Isavuconazole: A new extended spectrum triazole for invasive mold diseases

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Isavuconazole: a new extended spectrum triazole for invasive mold diseases

Michelle R Ananda-Rajah1 & Dimitrios Kontoyiannis*2

ABSTRACT Isavuconazole is the first broad spectrum prodrug triazole with efficacy against invasive fungal diseases including aspergillosis and mucormycosis. Characteristics include linear dose-proportional pharmacokinetics, intravenous and oral formulations allowing therapeutic streamlining, once daily dosing, absence of nephrotoxic solubilizing agents and excellent oral bioavailability independent of prandial status and gastric acidity. An open label noncomparator study demonstrated encouraging results for isavuconazole as primary or salvage therapy for a range of fungi including mucormycosis. Isavuconazole had fewer premature drug discontinuations and adverse events in the eye, hepatobiliary and psychiatry systems than the comparator agent, voriconazole in a randomized double-blind clinical trial. Cross-resistance of isavuconazole best correlates with voriconazole. In vitro resistance is not invariably predictive of clinical failure. Isavuconazole signals progress in pharmacokinetics, bioavailability and toxicity/tolerability supported by clinical efficacy from Phase III trials.

Isavuconazole is a triazole antifungal agent in advanced Phase III development with a broad spectrum of activity against a range of medically important fungi. It is active in in vitro against Candida spp., Aspergillus species and the Mucorales, and is an effective agent in animal models for the treatment of invasive candidiasis and invasive aspergillosis (IA) [1–3]. Isavuconazole is the active moiety of the water-soluble prodrug, isavuconazonium sulfate, which is available in once-daily intravenous (iv.) and oral formulations. It recently achieved orphan drug designation by the US FDA and the EMA for the treatment of invasive aspergillosis and mucormycosis in addition to invasive candidiasis by the FDA. This review extends several comprehensive reviews [4–6] and will largely focus on the clinical role of isavuconazole for the management of invasive mold diseases (IMDs).

Structure & mode of action
Isavuconazole is administered as a water-soluble prodrug, isavuconazonium (BAL8557), which is almost completely (>99%) and rapidly converted to the active moiety isavuconazole (BAL 4815) and a pharmacologically inactive cleavage product (BAL8728) by plasma esterases [7]. The chemical structure of the prodrug, active moiety and prodrug fragment are shown in Figure 1. Unlike the iv. formulations of voriconazole, posaconazole and the now unavailable itraconazole, isavuconazonium does not require the addition of cyclodextrin to facilitate solubility, thereby obviating concerns regarding toxicity due to accumulation of the sulfobutylether-β-cyclodextrin component in the setting of renal impairment.

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Figure 1. Structure and mechanism of action of isavuconazole derived from the prodrug. Major cleavage products only are shown; sarcosine and acetaldehyde are also produced from prodrug cleavage (not shown).

Like other triazole antifungal drugs, isavuconazole inhibits ergosterol biosynthesis, resulting in the disruption of the fungal membrane. It binds to fungal P450-lanosterol 14-α-demethylases encoded by CYP51 genes, resulting in the accumulation of toxic methylated sterols thereby destabilizing the integrity of the fungal membrane [8]. Isavuconazole’s enhanced spectrum of activity is conferred by its side arm (Figure 1) that presumably allows better orientation for the triazole ring to engage with the heme moiety inside the binding pocket of the fungal CYP51 protein [6,9].

Isavuconazole, like voriconazole and posaconazole, is available in oral and iv. formulations with the oral formulation being a hard gelatin capsule [6,10]. Isavuconazole is administered as a loading dose of 200 mg three-times daily either iv. or orally for the first 2 days (six doses) followed by 200 mg (iv. or orally) once daily thereafter [11].

**Spectrum of activity & antifungal resistance**

Isavuconazole has potent in vitro activity against most clinically relevant species of Aspergillus, Candida [12] and Cryptococcus [13] and moderate activity against the Mucorales [14], although there have been far fewer numbers of non-Aspergillus molds tested to date. A recent study published in abstract form examined the in vitro activities of isavuconazole and comparator antifungal agents against 1613 clinical fungal isolates (1320 isolates of Candida spp., 155 of Aspergillus spp., 103 of non-Candida yeasts and 35 of non-Aspergillus molds) from a 2013 global survey [15]. The isavuconazole MIC\textsubscript{90} value against 120 A. fumigatus isolates was 2 μg/ml, which was higher than for posaconazole and voriconazole at 0.5 μg/ml each. Markedly elevated MIC values to isavuconazole were rare, with two A. fumigatus isolates demonstrating MIC values of 8 μg/ml with no information available on the mechanism of resistance [15].

An earlier study of 118 clinical Aspergillus isolates demonstrated that isavuconazole had fungicidal activity in vitro (i.e., the minimum fungicidal concentration presenting within two dilutions of the MIC) for four species including A. fumigatus, flavus, terreus and niger noting that A. terreus was least susceptible [16]. The same study explored the issue of cross-resistance, showing that isavuconazole retained activity against 14 strains with elevated MICs (≥8 mg/l) to itraconazole (posaconazole was not tested in this study but many of these isolates had previously demonstrated increased MICs to posaconazole) with the mean geometric MIC of 1.1 mg/l being approximately twofold higher than the geometric mean for all isolates but still within the expected therapeutic range of isavuconazole [16].

In comparison to Aspergillus spp., isavuconazole is less potent in vitro against the Mucorales. Using either European Committee on Antimicrobial Susceptibility Testing (EUCAST)
or Clinical and Laboratory Standards Institute (CLSI) methodology, five genera of 345 clinical isolates of Mucorales had MIC$_{90}$ values to isavuconazole of 4–16 μg/ml [14] corroborating findings from a smaller study of 36 isolates which had MIC$_{90}$ values of >8 μg/ml [17]. Posaconazole retains the greatest in vitro activity against the Mucorales, with isavuconazole and ravuconazole having similar activity [18]. Isavuconazole, like voriconazole and posaconazole is active against Aspergillus hyphae, which may be important, as this is the morphological form associated with tissue invasion [19].

An earlier study evaluated in vitro activity of isavuconazole and comparator antifungals against a large collection (n = 1534) of clinical fungal isolates including 101 isolates of Aspergillus species, and 21 non-Aspergillus molds from 2011 [20]. For Aspergillus species, isavuconazole was less active in vitro, using CLSI methodology than either posaconazole or voriconazole with MIC$_{90}$ values being 2, 1 and 1 μg/ml, respectively. Isavuconazole MIC results were ≤2 μg/ml for all species except A. niger, for which MIC values of ≥4 μg/ml were seen in 27% of the isolates tested, similar to findings reported elsewhere [12,17,21]. Possible cross-resistance was seen in only one isolate of A. fumigatus for which the itraconazole MIC was 2 μg/ml (non-wild-type) and isavuconazole MIC was 4 μg/ml. Among the few numbers of non-Aspergillus molds, isavuconazole, posaconazole and voriconazole were moderately active (MIC ≤2 μg/ml) against Penicillium spp., Paecilomyces spp. and Scedosporium apiospermum. For three Mucorales isolates (Rhizomucor pusillus and Rhizopus microsporus group) isavuconazole was less active than posaconazole with MIC results of 4, 1 and 2 μg/ml, respectively, to isavuconazole compared with 1 μg/ml for posaconazole [20].

Isavuconazole has some activity against emerging and infrequently encountered hyalohyphomycetes. For Fusarium species, MICs are equivalent to or higher than the other triazoles [4,22] either equivalent or lower than posaconazole and voriconazole for Scedosporium apiospermum but uniformly high for S. prolificans [18,21,23].

Attempts at characterizing mechanisms of resistance using fungal isolates from two Phase III clinical trials have been reported in abstract form [14,25]. Chandra et al. compared a subset of fungal isolates from the VITAL and SECURE studies with the following isavuconazole susceptibilities to species matched, sensitive control strains: Rhizopus spp. MIC 16 to >16 μg/ml (n = 7), Fusarium spp. MIC >16 μg/ml (n = 2); A. fumigatus MIC 8 to >16 μg/ml (n = 2) and A. niger MIC of 8 μg/ml (n = 3). Using a combination of techniques including sterol analysis, functional assays and gene expression of efflux pumps, these investigators concluded that changes in sterol content are the main contributor to azole resistance in Rhizopus, while elevated efflux pump activity contributes to azole resistance in Fusarium and Aspergillus species. Ergosterol levels were significantly higher in azole-resistant Rhizopus species (76.9 vs 2.6%) and resistant isolates accumulated higher quantities of sterol intermediates including squelene, calciferol and/or zymosterol. For azole resistant A. fumigatus, MDR2 (multidrug resistant protein) gene expression appeared abnormal being elevated twofold compared with the sensitive strain with no difference in MDR1, MDR3 and CYP51 gene expression observed [24].

However, overexpression of drug efflux transporters is likely one of several mechanisms underlying isavuconazole resistance. A study that used laboratory induced isavuconazole resistant strains of A. fumigatus strains with MICs ≥4–16 μg/ml [25] found no characteristic mutations in CYP51A or CYP51B nor was over-expression of drug efflux transporters (encoded by MDR1–4 genes) seen. No difference in virulence between wild-type and isavuconazole resistant strains was seen in an accompanying murine model of disseminated IA suggesting that acquired resistance was not associated with a fitness cost. Further studies are needed to elucidate the clinical significance of phenotypic resistance and the resistance mechanisms alternative to CYP51 mutations in A. fumigatus.

It appears that not all alterations in the CYP51A gene confer resistance to isavuconazole based on an evaluation of the largest dataset to date of clinical Aspergillus isolates (n = 1,237) from four European centers [12]. Howard et al. showed that TR34/L98H mutants of Aspergillus had the highest isavuconazole MICs with 72.5% of MICs being ≥2 mg/l including MICs of up to >8 mg/l suggesting that pan-azole resistance inclusive of isavuconazole may be an issue with this genotype [12]. In contrast, isolates with other mutations including G54 and M220 (M220K, M220T), had MICs in the wild-type range, demonstrating that isavuconazole activity varies depending on the underlying mutation. Among the Aspergillus species, A. niger appeared to be
less susceptible (higher MICs) to isavucona- 
zole [12] which is consistent with the overall 
trend of this subspecies toward lower suscep-
tibility to triazoles including itraconazole and 
voriconazole (i.e., A. niger has EUCAST ECVs of 
4 mg/l to itraconazole and 2 mg/l to voriconazole 
compared with 1 mg/l for both agents against 
A. fumigatus) [26,27]. The majority of A. fumi-

gatus, A. terreus and A. nidulans isolates with isavu-
conazole MICs above the suggested epidemiologi-

cal cut-off values (ECVs) also displayed reduced 
susceptibility to itraconazole and/or were found 
to harbor CYP51A mutations, suggesting that 
cross-resistance with other triazoles may occur, 
given their common mechanism of action. 

Cross-resistance to other triazoles was specifi-
cally explored in a study of clinical A. fumi-
gatus isolates, the majority of which came from 
patients with high prior azole exposure. Among 
a total of 40 isolates, 33 harbored a putative 
molecular resistance mechanism in addition 
to reduced susceptibility to at least one tria-
zole [28]. Isavuconazole MICs were higher in 
strains with reduced susceptibilities to other 
triazoles, mirroring changes in voriconazole 
susceptibility. There was a high degree of cor-
relation in MICs between isavuconazole and 
voriconazole (r = 0.885, Spearman’s correlation 
coefficient; p < 0.001) with a weaker relationship 
seen between isavuconazole and itraconazole or 
posaconazole, corresponding to the fact that isa-
vuconazole is structurally similar to voriconazole 
compared with posaconazole which has a long 
side chain like itraconazole [28]. 

This study demonstrated an association 
between specific CYP51A mutations and in vitro 
resistance: A. fumigatus isolates with L98H, 
G138C, Y431C, G434C and G458S alterations 
had elevated MICs to all triazoles, including isa-
vuconazole [28]. Isavuconazole and voriconazole 
MICs were lower with G54 amino acid alter-
tions, suggesting that this mutation, as others 
have described [29] only affects itraconazole 
and posaconazole susceptibility; isavucona-
zole and voriconazole MICs were variable with 
M220 alterations. This in vitro study suggests 
that isavuconazole MICs are more likely to be 
higher in strains with reduced susceptibilities to 
other triazoles and appear to best correlate with 
voriconazole MICs [28]. 

Pharmacokinetics/pharmacodynamics 
Pharmacodynamic (PD) studies provide a 
framework for predicting drug exposures that 
maximize clinical outcomes, by integrating phar-
macokinetic parameters, in vitro potency (MIC) 
and treatment efficacy of a drug [2]. When inter-
preting PD data it is worth noting that clinical 
break points have not been established for any 
antifungal agent and the less common species of 
Candida, non-Candida yeasts, Aspergillus spe-
cies or the non-Aspergillus molds [20]. Similarly, 
although ECVs do not predict clinical outcome 
they are useful for phenotypically discrimina-
ting wild-type from non-wild-type isolates which 
may harbor resistance mechanisms. For exam-
ple, ECVs proved useful in one study where the 
minority of Aspergillus isolates (fumigatus, terreus 
and nidulans) with MICs above ECVs to isavu-
conazole also had reduced susceptibility to itra-
conazole and/or were found to harbor CYP51A 
mutations [12]. 

Isavuconazole, like the other triazoles, is 
fungistatic in vivo and dose-fractionation stud-
ies in a murine model of disseminated candidi-
asis [30] and limited animal data of IA [2] suggest 
that the PD index most closely correlated with 
efficacy is the ratio of the 24-h area under the 
concentration-time curve (AUC) to the MIC. 
In an invasive pulmonary aspergillosis murine 
model, the free-drug AUC/MIC ratio associ-
ated with net stasis in the wild-type group 
ranged from 4.15 to 11.1 and was slightly lower 
for the two CYP51 mutant isolates at 3.61 to 
3.67 [2]. The median total and free-drug 24-h 
AUC/MIC PD targets (503 and 5, respectively) 
for net stasis identified in this study for isavu-
conazole, are consistent with PD values seen 
with other triazoles [31–33]. As described by 
others [12,28] mutations associated with elevated 
MICs in other triazoles did not uniformly cor-
relate with elevated isavuconazole MICs or, in 
this model with differences in fungal burden 
reduction in lung tissue [2]. 

A population pharmacokinetic model de-
veloped from Phase I and III studies estimated the 
probability of PD target attainment (using the 
AUC/MIC ratio) over a range of isavuconazole 
MICs to Aspergillus species [34]. Simulations 
suggested that the standard adult clinical dose 
of isavuconazole would adequately treat iso-
lates up to MICs of 0.06–4 mg/l under CLSI 
methodology and 2–4 mg/l under EUCAST 
methodology [34]. However, the correlation 
between clinical outcome and MIC is poor 
Based on Aspergillus isolates recovered at base-
line from patients enrolled in a Phase III clin-
ical trial (SECURE) [35]. In this trial, outcome
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DRUG EVALUATION

Isavuconazole appeared to be independent of the MIC with survival seen among patients with elevated MICs to isavuconazole (i.e., all cause mortality was 0/6 among isolates with MIC: 4 μg/ml and 0/1 with MIC: 8 μg/ml). These are early data and firm conclusions cannot be drawn, as numbers were small [35].

There is limited in vitro data on synergistic interactions using isavuconazole in combination therapy [36]. The isavuconazole-micafungin combination has been found to be synergistic against A. terreus, A. fumigatus, A. flavus and a Mucorales species, Cunninghamella bertholletiae. Low-grade antagonistic effects were observed for isavuconazole-amphotericin combination against A. fumigatus, A. flavus, F. solani and R. microsporus. Most intriguing was the observation that synergism/antagonism was dependent on isavuconazole concentrations suggesting that in tissues, it may be a dynamic process. In detail, for C. bertholletiae, low-level synergistic interactions were noted at low concentrations of amphotericin (0.125–0.5 mg/l) and at high concentrations of isavuconazole (4–32 mg/l), while at higher concentrations of amphotericin (1–8 mg/l) and isavuconazole (from 2 to 32 mg/l), the interactions were antagonistic [36].

Penetration of isavuconazole at sanctuary sites appears good, but data are limited. A preclinical rat study using radiolabelled isavuconazole showed wide tissue distribution including the brain and eye with levels 30 min postinfusion being above unity in all tissues with the exception of the ocular lens where the tissue/plasma ratio was 0.11. Ratios in other tissues ranged from 1.86 in brain, 1.95 in ocular uveal tract, 2.28 in lung and 13.5 in liver [37]. Pharmacodynamic in vivo murine models support efficacy of isavuconazole in CNS mucormycosis and candidiasis [3,38]. Luo et al. using disseminated Rhizopus delemar infection demonstrated that isavuconazole was comparable to liposomal amphotericin in improving survival and reducing fungal burden in murine lung and brain tissue. Survival at 21 days was 40% for mice treated with liposomal amphotericin and 65% for mice treated with the prodrug isavuconazonium sulfate [3]. Interestingly, in this study isavuconazole was fungicidal against two species of Rhizopus as the MIC100 (defined as the lowest concentration that produced 100% growth inhibition relative to the drug-free growth control) was equivalent to the minimum fungicidal concentrations being 0.188 μg/ml for R. delemar and 0.125 μg/ml for R. oryzae [3]. An earlier murine study demonstrated dose dependent activity of isavuconazole in C. kruzei brain infection in neutropenic mice, with isavuconazole being as effective as high dose voriconazole [38]. The penetration of isavuconazole into other relevant tissue compartments such as pulmonary epithelial lining fluid, alveolar macrophages or polymorphonuclear leukocytes in humans is unknown but quantification techniques exist to answer these questions [39].

Human pharmacokinetics

Isavuconazole has a favorable pharmacokinetic profile. Oral bioavailability is excellent being 98%, and is unaffected by food or gastric pH [6]. Isavuconazole is slowly metabolized in the liver by CYP3A4 [40] followed by the formation of glucuronides by uridine diphosphate-glucuronosyltransferase [41]. Isavuconazole has a high volume of distribution of approximately 470 l following iv. administration, in healthy volunteers, suggesting extensive distribution from plasma to tissues [7,10,41]. With both formulations, isavuconazole displays linear pharmacokinetics with peak concentration (Cmax) and AUC increasing proportionally to the administered dose [7]. Isavuconazole achieves peak concentration (Cmax) 2–3 h after oral administration with Cmax being 22% lower with oral compared with iv. administration [41]. Intersubject variability of the AUC is moderate and similar between oral and iv. dosing. The intersubject geometric coefficient of variation in healthy volunteers following oral dosing ranged from 22 to 37% while predicted AUCs based on population pharmacokinetic modeling of Phase III data (n = 232 patients) was 46% [41]. Over 90% of the drug is protein bound and it has a long terminal half life of 130 h [41]. Simulations reveal that against Aspergillus spp. therapeutic concentrations using the loading dose regimen are attained within 3 days [41]. In healthy volunteers plasma levels of isavuconazole remained detectable at 20 days after the last administered iv. and oral dose [7]. Urinary excretion of isavuconazole is negligible, being less than 0.4% of the infused dose and less than 0.04% when administrated orally [10]. The pharmacokinetics of isavuconazole is not affected by renal impairment, therefore no dosage adjustment is required for patients with renal impairment or end stage renal disease [41]. No evidence of auto-induction of CYP3A4 was seen with oral dosing over the 21-day study duration in healthy volunteers [7]. Isavuconazole has a
Drug–drug interactions

Like other triazoles, isavuconazole has significant interactions with drugs metabolized by the CYP450 system, particularly isoenzyme CYP3A4. Interactions can be expected with substrates, inducers or inhibitors of the CYP3A4 isoenzyme including rifampicin, rifabutin, efavirenz, ritonavir, carbamazepine, long-acting barbiturates, phenytoin, St John’s wart and oral contraceptives [8,9]. Rifampicin, a potent CYP3A4 inducer substantially increases systemic clearance thereby reducing levels of isavuconazole by 36-fold (personal communication Astellas Pty Ltd). Preliminary studies suggest that isavuconazole has no significant interaction with warfarin [42] and cyclosporine [43], which are substrates for CYP2C9 [9] and CYP3A4, respectively. Coadministration of a single 300-mg dose of cyclosporine with multiple doses of isavuconazole resulted in a mild (1.29-fold) increase in cyclosporine exposure among healthy volunteers [43] but further study in transplant recipients is warranted.

Isavuconazole-drug interactions have been evaluated in several recent studies presented in abstract form. Coadministration of multiple doses of isavuconazole and a single dose of methotrexate (7.5 mg) did not alter the pharmacokinetics of methotrexate however, a 29% increase in the metabolite 7-hydroxy-methotrexate was observed, suggesting that renal monitoring may be advisable with coadministration of high dose methotrexate [44]. Tacrolimus and sirolimus exposure increased just over twofold when a single dose of each drug was coadministered with multiple doses of isavuconazole in healthy subjects [45,46]. Isavuconazole did not potentiate the toxicities associated with prednisolone, the active metabolite of prednisone, which is metabolized by the CYP3A4 enzyme [47].

Clinical efficacy for invasive fungal infections

Isavuconazole is in the advanced stages of clinical development following completion of two Phase III clinical studies. The recently presented SECURE study (ClinicalTrials.gov identifier: NCT00412893 [48]) was a multicenter double-blind randomized trial which evaluated the noninferiority of isavuconazole compared with voriconazole for the primary treatment of invasive fungal diseases (IFDs) caused by Aspergillus spp. or other filamentous molds. The study included adults (≥18 years old) with possible, probable or proven IMD according to consensus criteria [49]. Isavuconazole was administered as an iv. loading dose followed by oral dosing up to day 84 of treatment. The primary outcome measure was all cause mortality through day 42 in the intention-to-treat population using a 10% noninferiority margin and secondary outcomes were overall, clinical, mycological and radiological response. Exclusion criteria were patients with other invasive fungal diseases (neither Aspergillus nor filamentous fungi), hepatic or moderate–severe renal dysfunction, chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis), receipt of >4 days of systemic antimold therapy within 7 days prior to study drug, advanced HIV infection (CD4 <200 cells/mm³) or an AIDS-defining condition, low likelihood of survival at 30 days or mechanical ventilation at study onset [50].

Overall, 527 patients were randomized of whom 516 received at least one dose of study drug and were included in the intention to treat population (ITT) [50]. Baseline characteristics in the ITT population were similar between groups. Key demographic characteristics for isavuconazole and voriconazole groups respectively were mean age: 51 years for both groups; male gender: 56 versus 63%; patients residing in North America, Western Europe, Australia or New Zealand: 52 versus 52.4%; Caucasian background: 82 versus 74%; Asian background: 17 versus 25%. The majority of patients in the isavuconazole and voriconazole groups respectively, had an underlying hematological malignancy (82 vs 86%); were neutropenic at baseline (63 vs 68%); were alogeneic hematopoietic stem cell transplant (HSCT) recipients (21 vs 20%) and uncontrolled malignancy, a poor prognostic feature was present in 67 and 72% of patients receiving isavuconazole and voriconazole, respectively. With respect to features of IMD, proven/probable disease occurred in 55% (143/258) and 51% (129/259) of isavuconazole and voriconazole groups, respectively, with pulmonary involvement seen in the overwhelming majority (>90%) of cases with proven/probable disease [11]. The diagnosis of probable IA could
be made by a positive serum galactomannan, only, using a single optical density of ≥0.7 or two serial consecutive values of ≥0.5 but <0.7 as cut-off for positivity, which occurred in 50.3 and 52.7% of isavuconazole and voriconazole groups, respectively, while non-Aspergillus molds were few being isolated in 5 and 6 of patients in each group, respectively [11]. A bronchoalveolar lavage galactomannan value of ≥1.0 was only accepted as microbiological criterion for possible disease. There were significantly fewer study drug related adverse events among the isavuconazole group as discussed below.

In SECURE, the primary end point of crude all-cause-mortality through day 42 was 18.6% in the isavuconazole arm and 20.2% in the voriconazole arm with the upper bound of the 95% CI of the treatment difference below the prespecified noninferiority margin of 10%, denoting noninferiority of isavuconazole to voriconazole. The comparability of isavuconazole with voriconazole in terms of treatment efficacy persisted after adjustment for geographic region, allogeneic HSCT status and uncontrolled malignancy. All-cause mortality through day 84 was consistent with the primary end point result, with no difference between groups seen. There were no significant differences in the main secondary end point of overall success at the end of therapy (a composite of clinical, mycological and radiological responses) as determined by an independent blinded data review committee (DRC), being 35% in the isavuconazole group and 36% in the voriconazole group [11].

In the subset of patients with hematological malignancies (n = 433), all-cause mortality was similar between groups being 22% for isavuconazole and 24% for voriconazole [51]. Of note, acute lymphoblastic leukemia (ALL) was the third most common condition after acute myeloid leukemia (AML) and allogeneic HSCT, respectively [51], highlighting the growing recognition that ALL is a predisposing factor for IFD as others have also noted [52,53].

Subgroup analysis of 412 patients with pulmonary IMD from SECURE showed that isavuconazole had comparable efficacy to voriconazole [54]. Of this subgroup (n = 200 on isavuconazole, n = 212 on voriconazole), 54% had proven or probable pulmonary disease; 46% had possible pulmonary IMD with nodules the most common radiological feature seen. All cause mortality in the ITT population with pulmonary IMD for isavuconazole and voriconazole through day 42 (17 vs 21%, respectively) and day 84 (28 vs 32%, respectively) in addition to a secondary end point of DRC assessed overall success in patients with proven/probable pulmonary IMD (i.e., complete and partial responses; being 37 vs 36%, respectively) was similar with no statistically significant differences noted between isavuconazole and voriconazole treatment arms [54].

Outcomes were consistent in the subgroup of patients with probable or proven IA from SECURE [50]. All-cause mortality through day 42 was comparable in the isavuconazole (n = 123, 19%) and voriconazole (n = 108, 22%) groups with IA, irrespective of host characteristics such as the presence or absence of baseline neutropenia, persistence or resolution of neutropenia; presence of haematological malignancy and stage of infection. Comparable responses were seen in those patients who isolated Aspergillus or a positive serum galactomannan alone — the former reflecting a more advanced stage of infection. Not unexpectedly, patients in the SECURE study who had uncontrolled malignancy defined as active malignancy or newly diagnosed/relapsed disease at baseline, had poorer outcomes than patients without uncontrolled malignancy [55]. All cause mortality through day 42 in patients with uncontrolled malignancy was higher than in those without uncontrolled malignancy in both treatment arms of the ITT population being 21% versus 22% in isavuconazole and voriconazole groups, respectively, for patients with uncontrolled malignancy and 13% versus 15% in patients without uncontrolled malignancy. Importantly, within the subset of patients with uncontrolled malignancy there was no significant difference in all cause mortality in either group (21% for isavuconazole vs 22% for voriconazole).

The VITAL study (ClinicalTrials.gov identifier: NCT00634049 [48]) was an open-label Phase III multicenter noncomparator trial that evaluated the efficacy and safety of isavuconazole for treatment of proven or probable IFDs due to Aspergillus species and other filamentous fungi, yeasts or dimorphic fungi in patients with and without pre-existing renal impairment. It is noteworthy, that VITAL enrolled patients for primary treatment or those who were refractory to or intolerant of prior antifungal therapy. Isavuconazole was administered as a 200 mg iv. or oral loading dose three-times daily on days 1 and 2, followed by either iv. or oral isavuconazole...
200 mg once daily from day 3 up to a duration of 180 days. VITAL enrolled 149 patients of whom 37 had proven or probable mucormycosis [56]. The primary end point was overall success at the end of treatment based on DRC adjudicated clinical, mycological and radiological response. Efficacy outcomes in the subgroup with mucormycosis will be discussed below.

Isavuconazole has potent in vitro activity against dimorphic fungi, with MICs that are similar to other agents and lower than those of fluconazole [4] but clinical data on its efficacy against the endemic mycoses are scant. A subset of 29 patients in the VITAL study were treated for proven/probable IFDs due to dimorphic fungi including Paracoccidioides spp. (n = 10), Coccidioides spp. (n = 9), Histoplasma spp. (n = 7) and Blastomyces spp. (n = 3) [57]. Pulmonary involvement was present in all patients infected with Coccidioides and Blastomyces spp. Treatment duration ranged from 2 to 331 days and was ≥175 days in 24 patients. The primary end point in VITAL, being overall success at the end of treatment based on clinical, mycological and radiological response, was achieved in 18 (64%) of patients. Of this group complete response was seen in 5 (18%) and partial response in 13 (46%) of patients [57]. Twenty-six patients were alive ≥100 days after starting isavuconazole therapy; 3 patients died: 1 on day 20 (Blastomyces), and 2 on days 27 and 91 (Paracoccidioides) with all considered treatment failures by the DRC due to IFD progression.

There are limited data on outcomes of infections due to rare molds from SECURE and VITAL. From these trials, Fusarium species were isolated in 9 patients and Scedosporium species in 3 patients, the latter comprising S. apiospermum in one patient and in 2 patients, coinfections with S. prolificans and Rhizopus spp. as well as Scedosporium spp. and Aspergillus spp. not otherwise specified [58]. Isavuconazole was administered as salvage therapy in 2 patients with Fusariosis and 1 patient with Scedosporiosis. Baseline neutropenia was present in 6/9 patients with Fusariosis and 1/3 patients with Scedosporiosis. At the end of treatment, 3 of 9 patients with Fusarium IMD had a successful outcome being a complete (n = 2) or partial response, while 6 failed therapy (corresponding to stable or progressive infection). Outcomes for Scedosporium infection were poor with one patient each having a partial response, stable disease or disease progression [58]. Mortality was high being 5/9 among patients with Fusariosis and 1/3 in patients with Scedosporiosis with disease progression evident in all patients as assessed by the DRCs. These poor outcomes should be contextualized bearing in mind that these patients were at high risk for clinical failure at baseline.

The ACTIVE study (ClinicalTrials.gov identifier: NCT00413218 [48]) is a double blind randomized Phase III trial comparing isavuconazole to caspofungin followed by oral voriconazole for treatment of invasive Candida infections, which has been completed. Isavuconazole as prophylaxis in patients undergoing chemotherapy for AML has completed recruitment (ClinicalTrials.gov identifier: NCT00413439 [48]). The primary outcome is safety and secondary outcomes are efficacy and pharmacokinetic parameters. Results of these trials are anticipated.

Mucormycosis
Mucormycosis is less common than IA but is an aggressive invasive fungal disease associated with a higher mortality [59–61]. There are few therapeutic options available against mucormycosis with only the amphotericin formulations and posaconazole being reliably active. Isavuconazole has demonstrated modest activity in vitro against the Mucorales [4] but preclinical in vivo [3] and clinical data are promising.

Analysis of 37 patients with mucormycosis from the VITAL study has been reported in abstract form [56]. Primary therapy with isavuconazole was administered to 21 patients; 16 patients received isavuconazole as salvage treatment (i.e., due refractory disease or intolerance to other antifungal therapy) for mucormycosis. Clinical success defined as a combination of clinical, mycological and radiological response, at the end of treatment among 35 evaluable patients was 31% (11/35; 2 patients continued treatment beyond day 180 and therefore did not have end of treatment assessment by the DRC but were considered to have stable disease and clinical response at the day 84 assessment). Complete and partial response was seen in 5 and 6 patients, respectively, and stability (regarded as failure) was achieved in 10 patients. Of the 5 patients with a complete response at the end of treatment, 3 received isavuconazole as primary treatment lasting 179, 180 and 509 days and 2 were refractory to other systemic antifungal therapy but nevertheless achieved a complete response after 86 and 735 days of treatment [41].
Survival through day 42 and day 84 follow-up was 62% (n = 23) and 43% (n = 21), respectively. Among patients refractory to prior antifungal therapy, more than half (n = 6/11; 55%), were alive through to 12 weeks. In summary, a successful overall response at end of treatment was observed in 31.6% of patients treated with isavuconazole as primary therapy and 36.4% of patients refractory to prior antifungal therapy.

Study discontinuation among the subgroup with mucormycosis was high (n = 24 of 37, 65%) with death being the most common reason (n = 11) followed by adverse events/intercurrent illness (n = 6). Insufficient therapeutic response was cited in two patients with mucormycosis bearing in mind that VITAL enrolled patients who required salvage therapy and were therefore at high risk for clinical failure from the outset. Most patients had either hematological malignancies (AML in 10 and ALL in three patients) or diabetes (n = 4). Pulmonary involvement was seen in 60% (n = 22) of patients while extrapulmonary disease alone was present in 41% (n = 15). The most common extrapulmonary sites were sinuses in 16, ophthalmic in 7 and CNS disease in 6 patients consistent with the predilection of this organism for rhino-cerebral involvement. Rhizopus species were most commonly isolated, accounting for 14 isolates while nonidentifiable mucormycetes accounted for 13 isolates, highlighting the well recognized challenges of laboratory identification of molds [62].

There have been isolated reports citing the successful use of isavuconazole as salvage therapy for mucormycosis [63,64]. Isavuconazole was administered to a patient with disseminated mucormycosis (identified as Rhizomucor pusillus/R. miehei) involving lung, brain and skin. The patient had a background of relapsed leukemia after allogeneic HSCT and had failed or was intolerant of posaconazole and liposomal amphotericin. Although the patient eventually succumbed to leukaemia, a clinical and radiological response with 29 weeks of isavuconazole treatment was seen. TDM demonstrated that a maintenance dose of 200 mg/day of isavuconazole was sufficient to keep serum levels above 1 μg/ml with the putative treatment range at this center being 1–2 μg/ml. Importantly, levels remained stable over several months consistent with a case reported elsewhere [40].

In a similar vein, a patient with sino-orbital mucormycosis caused by Rhizopus oryzae complicating high dose corticosteroid treatment of ulcerative colitis, received salvage treatment with isavuconazole following failure of >3 months of treatment with liposomal amphotericin and posaconazole [64]. Of interest, a durable clinical response with long term survival at 2 years follow-up was achieved despite elevated in vitro MIC values by both CLSI and EUCAST methodologies being 8 to >16 μg/ml. Subsequent sterol analysis demonstrated accumulation of ergosterol precursors with elevated levels of squalene (17.06 vs 9.95% in the control susceptible strain) and zymosterol (68.70 vs 0.00%) with corresponding reductions seen in ergosterol levels (2.3 vs 76.93% in the control susceptible strain) suggestive of azole resistance. In both case studies [63,64] isavuconazole was well tolerated despite prolonged treatment lasting 506 days [64] with mild adverse events such as skin photosensitivity, nausea and transient elevations in liver enzymes (that were less than two times the upper limit of normal coinciding with higher dosage of isavuconazole 400mg/day) and an absence of QTc abnormalities [63].

The high bioavailability of isavuconazole independent of gastric pH and food effect was relied upon for salvage treatment of pulmonary mucormycosis in a patient with diabetes following previous gastric bypass surgery [65]. The patient underwent a left pneumonectomy but was commenced on isavuconazole due to liposomal amphotericin induced nephrotoxicity and concerns regarding poor absorption of posaconazole. Standard dose isavuconazole initially resulted in peak and trough serum levels below the values reported from healthy volunteer studies (mean trough level of 3.458 μg/ml and the mean Cmin of 5.817 μg/ml) prompting a doubling of the dose to 200 mg bd, which resulted in levels above 3 μg/ml. No fungal recurrence was evident after 4 months treatment with isavuconazole and it was well tolerated with mild nausea and minor fluctuations in alkaline phosphatase observed. This case illustrates the challenges in managing IFDs especially in the setting of impaired GI absorption and/or rapid intestinal transit and limited therapeutic options.

**Special circumstances**

- **Liver disease**
  Liver impairment decreases the clearance of isavuconazole [40]. Volunteers with mild to moderate alcohol related liver disease (corresponding to Child-Pugh class A and B, respectively) administered 100 mg/day iv. had a reduction in systemic
clearance compared with healthy volunteers, from 2.73 l/h in healthy subjects to 1.93 l/h and 1.43 l/h in patients with mild to moderate liver impairment, respectively [40]. A corresponding increase in the elimination half-life from 123 h in healthy volunteers to 224 h and 302 h in patients with mild to moderate liver impairment respectively was seen. Similar pharmacokinetics was observed with orally administered drug. In summary, moderate liver impairment will reduce systemic clearance of isavuconazole by approximately 50% [40] but dose reduction is not recommended by the manufacturer as the risk of compromising efficacy may outweigh the risk of toxicity associated with standard dosing [41].

Safety & tolerability
Isavuconazole was better tolerated than voriconazole in the SECURE study. Overall, treatment emergent adverse events (defined as an adverse event occurring after study drug administration and up to 28 days from its cessation) that were recorded as drug related, were statistically fewer relative to voriconazole (42.4 vs 59.8%, p < 0.05) as were adverse events resulting in drug discontinuation (14.4 vs 22.8%, p = 0.05). These differences were driven by fewer events in the following organ systems; hepatobiliary (8.9 vs 16.2%, p = 0.016), skin (33.5 vs 42.5%, p = 0.037) and eye disorders (15.2 vs 26.6%, p = 0.002) [11]. Although skin disorders comprising rash, erythema and drug eruptions [41] were less common than voriconazole, they were still frequent. In subgroup analyses of patients with pulmonary IMD, significantly fewer patients in the isavuconazole compared with voriconazole groups experienced treatment emergent adverse events of the eye (16 vs 26%), skin (35 vs 44%), psychiatric (29 vs 34%) and hepatobiliary (9 vs 18%) systems, respectively [54]. A similar profile was seen in the subgroup with only proven or probable IA with significantly fewer patients treated with isavuconazole experiencing drug related adverse events (39 vs 62%, respectively, p < 0.05) and eye disorders inclusive of visual impairment, blurred vision, retinal haemorrhage and dry eyes (15 vs 29%, respectively, p < 0.05) [50].

Phase II data from healthy volunteers using single ascending doses of isavuconazole (100–400 mg orally; 50–200 mg iv.) documented minor side effects including headache, rhinitis, nasopharyngitis, moderate diarrhea, nausea and mild upper abdominal pain [7].

Conclusion & expert commentary
Isavuconazole will likely establish itself as an alternative agent for the treatment of invasive mold diseases in particular aspergillosis and mucormycosis. Against voriconazole, the current standard of care for treatment of IA, it proved noninferior and was better tolerated. Importantly, efficacy outcomes were consistent across subgroup analyses lending robustness to the primary end point (with the caveat that trials are not powered to show noninferiority in subgroup analyses). Differentiation of isavuconazole from the now available solid tablet and iv. formulations of posaconazole may be more difficult. Its extended spectrum of activity has not improved beyond posaconazole but while posaconazole was principally licensed as a prophylactic agent with treatment of IA a salvage indication, isavuconazole has an evidence base to promote its use both as primary and salvage treatment for IA and mucormycosis. Its role as prophylaxis in patients at high risk of IFD is awaited.

Isavuconazole has several attributes that distinguish it from both voriconazole and posaconazole. A Phase III comparator clinical trial (SECURE) demonstrated that it had better tolerability, fewer discontinuations and less toxicity than voriconazole affecting the eye, hepatobiliary and skin organ systems. Similarly, noncomparator clinical trial data for the treatment of mucormycosis (VITAL) showed activity, consistent with the in vitro activity of isavuconazole against this pathogen. Evidence of complete response in the primary and salvage treatment of mucormycosis is encouraging as is the prolonged treatment duration tolerated by these few patients. A clinical trial comparing isavuconazole to posaconazole for treatment of aspergillosis or mucormycosis seems unlikely, leaving choice dependent on other factors such as strength of evidence and cost.

Underpinning the clinical efficacy of isavuconazole are its favorable pharmacokinetic and physico-chemical properties. These include predictable linear pharmacokinetics, good tissue distribution, a long elimination half-life allowing once daily administration; excellent oral bioavailability that is not influenced by prandial status or gastric acidity and finally, the two formulations ease transitioning from iv. to oral step down therapy. The high solubility of the iv. formulation circumvents the need for potentially nephrotoxic solubilizing agents such as cyclodextrin allowing safe use in renal impairment.
Despite its many strengths, there remain several unanswered questions relating to the clinical use of isavuconazole that are outlined as areas of future research in Table 1. The issue of cross-resistance of isavuconazole with posaconazole and voriconazole is unclear given their common mechanism of action but limited data suggest that in vitro resistance best correlates with voriconazole. A corollary is whether prior mold active prophylaxis may compromise the effectiveness of isavuconazole for treatment of breakthrough IFDs. The significance of elevated MICs and specific CYP51A alterations on clinical outcome is unresolved, arguing for further epidemiological and PD studies. The many questions regarding TDM include the extent of intra- or interpatient variability and relationship of systemic exposure to clinical outcome noting that putative therapeutic or prophylactic thresholds for TDM are not established for isavuconazole. The effect of isavuconazole on the sensitivity of fungal biomarkers such as GM or Aspergillus PCR is unknown. Finally, cost effectiveness analyses will help inform clinical decision-making such as introduction of isavuconazole onto hospital formularies.

The evolving epidemiology of IFDs \[53,66–68\], is driven by multiple factors: changing chemotherapeutic, immunomodulatory and transplantation practices, an ageing population \[69\], improved diagnostic tools, environmental fungicide pressure \[70\], in partnership with waves of new potent antifungal drugs used in either prophylactic, empiric or targeted treatment strategies. This complex interplay of factors

**Table 1. Future areas of research regarding the clinical utility of isavuconazole.**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Clinical data</td>
<td>Chronic toxicities with long-term administration of ≥6 months duration documenting bone, skin and nervous system toxicities</td>
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<tr>
<td></td>
<td>Prospective surveillance in special groups and/or neglected populations: solid organ transplant recipients, pediatrics, chronic</td>
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<td>granulomatous disease, mycoses in resource limited settings, for example, HIV/AIDS associated Cryptococcosis and eumycetoma</td>
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<td>(Madura foot)</td>
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<td>Efficacy in chronic aspergillosis syndromes such as allergic bronchopulmonary aspergillosis and asthma with fungal sensitization</td>
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<tr>
<td>Pharmacokinetic/pharmacodynamic areas</td>
<td>Relationship between clinical effectiveness/toxicity and systemic exposure, delineating the putative role of therapeutic drug monitoring</td>
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<tr>
<td></td>
<td>Inter- and intra-patient variation in drug exposure; accelerated metabolism due to autoinduction especially with long-term administration</td>
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<td></td>
<td>Drug levels and clinical effectiveness in nonplasma compartments including pulmonary alveolar/epithelial cells, brain, cerebrospinal fluid,</td>
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<tr>
<td></td>
<td>bone and eye</td>
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<td>Novel dosing strategies incorporating extended dosing intervals given the long elimination half-life of the drug</td>
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<td></td>
<td>Pharmacokinetic parameters, safety and tolerability in underweight and extremely obese patients as well as at the extremes of age</td>
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<td>Activity of isavuconazole in biofilms</td>
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<td>Preclinical and clinical efficacy of combination therapy with other antifungal agents</td>
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<td>Antifungal stewardship</td>
<td>Active surveillance of invasive fungal diseases following introduction of isavuconazole to capture changes in fungal epidemiology</td>
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<td>Compliance with practice guidelines/unit protocols</td>
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<td>Cost–effectiveness studies including scenarios involving pre-exposure to mold-active triazoles, for example, voriconazole and posaconazole</td>
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<tr>
<td>Mechanisms of resistance</td>
<td>Cross-resistance or tolerance in the setting of pre-exposure to other triazoles</td>
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<td>Relationship between resistance and fitness cost</td>
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<td>Risk factors for the emergence and persistence of in vivo and environmental resistance</td>
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</table>
EXECUTIVE SUMMARY

Pharmacokinetics

- Isavuconazole is the active moiety of the water-soluble prodrug isavuconazonium sulfate that is rapidly hydrolyzed by plasma esterases to isavuconazole and an inactive cleavage product.
- Isavuconazole displays linear pharmacokinetics.
- It has an oral bioavailability of 98%, which is unaffected by food or gastric pH.
- Its mean elimination half-life is long, being 130 h.
- It exhibits extensive distribution from plasma to tissues with a volume of distribution being 400–500 l.
- Isavuconazole undergoes hepatic metabolism, urinary excretion is negligible.
- Intersubject variability appears moderate based on data from healthy volunteers and patients in Phase III studies.

Clinical efficacy

- Isavuconazole was noninferior to voriconazole for primary treatment of invasive aspergillosis (IA) based on a double blind multicenter Phase III randomized clinical trial (SECURE) in mostly hematological patients; the vast majority of the 516 evaluable patients had IA but SECURE also enrolled patients with other filamentous mold diseases; all cause mortality at 6 weeks was 18.6% for isavuconazole and 20.2% for voriconazole, within the prespecified margin of a 10% treatment difference thus meeting the criteria for noninferiority. The treatment effect was independent of presence of neutropenia at baseline, resolution of neutropenia and was durable at the 12-week follow-up and for secondary end points such as overall success.
- Phase III open label noncomparator trial (VITAL) in patients with invasive mold diseases due to a range of pathogens including Aspergillus, Mucomycetes, yeasts and dimorphic fungi revealed better than expected outcomes in 37 patients receiving isavuconazole as primary (n = 21) or salvage therapy (n = 16) for mucormycosis. Overall success at the end of treatment or up to day 180, based on a composite of clinical, mycological and radiological response as determined by an independent blinded data review committee, was 31.6% for primary therapy and 36.4% for patients who were refractory to prior antifungal therapy. All-cause mortality through day 42 and day 84 in patients with probable/proven mucormycosis was 38 and 43%, respectively. All cause mortality through day 42 and day 84 in 21 patients receiving isavuconazole as primary therapy was 33 and 43%, respectively.
- Results of Phase III trials evaluating the role of isavuconazole as prophylaxis in patients with acute myeloid leukaemia and in treatment of invasive candidiasis are anticipated.

Safety & tolerability

- Isavuconazole has a better safety and tolerability profile compared with voriconazole in a Phase III trial (SECURE). Significantly fewer treatment emergent drug-related adverse events and drug discontinuations were observed.
- Significantly fewer adverse events in the hepatobiliary, eye and skin organ systems compared with voriconazole were observed.
- No dose reduction is recommended for mild to moderate liver disease noting that systemic clearance of the drug is decreased.
- No dosage adjustment for any degree of renal impairment.
- Adverse events with long-term administration are unknown.
- Cyclodextrin is absent from the intravenous formulation, obviating concerns regarding renal toxicity.

Drug interactions

- Interactions with drugs metabolized by the CYP450 system, particularly CYP3A4 are expected.
- Coadministration of isavuconazole and rifampicin increases systemic clearance of isavuconazole.
- No clinically relevant drug–drug interactions with warfarin or cyclosporine were observed in healthy volunteers.
mandates the need for continuous multicenter surveillance programs combining microbiological with clinical outcome data to guide management strategies, support antifungal stewardship initiatives [71] and laboratory research. Isavuconazole is a welcome addition to the antifungal armamentarium but experience with other triazoles has taught us that postmarketing studies are as important as Phase III development in refining and optimizing the clinical utility of antifungal agents at the bedside.

Disclosure

In addition to the peer-review process, with the author(s) consent, the manufacturer of the product(s) discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made at the discretion of the author(s) and based on scientific or editorial merit only.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

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DRUG EVALUATION


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