISA and VRC group, respectively (Table 15). In the VITAL study, a total of 19 (13.0%) patients reportedly discontinued treatment due to adverse events (Table 15).

Mortality

In the SECURE study, the percentage of all deaths (i.e., “all known death,” which included all deaths reported after the first dose of the study drug, regardless of time post-dose) was 31.5% for the ISA group and 33.6% for the VRC group (Table 15). All deaths included

patient deaths during the course of the study due to an adverse event that started prior to the first dose of study drug. In the VITAL study, the percentage of all deaths during the study was 32.2% (Table 15).

Notable Harms

The notable harms (adverse events of special interest for this review) were hepatic impairment, cardiovascular harms (tachycardia), and visual impairments. In the SECURE study, the percentage of patients reporting these three notable harms was numerically lower in the ISA group than in the VRC group (Table 15). Especially, vision impairment occurred in 1.6% of patients treated with ISA, while it occurred in 7.3% of patients treated with VRC (Table 15).

In the VITAL study, hepatic impairment (reported as an increase in aspartate transaminase or gamma-glutamyl transferase), cardiovascular harms (i.e., tachycardia), and visual impairments were reported in 7.5%, 2.1%, and 1.4% of patients.

Table 15: Harms

	SECURE		VITAL
	ISA (N = 257) n (%)	VRC (N = 259) n (%)	ISA Total (N = 146) n (%)
Patients with ≥ 1 TEAE	247 (96.1)	255 (98.5)	139 (95.2)
Most Common AEs (> 10% of Patients in Either Arms)			
Nausea	71 (27.6)	78 (30.1)	34 (23.3)
Vomiting	64 (24.9)	73 (28.2)	36 (24.7)
Diarrhea	61 (23.7)	60 (23.2)	27 (18.5)
Pyrexia	57 (22.2)	78 (30.1)	24 (16.4)
Hypokalemia	45 (17.5)	56 (21.6)	–
Constipation	36 (14.0)	54 (20.8)	16 (11.0)
Headache	41 (16.0)	38 (14.7)	26 (17.8)
Dyspnea	34 (13.2)	29 (11.2)	–
Cough	33 (12.8)	35 (13.5)	15 (10.3)
Febrile neutropenia	32 (12.5)	38 (14.7)	–
Chills	27 (10.5)	23 (8.9)	–
Fatigue	27 (10.5)	18 (6.9)	–
Back pain	26 (10.1)	19 (7.3)	–
Peripheral edema	26 (10.1)	31 (12.0)	17 (11.6)
Abdominal pain	25 (9.7)	36 (13.9)	–
Hypertension	25 (9.7)	31 (12.0)	–
Decreased appetite	22 (8.6)	28 (10.8)	–
Epistaxis	21 (8.2)	28 (10.8)	–
Hypotension	21 (8.2)	28 (10.8)	–
Rash	17 (6.6)	28 (10.8)	–
Hypomagnesemia	14 (5.4)	27 (10.4)	–
Patients with ≥ 1 SAE	134 (52.1)	149 (57.5)	89 (61.0)
WDAE	37 (14.4)	59 (22.8)	19 (13.0)

	SECURE		VITAL
	ISA (N = 257) n (%)	VRC (N = 259) n (%)	ISA Total (N = 146) n (%)
Death[a]	81(31.5)	87 (33.6)	47 (32.2)
Notable Harms			
Abnormal hepatic function[b]	4 (1.6%)[b]	9 (3.5%)[b]	5 (3.4%)[c]
Tachycardia	12 (4.7)	21 (8.1%)	8 (5.5%)
Visual impairment	4 (1.6)	19 (7.3)	2 (1.4%)[d]

AE = adverse event; AST = aspartate transaminase; GGT = gamma-glutamyl transferase; ISA = isavuconazole; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VRC = voriconazole; WDAE = withdrawals due to adverse event.

Note: In the VITAL study, "–" signifies that the AE was reported in ≤ 10% of patients.

Note: AEs reported at end of treatment plus four weeks after last dose of treatment.

[a] All known deaths included all deaths reported after the first dose of study drug regardless of time post-dose.

[b] Hepatic dysfunction is defined as: Total bilirubin ≥ 3 times the upper limit of normal (ULN); alanine transaminase or aspartate transaminase ≥ 5 times the ULN; or patients with known cirrhosis or chronic hepatic failure.

[c] Reported as hepatobiliary disorders.

[d] Vision impairment, including reduced vision acuity and blurred vision only.

Source: Clinical Study Report.[23,24]

Discussion

Summary of Available Evidence

The evidence for this CDR submission was obtained from two studies: SECURE and VITAL. The SECURE study was a double-blind, noninferiority active-controlled, multi-centre trial, while the VITAL study was an open-label, single-arm trial. Both trials were conducted in multiple regions including Canada, North and South America, Europe, Africa, Asia, and Pacific. The SECURE study compared the efficacy and safety of IV and oral formulations of ISA (N = 258) (200 mg IV three times a day on days 1 and 2, then either IV or oral formulations once daily) with VRC (N = 258) (6 mg/kg IV twice daily on day 1, 4 mg/kg IV twice daily on day 2, then 4 mg/kg IV twice daily or 200 mg orally twice daily from day 3 onward) for the treatment of proven, probable, or possible IA and other mould infections. The maximum treatment duration was 84 days. The VITAL study assessed the efficacy and safety of IV and oral formulations of ISA (the same dose used in the SECURE study) in the treatment of proven, probable, or possible IM (N = 37), IA (N = 24), or other rare fungal infection. The treatment duration was a maximum of 180 days. From the VITAL study, only information on IM or IA was reported for the purpose of this review.

Interpretation of Results

Efficacy

For Invasive Aspergillosis

The appropriate design features of the SECURE study included in this review (e.g., randomization, blinding, allocation concealment, standardized assessment of the primary outcomes [i.e., all-cause mortality], the key secondary outcomes [i.e., the overall treatment response], and an acceptable a priori–defined noninferiority margin) minimize the risk of selection bias, performance bias, detection bias, and attrition bias. The findings derived from the SECURE study met the a priori–defined noninferiority margin: the upper limit of the 95% CI for a treatment difference was 10% or less.

For patients with proven, probable, or possible IFDs: ISA treatment showed a level of all-cause mortality through day 42 similar to that observed in the VRC group in the treatment of patients diagnosed with proven, probable, or possible IFDs (i.e., ITT population analysis). The results demonstrated that ISA was noninferior to VRC in terms of all-cause mortality based on a ≤ 10% pre-specified noninferiority margin. (The adjusted between-treatment group difference was −1.0%; 95% CI: −7.8 to 5.7.) The overall treatment response (a composite of clinical, mycological, and radiological responses) at the end of treatment in the ISA group was also reported as similar to that observed in the VRC group, although numerically more patients in the VRC group reported a treatment response than in the ISA group (39% in the ISA group versus 41% in the VRC group).

For patients with proven or probable IFDs: ISA also showed similar all-cause mortality through day 42 compared with that reported in the VRC group in the treatment of patients with proven, probable IFDs (i.e., mITT population analysis). (The adjusted between-group treatment difference was −2.6; 95% CI: −12.2 to 6.9.) The overall treatment response at the end of treatment in the ISA group was also similar to that observed in the VRC group, while numerically more patients showed an overall treatment response in the VRC group

than in the ISA group (35% in ISA versus 36.4% in the VRC group). (The adjusted between-group treatment difference was 1.6; 95% CI: −9.4 to 12.6.)

For patients with proven or probable IA: Theoretically, the most relevant population for the Health Canada–approved indication for IA is supposed to be the subpopulation, that is, the patients with proven or probable IA (i.e., myITT population) reported in the SECURE study. However, the CDR clinical expert consulted for this review indicated that due to the nature of difficulties in getting a confirmed diagnosis of IFDs such as IA or IM, the population with clinically suspected IFDs (i.e., the ITT population reported in the included studies with proven, probable, or possible IFDs) reflects the real populations in the treatment of IFDs in real-world clinical settings. ISA showed a level of all-cause mortality through day 42 similar to that reported with VRC in the treatment of patients with proven or probable IA (i.e., myITT population analysis). (The adjusted between-group treatment difference was −2.7; 95% CI: −12.9 to 7.5.) ISA also demonstrated a similar overall treatment response at the end of treatment compared with that reported in the VRC group, although numerically more patients in the VRC group reported a treatment response than in the ISA group (35% in ISA versus 38.9% in the VRC group, respectively).

The clinical efficacy of ISA treatment in patients with IA reported through day 42 extended to day 84. The evidence of the clinical efficacy of ISA in the treatment of IA discussed previously was also further supported by the findings observed in the open-label single-arm study (VITAL).

Similar clinical efficacy (in terms of all-cause mortality and overall response) was observed in all other clinically important subgroups, such as underlying medical conditions and use of an immunosuppressant specified in this review protocol. However, no evidence of clinical efficacy for ISA treatment in patients with prior antifungal treatment experience was identified.

For patients with proven, probable, or possible IFDs, health care resource utilization, reported as number of days in hospital, was reportedly similar in both the ISA and VRC treatment groups.

No evidence of the need for salvage therapy or information on health-related quality of life was reported for ISA treatment in patients with IA.

For Invasive Mucormycosis

The clinical efficacy evidence for ISA in the treatment of patients with IM was derived from an open-label, single-arm study (N = 37; the IM subpopulation of patients in the VITAL study). The nature of the open-label, single-arm design as well as the relatively small sample size limits the interpretation of the findings.

For patients with proven or probable IM: In the VITAL study, only patients with proven or probable IM requiring therapy were enrolled in the IM subpopulation, including primary-therapy patients (i.e., patients with no previous antifungal treatment or who received antifungal treatment for less than four cumulative days within the seven days prior to the first administration of the study drug [N = 21]), patients with refractory disease (N = 11), and patients who were intolerant of treatment (N = 5). Overall all-cause mortality through day 42 and day 84 was 37.8% and 43.2%, respectively. All-cause mortality was higher than that observed in the IA population in both the VITAL and SECURE studies. The CDR clinical expert consulted for this review indicated that the higher mortality observed in IM compared with IA is clinically reasonable and expected because the treatment of IM is

more challenging clinically. Based on the manufacturer's additional analysis (historical case-control analysis), which compared the all-cause mortality of the ISA treatment as the primary therapy for IM (N = 21) in the VITAL study[18] to that of the AmB therapy for IM reported in the FungiScope registry database (N = 33),[19] no statistically significant difference was identified between the two cohort groups (P = 0.775).[18] Despite some limitations of the case-control analysis for IM, the survival benefit of the ISA treatment in patients with IM observed in the VITAL study, which appeared similar to that of the AmB treatment reported in the FungiScope registry, was considered clinically meaningful because of the extremely high mortality associated with IM, if untreated.

For the IM subpopulation (N = 37) in the VITAL study, 11 out of 37 patients (29.7%) had disease that was refractory and 5 out of 37 patients (13.5%) were intolerant of prior antifungal treatment at baseline, which was considered in the trial as receiving ISA as salvage treatment for IM. These patients were also considered to be an antifungal treatment-experienced subgroup. Due to the very small sample size, the findings are hard to interpret. No evidence was identified for any other the clinically important subgroups, such as underlying medical conditions or use of the immunosuppressant specified in this review protocol for IM.

No information on health-related quality of life or health care resource utilization was reported regarding ISA treatment in patients with IM.

Harms

The overall frequency of adverse events for patients treated with ISA appeared to be similar to those treated with VRC for the treatment of IAs (96.1% in the ISA group and 98.5% in the VRC group, respectively). Compared with VRC, patients treated with ISA seemed to have a numerically lower risk of vomiting, nausea, constipation, and deceased appetite, but a higher risk of experiencing headache, dyspnea, fatigue, and back pain. More importantly, ISA showed a numerically better safety profile than VRC in terms of the adverse events of special interest, including hepatic impairment (1.6% versus 3.5%, respectively); cardiovascular harms (tachycardia; 4.7% versus 8.7%, respectively); and visual disturbances (1.6% versus 7.3%, respectively). The proportion of patients who discontinued the study drug due to adverse events appeared lower in the ISA group than in the VRC group. Furthermore, the overall frequency of patients with serious adverse events also appeared similar in both groups, despite being numerically lower in the ISA group than in the VRC group (52.1% and 57.5%, respectively). It is noted that a numerically higher percentage of patients in the ISA group reported serious adverse events such as febrile neutropenia, respiratory failure, and septic shock, while patients in the VRC group more often reported serious adverse events such as pyrexia, sepsis, acute renal failure, pneumonia, and acute myeloid leukemia.

Indirect Treatment Comparisons

The direct evidence of the comparative efficacy and safety of ISA in treating IA is limited to comparisons with VRC, which has been recommended as the first-line treatment for IA. An NMA[38] that assessed the comparative efficacy of ISA versus AmB formulations or VRC in the treatment of patients with IA was identified in the literature by CADTH.

The NMA found the efficacy of ISA, in terms of all-cause mortality and overall response in the treatment of the patients with IA, is similar to VRC and L-AmB. However, due to the various limitations, particularly the potential methodological and clinical heterogeneity and

sparsity of trials, no conclusion on the comparative efficacy of ISA and other available therapies could be credibly drawn.

No NMA evidence was identified to compare ISA with posaconazole, itraconazole, or caspofungin in the treatment of IA. No NMA was identified for the treatment of IM.

Potential Place in Therapy[2]

ISA is designed specifically for the treatment of IFIs. It covers *Candida* infection (which may be covered by other azoles, echinocandins, or polyenes), but the appeal of this drug is the expanded coverage for IA, covered by VRC, posaconazole, echinocandins, and polyenes, and IM, covered by posaconazole and polyenes.[20,21]

These severe, life-threatening infections typically present in patients with significant underlying immune suppression, such as from solid organ transplant or human stem cell transplant. The difficulty with managing these infections lies with the lack of readily available, economical, and expedited testing to make a diagnosis. Patients are often critically ill at the time the IFI is presented; thus, the preferred diagnostic test — tissue biopsy for culture and pathologic examination — is not usually practical.[20,21]

This drug does provide an additional less toxic option, compared with AmBisome and other polyenes, for treatment of IFI in high-risk immune-compromised populations. ISA would not necessarily be first-line therapy, given currently available, less expensive therapies. This drug could certainly be an alternative therapy for IA in those unable to tolerate VRC and when the benefit of, for example, posaconazole, is unsure. In addition, for patients on initial therapy with polyenes for proven or probable IA, the oral option with ISA makes it a potential option for follow-on therapy. Many patients at high risk for IFI are not at as high a risk for IM and, thus, can be managed with VRC, posaconazole, or echinocandins. For these patients, there is not a clear need for ISA as first-line therapy; hence, this drug would be an alternative for those with IA, whether proven or probable. As for higher-risk patients where IM is of concern, ISA would be a first-line choice along with the existing recommended first-line therapies, polyenes[22] or posaconazole, when AmB formulations are absolutely contraindicated.[22] Of course polyenes are more difficult to administer and associated with more adverse drug reactions.

For IM, there are fewer options for therapy. Based on the VITAL study, ISA is similar to polyenes, and the SECURE study showed noninferiority for VRC, though the latter drug is not generally considered as primary therapy for IM. Neither of these studies compared ISA with posaconazole, an azole with recognized activity for treating mucormycosis. For that grave infection, ISA could be used in conjunction with surgical debridement.

In summary, the major role for this drug would be when IM is a possible cause of IFI, where polyenes are currently first-line therapy, but are often limited by toxicity. As there is additional benefit to oral follow-on therapy with the same drug, this drug would be an alternative to posaconazole. This drug is not as critical for IA, since VRC and posaconazole are other azole options with both oral and parenteral therapies available. However, it could be an alternative, given that data suggest less visual toxicity than VRC.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

For the treatment of patients with IA, ISA appeared to have a treatment effect similar to VRC in terms of overall response and all-cause mortality over a nearly three-month period. For the treatment of patients with IM, based on a small single-arm trial with comparison with a historical control, similar clinical efficacy (overall response and all-cause mortality) of ISA compared with AmB was suggested; however, uncertainty remained. No direct evidence was identified that compared ISA with other drugs used in the treatment of IA or IM. The NMA did not provide credible evidence for ISA versus AmB in the treatment of IA. No notable difference in adverse events or serious adverse events was observed between ISA and VRC. However, more patients reported adverse events of special interest (hepatic impairment, cardiovascular harms, and visual impairments) in the VRC group than in the ISA group.

Appendix 1: Patient Input Summary

No patient input was received for this submission.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	December 05, 2018
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY

Line #	Search Strategy
1	(cresemba* or isavuconazol* or isavuconazonium * or BAL 8557* or BAL8557* or bal 4815 or bal4815 or "RO 0098557" or RO0098557 or "RO 0094815" or RO0094815 or 31Q44514JV or VH2L779W8Q or 60UTO373KE).ti,ab,kf,ot,hw,rn,nm.
2	1 use medall
3	*isavuconazole/ or *isavuconazonium/
4	(cresemba* or isavuconazol* or isavuconazonium* or BAL 8557* or BAL8557* or bal 4815 or bal4815 or "RO 0098557" or RO0098557 or "RO 0094815" or RO0094815).ti,ab,kw,dq.
5	or/3-4
6	5 use oemezd
7	6 not conference abstract.pt.

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
8	2 or 7
9	remove duplicates from 8

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search — isavuconazole OR isavuconazonium sulphate OR Cresemba OR BA8557]
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms — isavuconazole OR isavuconazonium sulphate OR Cresemba OR BA8557]

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Central Register of Controlled Trials	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.

Grey Literature

Dates for Search:	November 23, 2018 to November 30, 2018
Keywords:	Cresemba OR isavuconazole OR isavuconazonium sulphate OR invasive aspergillosis OR invasive aspergilloses OR aspergillus OR invasive mucormycosis OR invasive mucormycoses
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- Internet search
- background.

Appendix 3: Excluded Studies

Table 16: Excluded Studies

Reference	Reason for Exclusion
ANDES, D. R., et al.[39]	Outcome not of interest and pooled analysis
BARG, A. A., et al.[40]	Population not of interest (pediatrics)
CUMMINS, K. C., et al.[41]	Study design not of interest (retrospective study)
KULLBERG, B. J., et al.[42]	Population not of interest (neither IA nor IM)

IA = invasive aspergillosis; IM = invasive mucormycosis.

Appendix 4: Detailed Outcome Data

Table 17: Pathogens at Baseline (SECURE: Modified Intention-to-Treat)

	SECURE (mITT)	
	ISA (N = 143) n (%)	VRC (N = 129) n (%)
***Aspergillus* only**	49 (34.3)	39 (30.2)
***Aspergillus* plus other**	3 (2.1)	1 (0.8)
Non-*Aspergillus* only	5 (3.5)	6(4.7)
Mould not otherwise specified	14 (9.8)	15 (11.6)
No pathogen identified: Mycology based on GM	72 (50.3)	68 (52.7)
Serum-positive GM only	64 (44.8)	56 (43.4)
BAL GM–positive only	0	0
Serum GM and BAL GM–positive	7 (4.9)	12 (9.3)

BAL = bronchoalveolar lavage; GM = galactomannan (GM antigen assay for invasive aspergillosis); ISA = isavuconazole; ITT = intention-to-treat; mITT = modified intention-to-treat; VRC = voriconazole.

Note: mITT population consisted of ITT patients who had proven or probable IFD.

Source: Clinical Study Report,[23] FDA report,[34] and Maertens (2016).[29]

Table 18: Location of Invasive Fungal Diseases at Baseline (SECURE: Modified Intention-to-Treat)

IFD Location Categories	SECURE (mITT)	
	ISA (N = 143) n (%)	VRC (N = 129) n (%)
LRTD only	116 (81.1)	107 (82.9)
LRTD plus other organ	12 (8.4)	15 (11.6)
Non-LRTD only	15 (10.5)	7 (5.4)
Non-LRTD location	27 (18.9)	22 (17.1)

BAL = bronchoalveolar lavage; GM = galactomannan (GM antigen assay for invasive aspergillosis); IFD = invasive fungal disease; ISA = isavuconazole; ITT = intention-to-treat; LRTD = lower respiratory tract disease; mITT = modified intention-to-treat; VRC = voriconazole.

Note: mITT population consisted of ITT patients who had proven or probable IFD.

Source: Clinical Study Report,[23] FDA report,[34] and Maertens (2016).[29]

Table 19: Characterization of Analysis Populations (SECURE)

	SECURE	
	ISA	VRC
	N = 258	N = 258
ITT Population	**N = 258**	**N = 258**
Proven	29 (11.2)	36 (14.0)
Probable	114 (44.2)	93 (36.0)
Possible	88 (34.1)	108 (41.9)
No IFD	27 (10.5)	21 (8.1)
mITT	**143**	**129**
Aspergillus only	49 (34.3)	39 (30.2)
Aspergillus plus other mould	3 (2.1)	1 (0.8)
Non-*Aspergillus* only	5 (3.5)	6 (4.7)

	SECURE	
	ISA	VRC
	N = 258	N = 258
Mould not otherwise specified	14 (9.8)	15 (11.6)
No pathogen identified	72 (50.3)	68 (52.7)
myITT	**123**	**108**
Probable by serum GM only	71 (57.7)	68 (63.0)
Proven or probable aspergillosis by culture or histology	52 (42.3)	40 (37.0)
Per-protocol	**172**	**175**
Safety (safety analysis set)	**257**	**259**

GM = galactomannan (GM antigen assay for IA); IA = invasive aspergillosis; IFD = invasive fungal disease; ISA = isavuconazole; ITT = intention-to-treat; mITT = modified intention-to-treat; myITT = mycological intention-to-treat; VRC = voriconazole.

Note: mITT population consisted of ITT patients who had proven or probable IFD. The myITT population consisted of mITT patients with proven or probable IA based on cytology, histology, culture, or GM criteria.

Source: Clinical Study Report,[23] FDA report,[34] and Maertens (2016).[29]

Table 20: Invasive Fungal Diseases at Baseline (VITAL: Invasive Mucormycosis or Invasive Aspergillosis)

	VITAL						
	IM				IA		
	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (N = 37)	RI (n = 20)	NRI (n = 4)	Total (n = 24)
Category, n (%)							
Proven	18 (81.8)	10 (90.9)	4 (80.0)	32 (84.2)	8 (40.0)	1 (25.0)	9 (37.5)
Probable	3 (13.6)	1 (9.1)	1 (20.0)	5 (13.2)	12 (60.0)	3 (75.0)	15 (62.5)
Possible (mould infections only)	1 (4.5)	0	0	1 (2.6)	0	0	0
Assessment							
Mycological Criteria, n (%)							
No mycological evidence available	0	0	0	0	0	0	0
Total serum GM	0	0	0	0	8 (40.0)	2 (50.0)	10 (41.7)
BAL GM (at least one value ≥ 1.0)	1 (4.8)	1 (9.1)	0	2 (5.4)	3 (15.0)	1 (25.0)	4 (16.7)
Histopathology	18 (85.7)	10 (90.9)	4 (80.0)	32 (86.5)	8 (40.0)	1 (25.0)	9 (37.5)
Culture evidence of IFD	7 (33.3)	3 (27.3)	1 (20.0)	11 (29.7)	10 (50.0)	3 (75.0)	13 (54.2)
Autopsy	2 (9.5)	0	0	2 (5.4)	0	0	0
Pathogen at Baseline, n (%)							
Absidia corymbifera	2 (9.5)	0	0	2 (5.4)	NA		
Cunninghamella	0	0	1 (20.0)	1 (2.7)			
Mucor NOS	7 (33.3)	0	0	7 (18.9)			
Mucormycetes NOS	6 (28.6)	5 (45.5)	2 (40.0)	13 (35.1)			
Rhizomucor	2 (9.5)	2 (18.2)	1 (20.0)	5 (13.5)			
Rhizopus NOS	0	1 (9.1)	1 (20.0)	2 (5.4)			
Rhizopus oryzae	4 (19.0)	3 (27.3)	0	7 (18.9)			

	VITAL						
	IM				IA		
	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (N = 37)	RI (n = 20)	NRI (n = 4)	Total (n = 24)
Aspergillus NOS	NA				3 (15.0)	0	3 (12.5)
Aspergillus flavus					4 (20.0)	1 (25.0)	5 (20.8)
Aspergillus fumigatus					9 (45.0)	1 (25.0)	10 (41.7)
Aspergillus niger					0	1 (25.0)	1 (4.2)
Aspergillus terreus					0	1 (25.0)	1 (4.2)
Aspergillus versicolor					1 (5.0)	0	1 (4.2)

BAL = bronchoalveolar lavage; GM = galactomannan; IA = invasive aspergillosis; IFD = invasive fungal disease; IM = invasive mucormycosis; ISA = isavuconazole; mITT = modified intention-to-treat; NA = not applicable; NOS = not otherwise specified; NRI = no renal impairment; RI = renal impairment.

Source: Clinical Study Report.[24]

Table 21: Study Drug Duration (SECURE Study)

	SECURE	
Characteristics	**ISA (n = 257)**	**VRC (n = 259)**
Total Treatment Duration (Days)	(n = 257)	(n = 259)
Mean (SD)	46.9 (32.34)	46.5 (32.08)
Median	45.0	47.0
Range	1 to 102	1 to 88
Duration of IV Dosing (Days)	(n = 257)	(n = 259)
Mean (SD)	8.1 (8.53)	8.9 (9.57)
Median	5.0	5.0
Range	1 to 84	1 to 63
Duration of Oral Dosing (Days)	(n = 194)	(n = 206)
Mean (SD)	51.5 (27.99)	47.3 (28.91)
Median	60.0	53.0
Range	0.5 to 99.5	1.0 to 85.5

ISA = isavuconazole; IV = intravenous; SD = standard deviation; VRC = voriconazole.

Source: Clinical Study Report.[23]

Table 22: Study Drug Exposure (VITAL: Invasive Mucormycosis or Invasive Aspergillosis)

	VITAL						
	IM				IA		
	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)	RI (n = 20)	NRI (n = 4)	Total (n = 24)
Total Duration (Days)							
Mean (SD)	149.0 (206.28)	117.0 (211.50)	97.4 (89.34)	132.5 (193.28)	69.4 (53.31)	200.3 (153.14)	91.2 (88.83)
Median	102.0	33.0	85.0	84.0	54.0	204.0	67.0
Range	2 to 882	6 to 735	10 to 232	2 to 882	4 to 174	50 to 343	4 to 343
IV Duration Only (Days)							
Mean (SD)	15.5 (14.46)	22.8 (22.45)	17.3 (12.45)	17.7 (17.47)	11.7 (10.40)	12.8 (8.40)	11.9 (9.88)
Median	9.5	11.5	15.5	10.0	8.0	11.0	9.5

	VITAL						
	IM				IA		
	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)	RI (n = 20)	NRI (n = 4)	Total (n = 24)
Range	2.0 to 51.0	6.0 to 77.0	5.0 to 33.0	2.0 to 77.0	2.5 to 35.0	5.5 to 22.0	2.5 to 35.0
Maximum Oral Duration Only (Days)							
Mean (SD)	178.1 (222.41)	122.8 (219.45)	104.5 (81.23)	150.8 (204.82)	67.3 (49.19)	190.6 (145.30)	89.8 (85.70)
Median	142.8	33.0	106.0	80.0	65.5	198.5	77.5
Range	16.0 to 882.0	8.0 to 690.0	7.0 to 199.0	7.0 to 882.0	4.0 to 168.0	44.5 to 321.0	4.0 to 321.0

IA = invasive aspergillosis; IM = invasive mucormycosis; ISA = isavuconazole; IV = intravenous; NRI = no renal impairment; RI = renal impairment; SD = standard deviation.

Source: Clinical Study Report.[24]

Table 23: All-Cause Mortality Through Day 42 (SECURE: Subpopulations)

	SECURE				
	ISA		VRC		Treatment Difference (%) 95% CI (%)
	N	n (%)	N	n (%)	
Diagnosis Category					
Proven IFD	29	7 (24.1)	26	7 (19.4)	NR
Probable IFD	114	21 (18.4)	93	23 (24.7)	NR
Possible IFD	88	15 (17.1)	108	19 (17.6)	NR
No IFD	27	5 (18.5)	21	3 (14.3)	NR
Aspergillus only	49	5 (10.2)	39	8 (20.5)	NR
Aspergillus plus other mould	3	3	1	0	NR
Non-*Aspergillus* only	5	3	6	0	NR
Mould not otherwise specified	14	2 (14.3)	15	6 (40.0)	NR
No pathogen identified	72	15 (20.8)	68	16 (23.5)	NR
myITT	123	23 (18.7)	108	24 (22.2)	−2.7 (−12.9 to 7.5)
Underlying Medical Condition					
Allogeneic BMT status					
Yes	54	12 (22.2)	51	9 (17.6)	4.6 (−12.7 to 21.9)
No	204	36 (17.6)	207	43 (20.8)	−3.1 (−11.2 to 5.0)
Uncontrolled malignancy status					
Yes	173	37 (21.4)	187	41 (21.9)	−0.5 (−9.6 to 8.6)
No	85	11(12.9)	71	11(15.5)	−2.6 (−15.0 to 9.8)
Baseline neutropenic status (ANC < 500/mm^3)					
Yes	163	34 (20.9)	175	37 (21.1)	−0.3 (−9.6 to 9.0)
No	95	14 (14.7)	83	15 (18.1)	−3.3 (−15.5 to 8.8)
Prior antifungal treatment	NR	NR	NR	NR	NR

ANC = absolute neutrophil count; BMT = bone marrow transplant; CI = confidence interval; IFD = invasive fungal disease; ISA = isavuconazole; myITT = mycological intention-to-treat; PP = per-protocol; NR = not reported; VRC = voriconazole.

Source: Clinical Study Report,[23] FDA medical review report.[34]

Table 24: Mortality Through Day 84 (SECURE)

	SECURE				
	ISA		VRC		Treatment Difference (%) 95% CI (%)
	N	n (%)	N	n (%)	
ITT	258	75 (29.1)	258	80 (31.0)	−1.4 (−9.150 to 6.340)
mITT	143	43 (30.1)	129	48 (37.2)	−5.5 (−16.059 to 5.148)
myITT	123	35 (28.5)	108	39 (36.1)	−5.7 (−17.062 to 5.577)
Per-protocol	172	43 (25.0)	175	48 (27.4)	−2.8 (−11.861 to 6.234)
Allogeneic BMT status					
Yes	54	17 (31.5)	51	15 (29.4)	2.1 (−17.609 to 21.748)
No	204	58 (28.4)	207	65 (31.4)	−3.0 (−12.326 to 6.387)
Uncontrolled malignancy status					
Yes	173	60 (34.7)	187	60 (32.1)	2.6 (−7.737 to 12.930)
No	85	15 (17.6)	71	20 (28.2)	−10.5 (−25.137 to 4.093)

BMT = bone marrow transplant; CI = confidence interval; ISA = isavuconazole; ITT = intention-to-treat; mITT = modified intention-to-treat; myITT = mycological intention-to-treat; VRC = voriconazole.

Source: Clinical Study Report.[23]

Table 25: Demographics and Baseline Characteristics for a Matched Control Analysis for Invasive Mucormycosis

	VITAL	FungiScope
	ISA	AmB
Number of patients	21	33
Year of diagnosis	2008 to 2013	2005 to 2013
Median age, years (IQR)	51 (46 to 57)	57 (49 to 65)
Sex		
Men	17 (81)	22 (67)
Women	4 (19)	11 (33)
Race		
White	12 (57)	31 (94)
Asian	8 (38)	2 (6)
Black	1 (5)	0
Median weight, kg (IQR)	81 (53 to 91)	70 (58 to 80)
Underlying Disorder		
Immunosuppressant use	9 (43)	9 (27)
Baseline neutropenia	4 (19)	8 (24)
Diabetes	4 (19)	6 (18)
HSCT	4 (19)	5 (15)
GVHD treatment	4 (19)	3 (9)
Solid organ transplant	1 (5)	3 (9)
Diagnostic Certainty		
Proven	18 (86)	20 (61)
Probable	3 (14)	13 (39)
Pathogen		
Actinomucor	1 (5)	0
Lichtheimia	2 (10)	6 (18)
Mucor	6 (29)	5 (15)

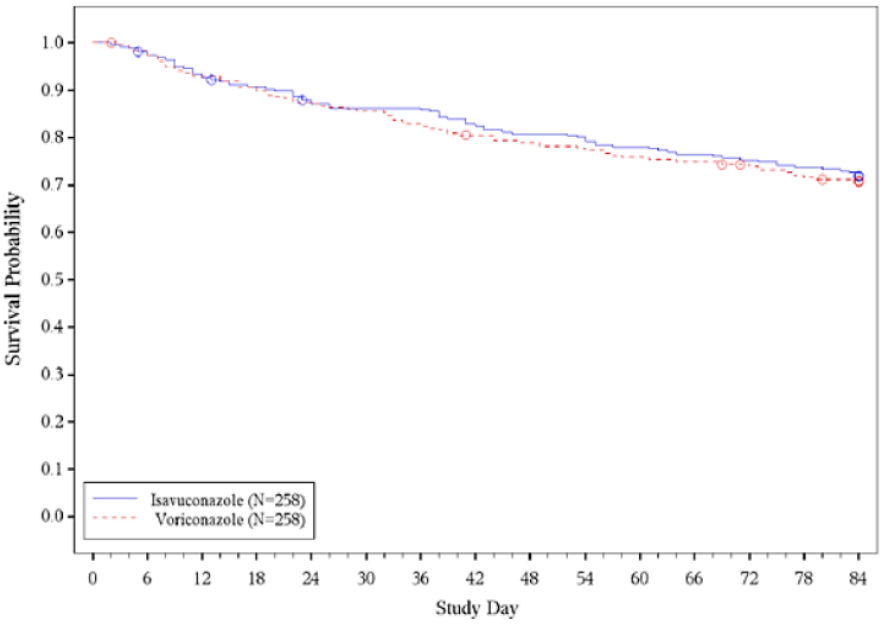
	VITAL	FungiScope
	ISA	AmB
Mucorales moulds	6 (29)	7 (21)
Rhizomucor	2 (10)	2 (6)
Rhizopus	4 (19)	13 (39)
Disease Location		
Pulmonary only	1 (5)	10 (30)
Pulmonary and other organ	8 (38)	7 (21)
Non-pulmonary only	12 (57)	16 (48)
Non-pulmonary locations		
Paranasal sinuses	13 (62)	11 (33)
CNS	6 (29)	8 (24)
Orbit	7 (33)	4 (12)
Bone	4 (19)	5 (15)
Deep soft tissues	1 (5)	6 (18)
Gastrointestinal tract	2 (10)	5 (15)
Skin	2 (10)	5 (15)
Other	7 (33)	9 (27)
Disseminated disease	8 (38)	8 (24)
Matching Covariate		
Hematological malignancy	11 (52)	18 (55)
Severe disease	12 (57)	13 (39)
Surgical treatment	9 (43)	13 (39)
Primary Treatment		
Isavuconazole	21 (100)	0
Deoxycholate AmB	0	7 (21)
Liposomal AmB	0	22 (67)
AmB lipid complex	0	4 (12)
Median Daily Dose, mg (Range)		
Isavuconazole	200	–
Deoxycholate AmB	–	70 (50 to 80)
Liposomal AmB	–	350 (20 to 1,000)
AmB lipid complex	–	325 (250 to 350)
Median Treatment Duration, Days (IQR)		
ISA	102 (27 to 180)	–
AmB	–	18 (13 to 34)
AmB followed by posaconazole[a]	–	34 (14 to 111)

AmB = amphotericin B; CNS = central nervous system; GVHD = graft-versus-host disease; HSCT = hemopoietic stem cell transplantation; IQR = interquartile range; ISA = isavuconazole.

[a] The FungiScope control group received posaconazole after AmB as continuing treatment; seven patients started posaconazole treatment before day 42.

Source: Reprinted from Lancet Infect Dis, Vol 16, Marty FM, Ostrosky-Zeichner L, Cornely OA, et al., Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis, pp. 828−837, Copyright 2016, with permission from Elsevier.[18]

Figure 2: Probability of Survival Through Day 84 (SECURE: Intention-to-Treat)



Number of Subjects at Risk

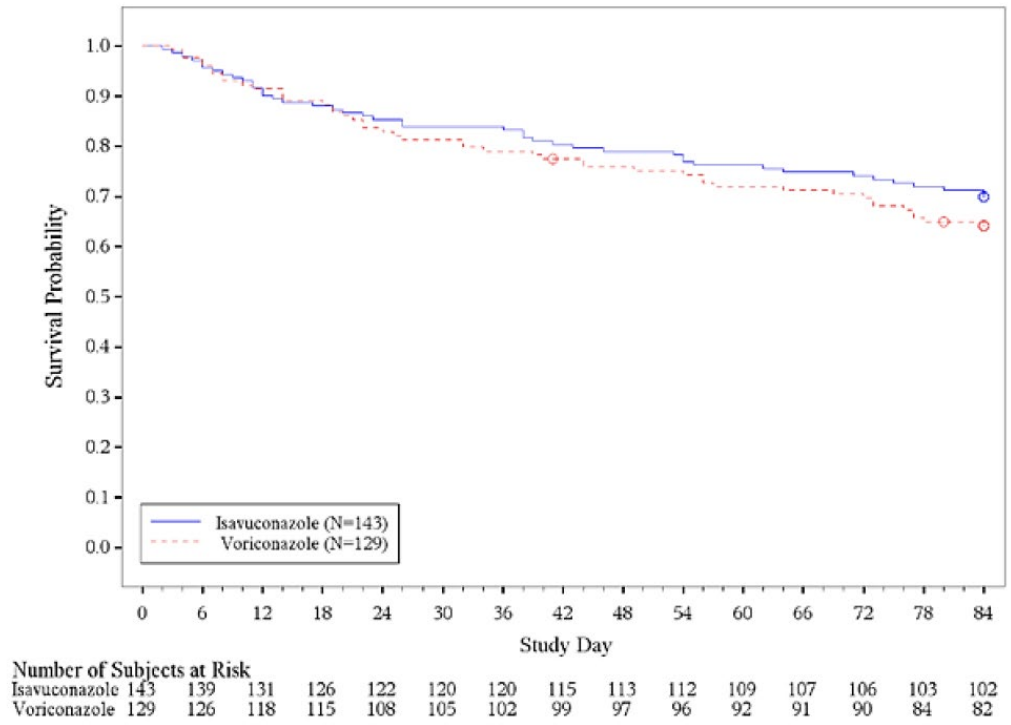
Isavuconazole	258	252	240	232	224	220	220	211	206	204	199	195	192	188	185
Voriconazole	258	253	239	233	225	220	213	206	202	199	194	192	188	182	179

Patients were censored on the patient's last assessment day.

Although there were patients who survived beyond day 85, this figure only shows the probability of survival up to day 84.

Source: Clinical Study Report.[23]

Figure 3: Probability of Survival Through Day 84 (SECURE: Proven and Probable Invasive Fungal Diseases Subpopulation [Modified Intention-to-Treat])

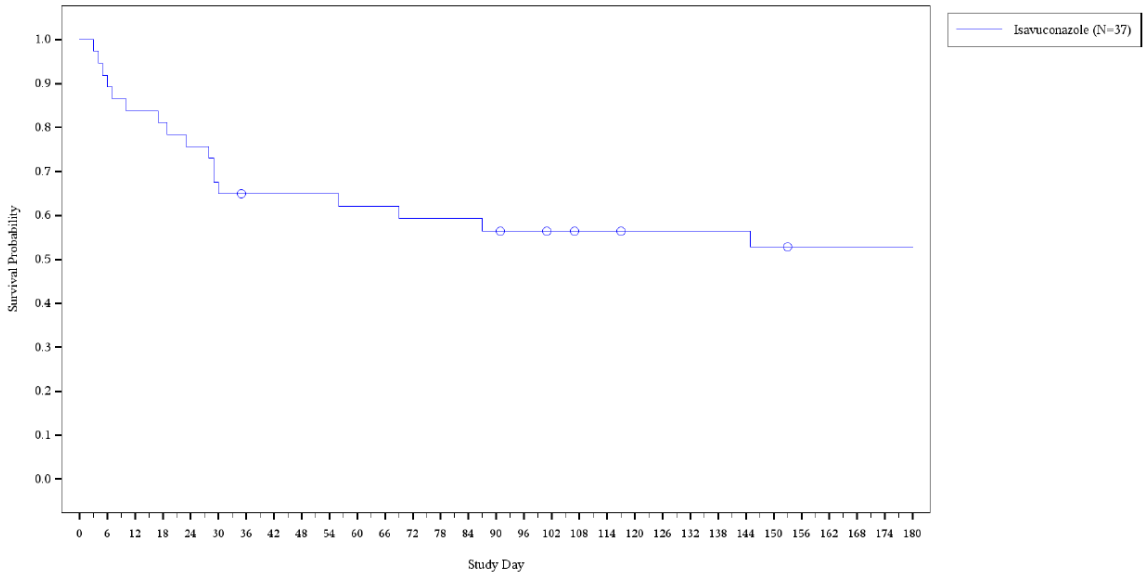


Note: Patients were **censored** on the patient's last assessment day. Although there were patients who survived beyond day 85, this figure shows only the probability of survival up to day 84.

Source: Clinical Study Report.[23]

Figure 4: Probability of Survival Through Day 180 (VITAL: Invasive Mucormycosis)

Figure 1 Probability of Survival Calculated by Kaplan-Meier Method (mITT-Mucorales Population)



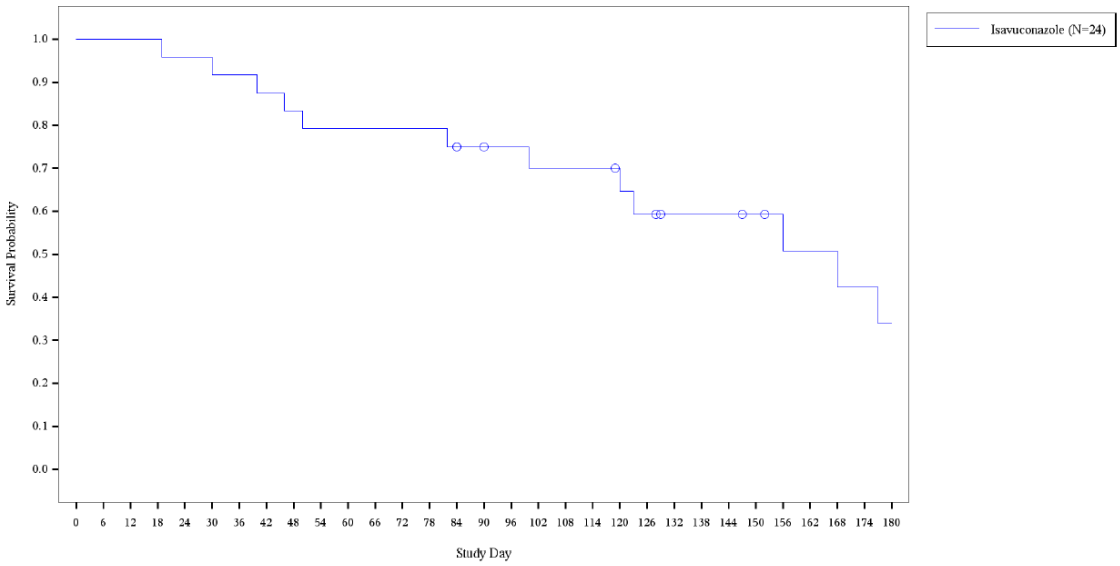
mITT = modified intention-to-treat.

Note: Probability of survival calculated by Kaplan–Meier method.

Source: Clinical Study Report.[24]

Figure 5: Probability of Survival Through Day 180 (VITAL: Invasive Aspergillosis)

Figure 2 Probability of Survival Calculated by Kaplan-Meier Method (mITT-*Aspergillus* Population)



mITT = modified intention-to-treat.

Source: Clinical Study Report.[24]

Table 26: Overall Response at Day 84 (Modified Intention-to-Treat)

	SECURE	
	ISA (N = 143)	VRC (N = 129)
Success, n (%)	36 (25.2)	42 (32.6)
Adjusted treatment difference (VRC minus ISA),[a] % (95% CI)	8.2 (−2.0 to 18.4)	
Complete	14 (9.8)	13 (10.1)
Partial	22 (15.4)	29 (22.5)
Failure, n (%)	107 (74.8)	87 (67.4)
Stable	30 (21.0)	14 (10.9)
Progression	5 (3.5)	8 (6.2)
Death	43 (30.1)	44 (34.1)
Missing	29 (20.3)	21 (16.3)

BMT = bone marrow transplant; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; ISA = isavuconazole; VRC = voriconazole.

[a] The adjusted treatment difference (VRC minus ISA) was calculated using a stratified CMH method with the strata of geographical region, allogeneic BMT status, and uncontrolled malignancy status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

Source: Clinical Study Report.[23]

Table 27: Overall Response at End of Treatment (SECURE: Mycological Intention-to-Treat)

	SECURE	
	ISA (N = 143)	VRC (n = 129)
Success, n (%)	43/123 (35.0)	42/108 (38.9)
Adjusted treatment difference (VRC minus ISA),[a] % (95% CI)	4.0 (−7.973 to 15.875)	
Complete	13 (10.6)	12 (11.1)
Partial	30 (24.4)	30 (27.8)
Failure, n (%)	80 (65.0)	66 (61.1)
Stable	36 (29.3)	29 (26.9)
Progression	44 (35.8)	37 (34.3)

CI = confidence interval; CMH = Cochran–Mantel–Haenszel; ISA = isavuconazole; VRC = voriconazole.

[a] The adjusted treatment difference (VRC minus ISA) was calculated using a stratified CMH method with the strata of geographical region, allogeneic BMT status, and uncontrolled malignancy status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

Source: Clinical Study Report.[23]

Table 28: Overall Response at End of Treatment by Subgroup (SECURE: Modified Intention-to-Treat)

	SECURE		
	ISA (N = 143)	VRC (N = 129)	Treatment Difference (%) 95% CI (%)
Allogeneic BMT Status, n/N (%)			
Yes	8/33 (24.2)	7/27 (25.9)	1.7 (−24.1 to 27.5)
No	42/110 (38.2)	40/102 (39.2)	1.0 (−13.1 to 15.2)
Uncontrolled Malignancy Status, n/N (%)			
Yes	32/89 (36.0)	30/89 (33.7)	−2.2 (−17.4 to 13.0)
No	18/54 (33.3)	17/40 (42.5)	9.2 (−13.1 to 31.4)
Baseline Neutropenic Status (ANC < 500/mm^3), n/N (%)			
Yes	34/88 (38.6)	29/73 (39.7)	1.1 (−15.5 to 17.6)
No	16/55 (29.1)	18/56 (32.1)	3.1 (−16.0 to 22)

	SECURE		
	ISA (N = 143)	VRC (N = 129)	Treatment Difference (%) 95% CI (%)
eGFR-MDRD Category (mL/min/1.73 m^2), n/N (%)			
< 60	4/13 (30.8)	6/17 (35.3)	4.5 (−37.3 to 46.4)
≥ 60	45/126 (35.7)	38/107 (35.5)	−0.2 (−13.5 to 13.1)

ANC = absolute neutrophil count; BMT = bone marrow transplant; CI = confidence interval; eGFR-MDRD = estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; ISA = isavuconazole; VRC = voriconazole.

Source: Clinical Study Report.[23]

Table 29: Overall, Clinical, Mycological, and Radiological Response (SECURE)

	Response	SECURE		
		ISA	VRC	Difference and 95% CI
mITT		N = 143	N = 129	
Day 42		N = 143	N = 129	
	Overall response	51 (35.7)	46 (35.7)	0.5 (−10.6 to 11.6)
	Clinical response	89 (62.2)	69 (53.5)	8.0 (−3.4 to 19.5)
	Mycological response	57 (39.9)	51 (39.5)	0.7 (−10.8 to 12.1)
	Radiologic response	40 (28.0)	44 (34.1)	−5.5 (−16.4 to 5.4)
Day 84		N = 143	N = 129	
	Overall response	36 (25.2)	42 (32.6)	−8.2 (−18.9 to 2.5)
	Clinical response	65 (45.5)	55 (42.6)	1.5 (−10.0 to 13.0)
	Mycological response	40 (28.0)	47 (36.4)	−9.1 (−20.2 to 2.0)
	Radiologic response	31 (21.7)	38 (29.5)	−9.0 (−19.6 to 1.5)
End of treatment		N = 143	N = 129	
	Overall response	NR	NR	NR
	Clinical response	85/143 (59.4)	73/129 (56.6)	0.6 (−10.6 to 11.8)
	Mycological response	54/143 (37.8)	53/129 (41.1)	−3.8 (−15.3 to 7.7)
	Radiologic response	41/143 (28.7)	42/129 (32.6)	−5.2 (−16.1 to 5.8)
myITT		N = 123	N = 108	
Day 42		N = 123	N = 108	
	Overall response	44 (35.8)	41 (38.0)	−0.5 (−12.9 to 11.8)
	Clinical response	77 (62.6)	61 (56.5)	5.7 (−6.9 to 18.4)
	Mycological response	50 (40.7)	46 (42.6)	−0.7 (−13.5 to 12.0)
	Radiologic response	38 (30.9)	40 (37.0)	−4.7 (−16.9 to 7.5)
Day 84		N = 123	N = 108	
	Overall response	31 (25.2)	38 (35.2)	−10.5 (−22.4 to 1.3)
	Clinical response	58 (47.2)	50 (46.3)	−0.3 (−13.0 to 12.3)
	Mycological response	35 (28.5)	43 (39.8)	−11.7 (−24.0 to 0.7)
	Radiologic response	28 (22.8)	35 (32.4)	−10.6 (−22.4 to 1.3)
End of treatment		N = 123	**N = 108**	
	Overall response	NR	NR	NR
	Clinical response	74 (60.2)	64(59.3)	−1.6 (−14.0 to 10.8)

	Response	SECURE		
		ISA	VRC	Difference and 95% CI
	Mycological response	47 (38.2)	48(44.4)	−6.9 (−19.5 to 5.8)
	Radiologic response	37 (30.1)	39 (36.1)	−7.1 (−19.4 to 5.1)

CI = confidence interval; ISA = isavuconazole; ITT = intention-to-treat; mITT = modified intention-to-treat; myITT = mycological intention-to-treat; NR = not reported; VRC = voriconazole.

Source: Clinical Study Report,[23] FDA report.[34]

Table 30: Overall Response at End of Treatment (VITAL: Invasive Mucormycosis or Invasive Aspergillosis)

	VITAL						
	IM				IA		
	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)	RI (n = 20)	NRI (n = 4)	Total (n = 24)
Success	6/19 (31.6)	4/11 (36.4)	1/5 (20.0)	11/35 (31.4)	6 (30.0)	2/3 (66.7)	8/23 (34.8)
Complete	3/19 (15.8)	2/11 (18.2)	0	5/35 (14.3)	3 (15.0)	1/3 (33.3)	4/23 (17.4)
Partial	3/19 (15.8)	2/11 (18.2)	1/5 (20.0)	6/35 (17.1)	3 (15.0)	1/3 (33.3)	4/23 (17.4)
Failure	13/19 (68.4)	7/11 (63.6)	4/5 (80.0)	24/35 (68.6)	14 (70.0)	1/3 (33.3)	15/23 (65.2)
Stable	6/19 (31.6)	2/11 (18.2)	2/5 (40.0)	10/35 (28.6)	4 (20.0)	0	4/23 (17.4)
Progression	7/19 (36.8)	5/11 (45.5)	2/5 (40.0)	14/35 (40.0)	10 (50.0)	1/3 (33.3)	11/23 (47.8)

IA = invasive aspergillosis; IM = invasive mucormycosis; ISA = isavuconazole; NRI = no renal impairment; RI = renal impairment.

Source: Clinical Study Report.[24]

Table 31: Overall Response at Day 42 and Day 84 (VITAL: Invasive Mucormycosis or Invasive Aspergillosis)

	VITAL						
	IM				IA		
	Primary Therapy (N = 21)	Refractory (N = 11)	Intolerant (N = 5)	Total (N = 37)	RI (N = 20)	NRI (N = 4)	Total (N = 24)
At day 42							
Success, n (%)	3 (14.3)	1 (9.1)	0	4 (10.8)	5 (25.0)	2 (50.0)	7 (29.2)
Complete	0	0	0	0	2 (10.0)	0	2 (8.3)
Partial	3 (14.3)	1 (9.1)	0	4 (10.8)	3 (15.0)	2 (50.0)	5 (20.8)
Failure, n (%)	18 (85.7)	10 (90.9)	5 (100.0)	33 (89.2)	15 (75.0)	2 (50.0)	17 (70.8)
Stable	9 (42.9)	4 (36.4)	3 (60.0)	16 (43.2)	7 (35.0)	1 (25.0)	8 (33.3)
Progression	1 (4.8)	0	0	1 (2.7)	2 (10.0)	1 (25.0)	3 (12.5)
Death	7 (33.3)	4 (36.4)	2 (40.0)	13 (35.1)	2 (10.0)	0	2 (8.3)
Missing	1 (4.8)	2 (18.2)	0	3 (8.1)	4 (20.0)	0	4 (16.7)
At day 84							
Success, n (%)	2 (9.5)	4 (36.4)	1 (20.0)	7 (18.9)	6 (30.0)	1 (25.0)	7 (29.2)
Complete	1 (4.8)	1 (9.1)	0	2 (5.4)	3 (15.0)	1 (25.0)	4 (16.7)
Partial	1 (4.8)	3 (27.3)	1 (20.0)	5 (13.5)	3 (15.0)	0	3 (12.5)
Failure, n (%)	19 (90.5)	7 (63.6)	4 (80.0)	30 (81.1)	14 (70.0)	3 (75.0)	17 (70.8)

	VITAL						
	IM				IA		
	Primary Therapy (N = 21)	Refractory (N = 11)	Intolerant (N = 5)	Total (N = 37)	RI (N = 20)	NRI (N = 4)	Total (N = 24)
Stable	9 (42.9)	0	2 (40.0)	11 (29.7)	3 (15.0)	1 (25.0)	4 (16.7)
Progression	0	1 (9.1)	0	1 (2.7)	0	1 (25.0)	1 (4.2)
Death	9 (42.9)	4 (36.4)	2 (40.0)	15 (40.5)	5 (25.0)	1 (25.0)	6 (25.0)
Missing	1 (4.8)	2 (18.2)	0	3 (8.1)	6 (30.0)	0	6 (25.0)

IA = invasive aspergillosis; IM = invasive mucormycosis; ISA = isavuconazole; NRI = no renal impairment; RI = renal impairment.

Source: Clinical Study Report.[24]

Table 32: Response at End of Treatment (VITAL: Invasive Mucormycosis or Invasive Aspergillosis)

	VITAL						
	IM				IA		
	Primary Therapy (N = 19[a])	Refractory (N = 11)	Intolerant (N = 5)	Total (N = 35)	RI (N = 20)	NRI (N = 4)	Total (N = 24)
Clinical success n/N (%)	10/18 (55.6)	2/9 (22.2)	2/4 (50.0)	14/31 (45.2)	11 (55.0)	2/3 (66.7)	13/23 (56.5)
Mycological success, n/N (%)	6/19 (31.6)	4/11 (36.4)	2/5 (40.0)	12/35 (34.3)	7 (35.0)	2/3 (66.7)	9/23 (39.1)
Radiological success, n/N (%)	3/18 (16.7)	2/10 (20.0)	1/5 (20.0)	6/33 (18.2)	3 (15.0)	2/3 (66.7)	5/23 (21.7)

IA = invasive aspergillosis; IM = invasive mucormycosis; ISA = isavuconazole; NRI = no renal impairment; RI = renal impairment.

[a] Two patients were receiving ongoing therapy at the time of assessment and were excluded.

Source: Clinical Study Report.[24]

Table 33: Response at Day 42 and Day 84 (VITAL: Invasive Mucormycosis or Invasive Aspergillosis)

Response	VITAL						
	IM				IA		
	Primary Therapy (N = 21)	Refractory (N = 11)	Intolerant (N = 5)	Total (N = 37)	RI (N = 20)	NRI (N = 4)	Total (N = 24)
At Day 42							
Clinical response	10/20 (50.0)	3/9 (33.3)	2/4 (50.0)	15/33 (45.5)	11 (55.0)	3 (75.0)	14 (58.3)
Mycological response	1/21 (4.8)	0	0	1/37 (2.7)	6 (30.0)	2 (50.0)	8 (33.3)
Radiological response	0	1/10 (10.0)	0	1/35 (2.9)	6 (30.0)	1 (25.0)	7 (29.2)
At Day 84							
Clinical response	8/20 (40.0)	2/9 (22.2)	2/4 (50.0)	12/33 (36.4)	9 (45.0)	1 (25.0)	10 (41.7)
Mycological response	2/21 (9.5)	3/11 (27.3)	2/5 (40.0)	7/37 (18.9)	7 (35.0)	1 (25.0)	8 (33.3)
Radiological response	1/21 (4.8)	2/10 (20.0)	1/5 (20.0)	4/36 (11.1)	4 (20.0)	1 (25.0)	5 (20.8)

IA = invasive aspergillosis; IM = invasive mucormycosis; ISA = isavuconazole; NRI = no renal impairment; RI = renal impairment.

Source: Clinical Study Report.[24]

Table 34: Serious Adverse Events

	SECURE		VITAL
	ISA (N = 257)	VRC (N = 259)	ISA (N = 146)
	n (%)	n (%)	n (%)
Patients with ≥ 1 Serious TEAE	134 (52.1)	149 (57.5)	89 (61.0)
Most Common SAE (≥ 3%)[a]			
Febrile neutropenia	14 (5.4)	5 (1.9)	–
Respiratory failure	14 (5.4)	12 (4.6)	5 (3.4)
Septic shock	14 (5.4)	10 (3.9)	6 (4.1)
Pyrexia	8 (3.1)	10 (3.9)	–
Sepsis	7 (2.7)	8 (3.1)	–
Renal failure acute	6 (2.3)	8 (3.1)	8 (5.5)
Pneumonia	5 (1.9)	10 (3.9)	7 (4.8)
Acute myeloid leukemia	3 (1.2)	8 (3.1)	–
Acute respiratory failure	–	–	3 (2.1)
Abdominal pain	–	–	5 (3.4)

ISA = isavuconazole; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VRC = voriconazole.

Note: "–" indicates events reported in < 3% of either the ISA or VRC group in SECURE or VITAL.

Source: Clinical Study Report.[23,24]

Appendix 5: Diagnostic Criteria and Treatment Response Definition

Table 35: Diagnostic Criteria for Proven, Probable, and Possible Invasive Fungal Disease (SECURE)

Category	Criteria
Proven IFD	Patients with a positive diagnostic test obtained within the 7 days after the first administration of study medication: • either histopathologic, cytopathologic, or wet mount examination of a needle aspiration or biopsy specimen showing hyphal forms with evidence of associated tissue damage (either microscopically or as an infiltrate or lesion by imaging) OR • recovery of a mould by culture from a sample obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding BAL and cranial sinus cavity.
Probable IFD	At least one host factor **(a)** (next row) PLUS at least one clinical feature **(b)** (list follows), PLUS at least one mycological criterion **(c)** (list follows). NB: Not required for patients with neutropenia or allogeneic BMT and lower respiratory tract disease.
	a) Host factors: • either recently resolved (up to 2 weeks prior) or ongoing neutropenia (neutropenia defined as absolute neutrophil count < 0.5 x 10^9/L [< 500/mm^3] for ≥ 10 days), temporally related to the onset of fungal disease OR • receipt of an allogeneic hematopoietic stem cell transplant or prolonged use of corticosteroids (excluding patients with allergic bronchopulmonary aspergillosis, autoimmune diseases) at an average minimum dose of 0.3 mg/kg/day prednisone equivalent for > 3 weeks OR • treatment with other recognized T-cell immune suppressants such as cyclosporin, tacrolimus, tumour necrosis factor alpha blockers, or specific monoclonal antibodies such as alemtuzumab, nucleoside, or analogues during the past 90 days.
	b) Clinical features: Lower respiratory tract disease: • The medical history must be established to exclude different etiology and to distinguish between a primary and chronic pulmonary infection. Onset within 2 weeks prior to the first dose of study medication defines a primary pulmonary infection AND • either the presence of at least one of the following "specific" imaging signs on CT: Well-defined nodule(s) with or without a halo sign; wedge-shaped infiltrate; air crescent sign; cavity; or the presence of a new "non-specific" focal infiltrate PLUS at least one of the following (not necessary if there is mycological evidence): pleural rub; pleural pain; hemoptysis. NB: Patients with neutropenia or allogeneic BMT (as defined previously) who meet criteria for clinical features of lower respiratory tract disease (as defined previously) can be classified as probable IFD even in the absence of mycological criteria. Tracheobronchitis: Tracheobronchial ulceration; nodules; pseudomembrane; plaque or eschar seen on bronchoscopy Sino-nasal infection: Imaging showing sinusitis PLUS at least one of the following: Acute localized pain (including pain radiating to eye), nasal ulcer, black eschar; extension from the paranasal sinus bony barriers, including into the orbit; Central nervous system infection: at least one of the following: focal lesions on imaging, meningeal enhancement on MRI.
	c) Mycological criteria (cytology, direct microscopy, culture, antigen detection): • Either sputum, BAL, or bronchial brush samples demonstrating the presence of fungal elements either by recovery by culture of a mould (e.g., *Aspergillus*) or detection by cytology or direct microscopy of hyphal forms; OR recovery by culture of moulds or detection of hyphal forms by cytology or direct microscopy from a sinus aspirate. If invasive diagnostic procedures are not successful or not possible (e.g., problematic location of the infection or clinical conditions prohibit successful sampling), a single serum GM value of ≥ 0.7 or two consecutive values of ≥ 0.5 to < 0.7 is acceptable mycological evidence for enrolment as probable IFD.

Category	Criteria
	NB: GM in BAL, pleural fluid, or cerebrospinal fluid is not acceptable as mycological evidence for enrolment.
Possible IFD	At least one host factor **(a)** PLUS at least one clinical feature **(b)** (defined previously).

BAL = bronchoalveolar lavage; BMT = bone marrow transplant; GM = galactomannan; IFD = invasive fungal disease.

Source: Clinical Study Report.[23,36]

Table 36: Response Criteria

Response	Criteria
Clinical Response	
Success	Resolution of all attributable clinical symptoms and physical findings; partial resolution of attributable clinical symptoms and physical findings
Failure	No resolution of any attributable clinical symptoms and physical findings and/or worsening
Not applicable	No attributable signs and symptoms present at baseline and no symptoms attributable to invasive fungal disease developed post baseline
Mycological Response	
Success	Eradication or presumed eradication
Failure	Persistence or presumed persistence
Not applicable	No mycological evidence available at baseline
Radiological Response	
Success	≥ 25% improvement from baseline, if EOT occurs prior to day 42 or ≥ 50% improvement from baseline if EOT occurs after day 42
Failure	No post-baseline radiology available for patient with baseline evidence of radiologic disease
Not applicable	Radiology not applicable at baseline

EOT = end of treatment.

Source: Clinical Study Report.[23]

Appendix 6: Summary of Indirect Comparisons

Introduction

The antifungal drugs for the treatment of invasive aspergillosis (IA) in Canada include isavuconazole (ISA), voriconazole (VRC), amphotericin B (AmB) formulations, posaconazole, itraconazole, and caspofungin. The relative efficacy of ISA versus other relevant comparators except VRC has not been directly compared.[9-14,16] One network meta-analysis (NMA) funded by Basilea Pharmaceutica International Ltd., that assessed the comparative efficacy of ISA versus AmB formulations and VRC in the treatment of patients with IA was identified in the CADTH literature search.[38] The following is a summary and critical appraisal of the methods and main findings of the NMA.

Methods

Systematic Review

The systematic review and the NMA were performed based on standards of the National Institute for Health and Care Excellence, the Centre for Reviews and Dissemination, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[43] The literature search was conducted in the following electronic databases: Embase, MEDLINE, the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the National Health Service Economic Evaluation Database (NHS EED), HTA, the Cochrane Central Register of Controlled Trials (CENTRAL), the International Clinical Trials Registry Platform (ICTRP), and the National Guideline Clearinghouse (NGC). Hand searching of reference lists was also performed. However, grey literature searches of recent congress abstracts and ClinicalTrials.gov providing further study records were not performed. The search was conducted in January 2015 and was limited to English literature published since 1995. The main study selection criteria (PICOS) were any randomized controlled trials (RCTs) on ISA versus any relevant comparators for the treatment of patients with invasive fungal disease (IFD) caused by *Aspergillus*. Clinical outcomes included mortality, overall response, hospitalization, discontinuation, and adverse events. All included RCTs were evaluated for methodological quality and bias based on the guidance provided by the Centre for Reviews and Dissemination.[44] Whether the study selection, data extraction, or quality assessment of included studies was performed by two reviewers independently was not reported.

Network Meta-Analysis

Because only one study was found for each comparison of treatments, no feasibility of an NMA for the outcomes of interest was assessed. The NMA was conducted within a Bayesian framework based on Markov chain Monte Carlo methods (Lu and Ades)[45] and Dias et al. (2011)[46] and 2013.[47] The models were run with OpenBUGS version 3.2.3 (www.openbugs.net/w/FrontPage). Outcome data were obtained from patients with proven or probable IFDs based on the 2008 criteria of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG).[36,48] A fixed-effects model (no random-effects model) was used because only one study was identified for each comparison. The outcomes evaluated were all-cause mortality and overall response. No NMA was conducted for safety outcomes due to lack of comparable data. Statistical significance was assessed using 95% posterior credible intervals; for mortality and response, odds ratios were assessed with a logistic regression model. Results (odds

ratios) were reported in forest plots as natural logs. No inconsistency was assessed on direct and indirect comparisons.

Results

Study and Patient Characteristics

Four studies[29,49-51] were included in the NMA (Figure 6). Briefly, Leenders et al.,1998 (Study 1) was an RCT that compared AmB deoxycholate (AmB-D) with liposomal AmB (L-AmB) in patients with neutropenia-associated IFDs, including suspected IA.[51] Cornely et al., 2011 (Study 2) was a clinical trial that compared standard and high doses of L-AmB (3 mg/kg versus 10 mg/kg) for the treatment of patients with IFDs.[49] Herbrecht et al. 2015 (Study 3) compared VRC with AmB-D.[50] Maertens et al., 2016 (Study 4) was a clinical trial of ISA versus VRC in patients with IFDs.[29] The key outcomes in all four included studies were all-cause mortality and treatment response. The mean ages of patients in the treatment groups were all within a range of 42 to 52.5 years. The majority of patients were male in all studies except for Leenders (Study 1), where the majority were female. The proportion of IFD infection sites and underlying medical conditions reported across the four included studies were variable and not very consistent, although the most common infection site was the lungs and the most common underlying medical condition was hematologic malignancy (Table 37).

Figure 6: Included Study Networks

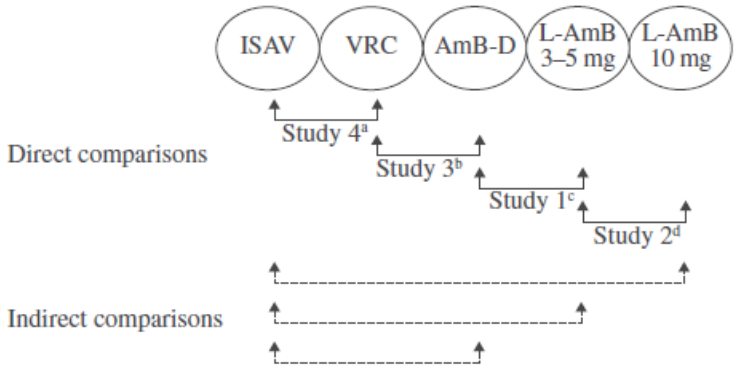


Figure 2. Comparisons in studies identified in the systematic review included in the network analysis. Abbreviations. AmB-D, amphotericin B deoxycholate; ISAV, isavuconazole; L-AmB, liposomal amphotericin B; VRC, voriconazole. [a]Maertens *et al.* 2016[4]. [b]Herbrecht *et al.* 2015[25]. [c]Leenders *et al.* 1998[20]. [d]Cornely *et al.* 2011[22].

Source: Systematic review and network meta-analysis of clinical outcomes associated with isavuconazole versus relevant comparators for patients with invasive aspergillosis. Herbrecht R, Kuessner D, Pooley N, Posthumus J, Escrig C. Curr Med Res Opin. 2018; 34(12):2187–2195. Reprinted by permission of Taylor & Francis Ltd., http://tandfonline.com.[38]

Table 37: Main Characteristics of Studies Included in the Network Meta-Analysis

Study	Intervention/ Comparison	Outcomes	Time Assessed	Diagnosis	Site of Infection	Primary Underlying Disease	Male (%)	Age (Years)
Leenders et al., 1998 (Study 1)[51]	• AmB-D 1 mg/kg (n = 34) • L-AmB 5 mg/kg (n = 32)	• Therapeutic response (CE, 2 weeks) • Clinical success and improvement, mortality	EOT and 4 weeks after EOT	Documented or suspected IFDs	Pulmonary, 56% to 65% Not reported, 35% 44%	• Acute non-lymphocytic leukemia / myelodysplastic syndromes, 56% to 59% ALL, 19% • Chronic leukemia, 6% • Other, 19% to 26% • Neutropenia:[b] 88% to 94%	19% to 29%	Median: 48 to 52.5
Cornely et al., 2011 (AmBiLoad trial) (Study 2)[49]	• L-AmB 3 mg/kg (n = 45) • L-AmB 10 mg/kg (n = 38)	• Overall response (ITT, mITT 12 weeks) • Survival	12 weeks	Proven, probable, or possible IFDs	Pulmonary only, 79% to 80%	• Hematologic malignancies, 89% to 92% • HSCT, 16% to 20% • Neutropenia, 88% to 94%[b]	58% to 68%	Median 51 to 54
Herbrecht et al., 2015 (Study 3)[50]	• VRC 4 mg/kg IV or 200 mg oral b.i.d. (n = 124) • AmB-D 1.0 mg/kg 1.5 mg/kg (n = 113)	• Successful outcome (ITT, mITT 12 weeks) • Successful response (favourable response) • Survival	12 weeks	IA	Pulmonary only, 85% to 88%	• AML, 36% to 38% • HSCT, 26% to 29% • ALL, 7% to 8% • Other hematologic malignancies, 12% to 15% • SOT, 4% to 6% • Other non-malignant disease, 8% to 10% • Neutropenia, 50%	62% to 65%	Median 42 to 52.5
Maertens et al., 2016 (SECURE) (Study 4)[29]	• ISA 200 mg q.d. (n = 143) • VRC 4 mg/kg or 200 mg oral b.i.d. (n = 129)	• All-cause mortality • Response	EOT, 42 days, 84 days	Proven, probable, or possible IFDs	Pulmonary only, 81% to 83%	• AML, 38% to 49% • ALL, 9% to 12% • Lymphoma, 9% to 13% • Myelodysplastic syndrome, 5% to 9% • CLL, 4% to 5% • Aplastic anemia, 3% • CML, 2% to 3% • Multiple myeloma, 2% to 3% • COPD, 1% to 2% • Hodgkin's disease,1% • Diabetes mellitus, 2% • Neutropenia 63.2% to 67%	56% to 63%	Mean: 51

ALL = acute lymphoblastic leukemia; AmB-D = amphotericin B deoxycholate; AML = acute myeloid leukemia; b.i.d. = twice daily; CE = clinical evaluable population; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; COPD = chronic obstructive pulmonary disease; EOT = end of treatment; HSCT = hematopoietic stem cell transplantation; IA = invasive aspergillosis; IFD = invasive fungal disease; ISA = isavuconazole; ITT = intention-to-treat; IV = intravenous; L-AmB = liposomal amphotericin B; mITT = modified intention-to-treat; q.d. = once daily; SOT = solid organ transplantation; VRC = voriconazole.

Note: Neutropenia defined as absolute neutrophil count < 0.5×10^9/L.

Source: Herbrecht, 2018.[38]

Results From the Network Meta-Analysis

All-cause mortality*:* For patients with proven or probable IFDs, a statistically significant difference between treatment arms was reported as favouring ISA over AmB-D, whereas the treatment difference was not statistically significant (for either ISA versus VRC or ISA versus L-AmB) (Table 38). Sensitivity analyses were performed that also included patients with a possible IFD. A similar result to the proven or probable population was observed (Table 38).

Treatment response: For overall response, a statistically significant difference favouring ISA over AmB-D was reported, whereas the treatment difference between ISA and VRC and between ISA and L-AmB were not statistically significant (Table 38). In a sensitivity analysis (by including possible IFDs), a result similar to that for the proven or probable population was observed (Table 38).

Table 38: Results Reported in the Network Meta-Analysis

Outcomes	Different Antifungal Drugs Versus ISA	Odds Ratio (95% CrI) Presented in Natural Log	Odds Ratio (95% CrI) Presented in Natural Log
		For Proven or Probable IA	For Proven, Probable, or Possible IA
All-Cause Mortality			
	L-AmB 3 mg/kg to 5 mg/kg versus ISA	0.18 (−1.17 to 1.52)	−0.07 (−1.37 to 1.17)
	L-AmB 10 mg/kg versus ISA	0.50 (−1.11 to 2.13)	0.51 (−0.90 to 1.88)
	AmB-D versus ISA	1.00 (0.26 to 1.74)	0.76 (0.15 to 1.35)
	VRC versus ISA	0.32 (−0.19 to 0.84)	0.09 (−0.29 to 0.47)
Overall Response			
	L-AmB 3 mg/kg to 5mg/kg versus ISA	−0.99 (−2.21 to 0.29)	−1.00 (−2.21 to 0.28)
	L-AmB 10 mg/kg versus ISA	−0.89 (−2.41 to 0.65)	−1.15 (−2.48 to 0.26)
	AmB-D versus ISA	−1.39 (−2.21, −0.63)	−1.45 (−2.14, −0.74)
	VRC versus ISA	0.06 (−0.43 to 0.57)	0.07 (−0.44 to 0.57)

AmB-D = amphotericin B deoxycholate; CrI = credible interval; IA = invasive aspergillosis; ISA = isavuconazole; L-AmB = liposomal amphotericin B; VRC = voriconazole.

Note: Odds ratio presented in natural log. For mortality: odds ratio > 0 indicates in favour of ISA. For overall response: odds ratio < 0 indicates in favour of ISA.

[a] Calculated using exact logistic regression factoring in malignancy status.

Source: Herbrecht, 2018.[38]

Critical Appraisal of the Network Meta-Analysis

The methodological quality of the NMA was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons,[52] and commentary for each of the relevant items identified by ISPOR is provided in Table 39.

Strengths

The NMA was based on a systematic review to identify relevant studies. Study-level information (design, main baseline characteristics, outcome measures, etc.) were reported. The process of study selection, data extraction, and the methodologic quality assessment of the individual study were all reported. The validity and quality of all individual studies included in the meta-analysis were assessed using the guidance by the Centre for Reviews and Dissemination.[44] The NMA was conducted using an appropriate and well-reported

methodology (i.e., Bayesian Markov Chain Monte Carlo methods using OpenBUGS version 3.2.3). Because only one study was included for each comparison, only a fixed-effect model was used. A sensitivity analysis was performed by including possible IFDs (i.e., intention-to-treat population). The outcome measures assessed in the NMA were appropriate and consistent with the key efficacy outcomes assessed in the pivotal studies included in this CDR review.

Limitations

A few limitations regarding the methodology and/or the overall body of evidence are discussed subsequently. Although the study selection, data extraction, and quality assessment of each included study were well reported, whether those processes were conducted by two reviewers independently was not described. Leenders (Study 1)[51] was an open-label trial design and the primary analysis was based on the per-protocol population; Herbrecht et al. (Study 3),[50] was partially blinded (only for assessors of outcomes); some differences in baseline trial characteristics were observed. For example, pulmonary infection varied from 55% to 88% across studies (Table 37). The proportion of the underlying medical conditions also showed some variations across the studies. Because the included studies were conducted as early as 1998[51] or as late as 2016[29] over an 18-year time span, changes in health care related to underlying diseases (such as concomitant medications) probably had different effects on outcomes. No study-level information on the definition of the outcome measurement, especially for the overall response, was reported. Therefore, potential methodological and clinical heterogeneity is a major limitation, which may limit the interpretation of the NMA findings. The clinical expert consulted for this review indicated that AmB-D is no longer commonly used in clinical practice in Canada due to its poor safety profile. Therefore, the evidence of comparative efficacy (ISA versus AmB-D) obtained from this NMA had very limited value for this review.

Conclusion

The NMA found that the efficacy of ISA in terms of all-cause mortality and overall response in the treatment of patients with IA is similar to VRC and L-AmB. However, due to the various limitations, particularly the potential methodological and clinical heterogeneity and sparsity of trials, no conclusion on the comparative efficacy of ISA and other available therapies could be credibly drawn.

Table 39: Appraisal of Network Meta-Analysis Using International Society for Pharmacoeconomics and Outcomes Research Criteria

	ISPOR Checklist Item[52]	Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting a network meta-analysis and the study objectives were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCT were clearly stated. • Information sources and search strategy were well reported. • Methods for selection process, data extraction, and quality assessment were clearly reported; however, whether they were conducted by two reviewers independently was not described. • The validity of individual studies was assessed using the criteria provided by the Centre for Reviews and Dissemination's *Guidance for Undertaking Reviews in Health Care.*
3.	Are the outcome measures described?	• The outcomes assessed in the network meta-analysis were clearly stated. • A justification of the outcome measures was provided.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the statistical model was provided. • An analysis framework was provided.
5.	Are sensitivity analyses presented?	• A sensitivity analysis was performed and presented.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A detailed table with study/patient characteristics was provided. • Figures showing the network of studies were provided.
7.	Does the study describe an assessment of model fit?	• Only a fixed-effect model was used because model fit was not applicable, as there was only one study for each comparison arm.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure including point estimates and 95% credible intervals as a measure of uncertainty.
9.	Sensitivity/scenario analyses	• Results of the sensitivity analyses were presented in the report.

ISPOR = International Society for Pharmacoeconomics and Outcomes Research; RCT = randomized controlled trial.

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