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EXPERT OPINION

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Evaluation of the pharmacokinetics and clinical utility of isavuconazole for treatment of invasive fungal infections

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Introduction: Invasive fungal infections remain a leading cause of infectious morbidity and mortality in immunocompromised patients. There are relatively few effective antifungal agents, and currently available agents all have significant limitations. Isavuconazole is a novel second-generation triazole with broad-spectrum antifungal activity, and a favorable pharmacokinetic–pharmacodynamic profile. Isavuconazole is available as an oral and intravenous formulation. Phase III studies that are examining the efficacy of isavuconazole for invasive candidiasis and invasive aspergillosis are currently in progress.

Areas covered: This review provides a summary of the pharmacological characteristics of isavuconazole and the potential future use of this agent. The preclinical and clinical pharmacokinetics and pharmacodynamics are discussed. This review was constructed by searching isavuconazole, triazole, pharmacokinetics and pharmacodynamics in PubMed. References and abstracts that were not identified by this method were retrieved from the respective publications.

Expert opinion: Isavuconazole has the potential to become an important agent for the treatment of invasive fungal infections, principally because of its relatively broad and potent *in vitro* antifungal activity, and its favorable pharmacokinetic profile. Further preclinical and clinical studies are required to define the clinical utility of this agent, especially for invasive candidiasis and invasive aspergillosis. Further information is required on the likely drug interactions, and *in vitro* susceptibility breakpoints for medically important invasive fungal pathogens. Further pharmacokinetic studies are also required in a range of patient populations to quantify the extent and sources of pharmacokinetic variability.

Keywords: *Aspergillus*, itraconazole, pharmacodynamics, pharmacokinetics, resistance, triazole

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1. Introduction

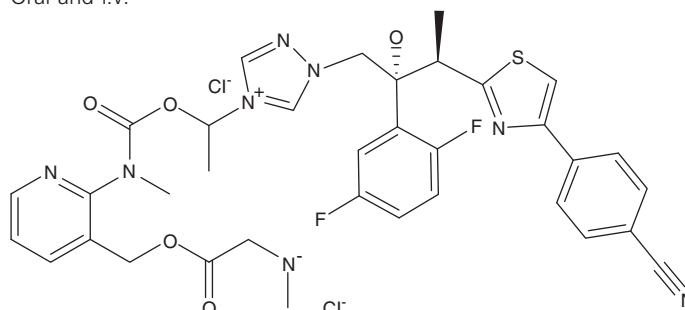
The triazoles are first-line agents for the treatment of invasive syndromes caused by a range of medically important opportunistic fungal pathogens [1]. Importantly, however, there are significant differences within this class in terms of structure–activity relationships, clinical pharmacokinetics, toxicity and drug–drug interactions. These differences have a significant impact on the clinical utility of the triazoles. The

Box 1. Drug summary.

Drug name	Isavuconazole
Phase	In Phase III clinical trials
Indication	Invasive fungal infections (invasive candidiasis and invasive aspergillosis)
Pharmacology description	Triazole
Route of administration	Oral and i.v.
Chemical structure	

Pivotal trial(s)

[5-7]



relative strengths and weaknesses of the triazoles mean that there are potential opportunities for the development of newer agents that are effective and safe.

Isavuconazole (**Box 1**) is a second-generation triazole that was developed to overcome some of the inherent limitations of itraconazole and fluconazole. Isavuconazole has relatively broad-spectrum antifungal activity against medically important opportunistic fungal pathogens such as *Candida* spp., *Aspergillus* spp. and potentially the Mucorales. Furthermore, isavuconazole has a number of favorable pharmacokinetic attributes that may be advantageous compared with existing antifungal compounds. The pharmacology, spectrum of antifungal activity and clinical utility of isavuconazole are considered in this review.

2. Structure, activity and formulation

Isavuconazonium (BAL 8557) is the water-soluble pro-drug of isavuconazole (BAL 4815). BAL 8557 consists of a [*N*-(3-acetoxypropyl)-*N*-methylamino]-carboxymethyl group attached to isavuconazole via an ester linkage (**Figure 1**). The chemical formula of isavuconazole is 4-{2-[(2*R*,3*R*)-3-(2,5-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]-1,3-thiazol-4-yl}benzonitrile and its molecular formula is C₂₂H₁₇F₂N₅OS. The structures of the prodrug, active moiety and prodrug fragment are shown in **Figure 1**. Unlike the i.v. formulations of itraconazole and voriconazole, isavuconazonium does not require the addition of cyclodextrin to facilitate solubility. BAL 8557 can be administered orally or i.v. The oral formulation is a hard gelatin capsule.

Following systemic administration, the prodrug is cleaved by plasma esterases to form BAL 8728 (the prodrug cleavage product) and isavuconazole. Precise details about the nature of the esterases and the thermodynamics of this conversion are not available. The current convention is to express the dosage of the prodrug in terms of mg-equivalent of the active compound

(isavuconazole). The current regimen that is being used in the various clinical trials (see below) is 200 mg Q8h i.v. (or orally) for the first 2 days followed by 200 mg/day i.v. or orally [2].

3. Drug target, mechanism of action, toxicity and antifungal resistance

In common with other members of the triazole class, isavuconazole inhibits ergosterol biosynthesis and results in the disruption of fungal membrane structure and function. The active site of isavuconazole is shown in **Figure 1**. The antifungal spectrum is conferred by the side arm of isavuconazole, which is responsible for orientating the molecule so that the triazole ring can engage with the heme moiety at the bottom of the binding pocket in the fungal Cyp51 protein [1].

The side arm of isavuconazole will also influence the activity of isavuconazole against other fungal pathogens that are resistant to other triazoles (itraconazole, voriconazole and posaconazole). At this stage, the extent of cross-resistance is not well defined, but the relevant studies are in progress. A recent study from India showed two *Aspergillus fumigatus* isolates that were pan-triazole resistant related to a tandem repeat/L98H mutation (itraconazole > 16 mg/l, voriconazole 2 mg/l, posaconazole 2 mg/l), but also had elevated isavuconazole MICs of 8 mg/l [3]. There is no information on whether isavuconazole is a substrate for efflux pumps in *Aspergillus* spp. A further understanding of the extent of cross-resistance is likely to be important in the context of a potential looming public health crisis of triazole resistance [4].

Little information is published on the preclinical toxicity of isavuconazole. Isavuconazole is well tolerated in healthy volunteer studies and (to date) is devoid of serious adverse events [5-7]. The incidence of hepatotoxicity, which is common to all members of the triazole class, is not known.

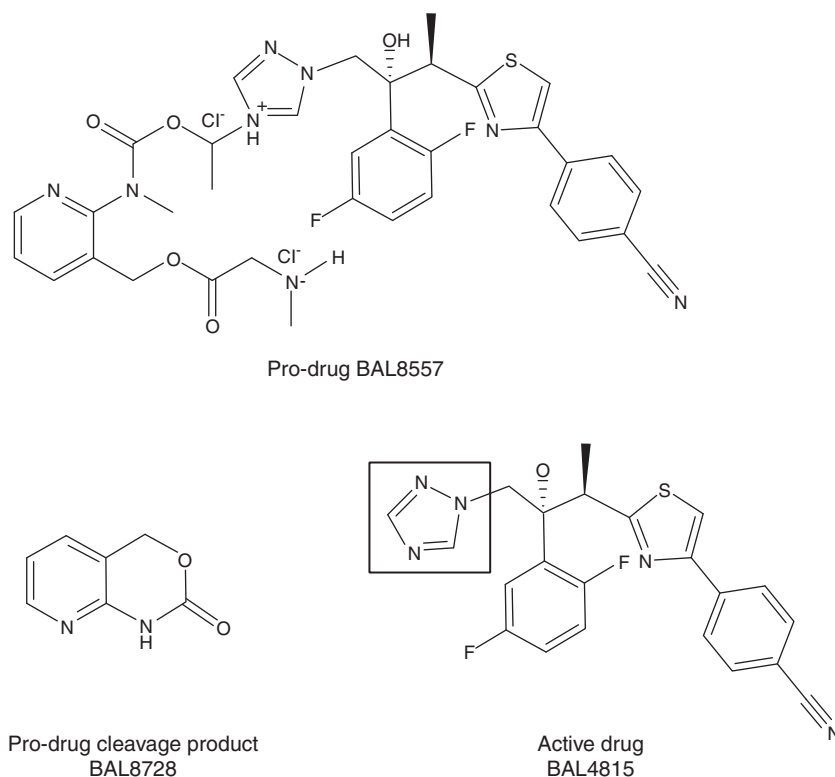


Figure 1. Isavuconazole structure, active moiety and prodrug fragment. The active site is indicated by being enclosed in a box.

4. Preclinical pharmacology

There is relatively little information on the preclinical pharmacology of isavuconazole. The pharmacokinetics of isavuconazole have been defined in rats and cynomolgus monkeys and these studies were important in identifying human dosages for further study in clinical trials. Currently, this information is not in the public domain. In rats receiving either i.v. or oral ^{14}C -labeled isavuconazole, the majority (81%) is excreted in the feces and the remainder is found in the urine [5].

The pharmacokinetics of isavuconazole have been defined in a murine model of disseminated candidiasis. The concentration–time profile in mice is completely different from humans. Isavuconazole has a terminal half-life of 3.41 h in mice (compared with ~ 100 h in humans) [5,6,8]. There is rapid tracking of drug into the kidney with no evidence of hysteresis [8]. The area under the curve (AUC) in murine kidney homogenate is approximately six times higher than that achieved in plasma [8]. Extensive distribution into tissues is consistent with the relatively large estimates for the volume of the central compartment from pharmacokinetic models, which is consistent with other triazoles.

The pharmacokinetics of isavuconazole in other relevant tissues, such as the lung, brain, cerebrospinal fluid, vagina, liver, spleen, skin and nails are yet to be defined. A further insight into this issue will be helpful for deciding whether infections at these specific sites can potentially be treated with isavuconazole.

5. Human pharmacokinetics

Isavuconazole is extensively protein bound (~ 98%). Protein binding is linear, and albumen is quantitatively the most important protein (unpublished data from Basilea) [5]. At the current time, these data have not been published nor submitted for peer review.

Heretofore, the pharmacokinetics of isavuconazole have only been described in healthy volunteers [5–7]. Pharmacokinetic sub-studies have been embedded in the current clinical trials that are recruiting patients with invasive fungal infections. These studies will provide some indication as to whether the pharmacokinetics in patients and healthy volunteers are different (as is the case for voriconazole [9]). The pharmacokinetics of the i.v. and oral formulation of isavuconazole in humans were initially described in a study that consisted of a single ascending dosage of isavuconazole in healthy male volunteers [5]. Volunteers received BAL 8557 50, 100 and 200 mg as isavuconazole equivalents i.v., infused over 1 h, or 100, 200 and 400 mg orally. Plasma concentrations of isavuconazole were then determined over the ensuing 2- to 3-week period. Interestingly, in this single-dose study there was a disproportionate increase in AUC with dose, raising the possibility of non-linear pharmacokinetic, which is also characteristic for both itraconazole and voriconazole. Importantly, however, this was the only indication in this study of saturable clearance: there were no significant

differences in the estimates for clearance between the various dosages used in this study and a visual inspection of the raw pharmacokinetic data certainly does not suggest classical Michaelis–Menten pharmacokinetics. A similar multiple dosing study in healthy volunteers receiving oral and i.v. isavuconazole suggests that the pharmacokinetics are linear [6].

There have not been any published population pharmacokinetic models of isavuconazole, meaning there are no robust estimates for the extent of inter-individual pharmacokinetic variability. Using a naïve pooled approach for data obtained from healthy volunteers, the estimate for the percent coefficient of variation (CV%) for clearance (and therefore AUC) following i.v. drug is approximately 28% [6]. Undoubtedly, the CV% will be higher in infected patients, and this information will be available when the current pharmacokinetic studies are completed. The extent of variability may ultimately have an impact on appropriate dosages, *in vitro* susceptibility breakpoints and the requirement for therapeutic drug monitoring.

Following oral dosing, the concentrations of the fragment (BAL 8728) are beneath the limit of detection (i.e., 0.01 mg/l). Similarly, only very low concentrations of the pro-drug BAL 8557 are detectable following oral administration (e.g., 0.004 – 0.006 mg/l) and only in a limited number of study samples [5,6]. Higher concentrations are detectable following i.v. dosing, with the prodrug being measurable for up to 1 – 2 h [5,6]. Taken collectively, therefore, the conversion from prodrug to active moiety under the influence of plasma esterases is near-complete (circa. 98%). There do appear to be some subtle differences in the extent of conversion between oral and i.v. administration. The systemic drug exposure of isavuconazole following the oral administration of the pro-drug tends to be slightly higher than i.v. therapy [5,6]. This may be related to more intensive enzyme activity in the gut wall or portal circulation. The current pharmacokinetic data suggest the oral bioavailability is very high [5,6]. The determinants of oral bioavailability are difficult to disentangle (i.e., absorption of the prodrug vs the potentially incomplete conversion of the prodrug to isavuconazole).

Relatively little is known about the tissue penetration of isavuconazole. The relatively high estimates for the volume of distribution in healthy volunteers suggest extensive distribution from the plasma to the tissues. The only information that is currently available from patients are related to urinary concentrations. There are negligible urinary concentrations following oral administration of drug, amounting to only 0.02 – 0.04% of administered dose. Urinary concentrations are higher following i.v. dosing [5].

The pharmacokinetics of isavuconazole can be summarized in the following manner (collated from [5,6]):

- Large volume of distribution (circa. 470 – 542 l following i.v. administration)
- Long terminal half-life (estimates ranging from 56 to 104 h) with no evidence for dose-dependency in the estimates for $t_{1/2}$

- Time to steady state ~ 300 – 500 h (~ 2 – 3 weeks)
- High F, but a precise estimate is not possible
- AUC_{0-24} (day 14, near steady state) 200 mg load on day 1 then 100 mg/day i.v. 33.6 mg h/l
- AUC_{0-24} (day 14, near steady state) 200 mg load on day 1 then 100 mg/day orally 41.5 mg h/l
- Clearance 3 – 4 l/h
- Serum trough concentrations at steady state with a dosage of 100 mg/day are ~ 1 mg/l
- Absorption time 2 – 3 h

There is no clinically relevant effect of food on oral absorption of isavuconazole, although these data are only available in abstract form [10]. There is no information on the effect of acid on oral bioavailability, as is the case for both itraconazole and posaconazole [1]. This information would be helpful because patients with invasive fungal infections often have hypo- or achlorhydria, either as a result of critical illness or for iatrogenic reasons (e.g., use of histamine antagonists or proton pump inhibitors).

6. Clinical toxicity

In 15 healthy volunteers, single dosages of isavuconazole up to 200 mg were well tolerated, and no severe adverse effects were noted [5]. Similarly, in a multiple dose study of 24 healthy males who received isavuconazole orally for 21 days or i.v. for 14 days, the side effects were mild-to-moderate and included headaches, nasopharyngitis and rhinitis. One volunteer experienced mild transient abnormal liver function on day 14 of therapy, but this resolved despite continuing to receive study medication. No clinically relevant changes in vital signs or electrocardiogram were noted [6].

7. Drug–drug interactions

The only current information on drug–drug interactions for isavuconazole is currently only in abstract form. The current data are consistent with other triazoles, which are typically metabolized via oxidative mechanisms mediated by various Cyp isoenzymes. Cyp3A4 is likely to be the most important enzyme for metabolism of isavuconazole, but specific data are not available. Critical studies have either not been performed or not submitted for peer review. Rifampicin is a potent Cyp3A4 inducer and decreases isavuconazole concentrations by 40-fold [11]. Ketoconazole, a potent inhibitor of Cyp pathways increases exposure of isavuconazole [12]. Warfarin does not appear to be affected by the co-administration of isavuconazole [13]. Isavuconazole increases tacrolimus levels [14], but allegedly has no effect on cyclosporine [15]. The precise details related to the latter need to be confirmed because this is a frequent complication of triazole therapy in hematopoietic stem cell transplant (HSCT) or solid organ transplant recipients.

8. Special populations

The pharmacokinetics of isavuconazole (for oral and i.v. 100 mg equivalent) were investigated in 32 patients with mild ($n = 16$) to moderate ($n = 16$) liver impairment due to alcohol-related liver disease [7]. The pharmacokinetics was compared with 16 healthy volunteers. All patients received 100 mg/day of isavuconazole. The clearance in patients with liver impairment was much lower (estimates ranging from 2.73 to 1.43 l/h) compared with healthy volunteers. The elimination half-life approximately doubled from 123 (healthy volunteers) to 224 (mild liver impairment) and 302 h (moderate liver impairment). There is no change in the AUC of the prodrug BAL 8557 in patients with liver impairment, suggesting that liver disease does not have an impact on the extent of conversion. Because of the higher drug exposure in patients with hepatic impairment, dosing of isavuconazole needs to be adjusted. Pharmacokinetic simulations suggest a normal loading dose should be used, but the maintenance dose should be halved.

Currently, there are no data for other special populations. In particular, there are no data for patients with renal impairment (dosage adjustment unlikely and the absence of cyclodextrin formulation will likely be an advantage). There is no information on the impact of hemodialysis or hemofiltration on the pharmacokinetics of isavuconazole, although both will be important considerations in the future. There are no pediatric pharmacokinetic data that are currently available.

9. Pharmacodynamics

9.1 *In vitro* studies

The *in vitro* activity of isavuconazole has been extensively reviewed elsewhere [16]. The MIC₅₀ and MIC₉₀ results of isavuconazole against the common medically important fungi are summarized in Table 1. In general, isavuconazole is highly potent, but the implications for clinical use remain relatively poorly defined. Currently, there is inadequate information to define breakpoints for isavuconazole, and MICs should therefore be interpreted with considerable caution.

9.2 *In vivo* studies

The efficacy of isavuconazole has been investigated in experimental models of disseminated aspergillosis and candidiasis [17,18]. Isavuconazole causes a dose-dependent decline in kidney burden in neutropenic murine models of disseminated *Candida krusei* and *Candida tropicalis* infection [17]. Isavuconazole also leads to survival prolongation in a neutropenic murine model of disseminated *Aspergillus flavus* infection [18].

As is the case for the other triazoles, the AUC:MIC is the pharmacodynamic index that best links drug exposure of isavuconazole with the observed antifungal effect for infections caused by *Candida albicans* [8]. A corollary of this observation is that the antifungal effect is the same regardless of the schedule of drug administration. One caveat for isavuconazole,

however, is that the very rapid drug elimination has a large impact on appropriate experimental design. Because the half-life is so short in mice, extending the dosing interval beyond 4–5 half-lives (i.e., beyond ~15 h) potentially enables fungal regrowth, and the pharmacodynamics (erroneously) begin to appear time-dependent. This observation will be important for future preclinical studies. A further limitation is that isavuconazole is lethal for laboratory animals when given as a rapid i.v. push (in much the same way as amphotericin B deoxycholate) [8]. The precise underlying mechanism is not clear, but does mandate routes of administration where absorption into the blood stream is slower (e.g., oral or subcutaneous administration). Importantly, however, this phenomenon is not seen with oral dosing, nor is it seen when the drug is injected subcutaneously, suggesting that the toxicity may be related to peak concentrations. Furthermore, there is no evidence of infusional toxicity in humans, where the drug is usually administered i.v. over a period of 1 h.

Isavuconazole causes retardation of growth rather than overt killing in experimental models of disseminated candidiasis [8]. In this regard, the fungistatic effect of isavuconazole is consistent with pattern of antifungal effect observed with other triazoles. A murine model of disseminated candidiasis suggests survival progressively increases with increasing AUC:MIC. The pharmacodynamic target varies according to the underlying immunological deficit. The total drug AUC:MIC associated with 90% survival in persistently versus temporarily neutropenic mice is 270 versus 670, respectively [8]. If one assumes protein binding is ~98%, then the free drug AUC:MIC targets are comparable with other triazoles. These pharmacodynamic targets will be helpful for determining *in vitro* susceptibility breakpoints in the future.

10. Clinical efficacy

Three regimens of BAL 8557 (a single 200 mg dose followed by 50 mg/day, single 400 mg dose followed by 100 mg/day and single 400 mg dose followed by 400 mg weekly) are as effective as fluconazole in a Phase II study of esophageal candidiasis. This study has only been presented in abstract form [19].

A multicentre trial to determine the safety and efficacy of various regimens of isavuconazole for the prophylaxis of patients undergoing chemotherapy for acute myeloid leukemia was completed in June 2007 [2]. Pharmacokinetic data were also acquired, but have not been published. The clinical results of this study are yet to be published. A number of trials are currently recruiting patients to further define the clinical utility of isavuconazole: i) treatment of candidemia and other invasive *Candida* infections (isavuconazole vs initial induction therapy with caspofungin, followed by consolidation therapy with voriconazole; estimated sample size 526 patients); ii) primary treatment of invasive aspergillosis (isavuconazole

Table 1. Minimum inhibitory concentrations for isavuconazole for 50 and 90% (MIC₅₀ and MIC₉₀, respectively) of common medically important fungal pathogens.

Pathogen	MIC ₅₀ (mg/l)	MIC ₉₀ (mg/l)
<i>Candida albicans</i>	< 0.002 – 0.03	< 0.002 – 0.03
<i>Candida glabrata</i>	0.25 – 2	0.5 – 8
<i>Candida krusei</i>	0.125 – 0.5	0.25 – 1
<i>Candida parapsilosis</i>	< 0.015 – 0.03	0.03 – 0.125
<i>Candida tropicalis</i>	< 0.015 – 0.03	0.03 – 0.125
<i>Cryptococcus gattii</i>	0.03 – 0.32	0.06 – 0.125
<i>Cryptococcus neoformans</i>	0.004 – 0.03	0.016 – 0.125
<i>Aspergillus fumigatus</i>	0.25 – 1	0.5 – 2
<i>Aspergillus terreus</i>	0.5 – 1	0.5 – 4
<i>Aspergillus flavus</i>	0.5 – 2	1 – 16
<i>Aspergillus niger</i>	0.5 – 2	2 – 4
<i>Rhizopus</i> spp.	0.25 – 4	1 – > 8
<i>Fusarium</i> spp.	8 – > 16	> 8 – > 16
<i>Scedosporium apiospermum</i>	1 – 2	2 – 4
<i>Scedosporium prolificans</i>	> 16	

Modified from Thompson and Wiederhold [16] with permission of Springer Science + Business Media.

vs voriconazole; estimated sample size 510 patients); iii) single group assessment of patients with renal impairment with aspergillosis or other rare fungi (moulds, yeasts and dimorphic fungi; estimated sample size 100 patients) [2].

11. Conclusions

Isavuconazole may have a central role for treatment of common medically important fungal pathogens such as *Candida* and *Aspergillus* spp. Isavuconazole may also be important for the treatment of less common pathogens that are frequently resistant to other antifungal agents. The clinical utility will be influenced by the outcome of further preclinical studies as well as insights from the large randomized clinical trials that are soon to complete enrolment.

12. Expert opinion

There are many aspects related to the clinical utility of isavuconazole that still need to be addressed. One obvious question is the potential role for isavuconazole when there are already a number of licensed and well-characterized triazoles each with a relatively broad spectrum of antifungal activity. In this regard, the potential advantages of isavuconazole are as follows: i) availability of both an i.v. and oral preparation enabling a seamless transition from induction therapy to

longer-term maintenance, using the same dosage and schedule of administration; ii) absence of a cyclodextrin excipient that may accumulate in renal failure; iii) a linear pharmacokinetic profile; iv) the potential for activity against Mucorales; v) the potential for activity against fungi that are resistant to other commonly used antifungal agents and vi) the very long terminal half-life may make innovative dosing strategies possible (e.g., once-weekly dosing). Aspects that are currently not known, but are likely to be important include: i) the extent of inherent pharmacokinetic variability in patients; ii) the toxicity profile, especially in terms of the incidence of hepatitis and iii) the impact, if any, of pharmacogenetic determinants of pharmacokinetic behavior.

Population pharmacokinetic models in patients will provide estimates of the 'average' drug exposure and the extent of inter-individual pharmacokinetic variability. These estimates can be combined with information related to exposure–response relationships for medically important fungal pathogens to further inform: i) appropriate antifungal regimens for those pathogens; ii) decision support for setting *in vitro* susceptibility breakpoints for both *Candida* and *Aspergillus* spp. and iii) the requirement, if any, for therapeutic drug monitoring.

Further issues that will have an impact on the clinical utility of isavuconazole include the extent and degree of cross-resistance with other triazoles. Preservation of susceptibility for isolates that are resistant to voriconazole, itraconazole or posaconazole would be an advantage. An additional consideration is the potential benefit of an isavuconazole-based antifungal combination regimen. Based on previous studies, a combination with either an echinocandin would seem reasonable, but other combinations may also be possible.

Further preclinical and clinical studies are required to resolve these issues and questions. Some of the studies that have been performed still need to be submitted for publication and peer review. Further pharmacokinetic data in special populations (i.e., obese, renal replacement therapy, critically ill, children, neonates) will be important to deliver safe and effective therapy for a broad range of patients.

Declaration of interest

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