**Isavuconazonium sulfate: A New Agent for the Treatment of Invasive Aspergillosis and Invasive Mucormycosis**

### Abstract

Introduction: Invasive fungal infections are serious and life-threatening complications of many of today’s medical enhancements. While we have seen an insurgence of new antifungal therapies on the market since the early 1990s that have contributed significantly to saving lives, there are still important gaps including narrow spectrum of activity, dose-limiting toxicities, or unpredictable pharmacokinetics. Isavuconazonium sulfate hopes to fill several of these gaps.

Areas covered: The *in vitro* and *in vivo* pharmacology, pharmacokinetic characteristics, and phase 3 clinical trials for isavuconazole are described with a specific focus on the treatment of invasive aspergillosis and mucormycosis. A literature search was conducted in PubMed as well as FDA and EMA websites, and abstracts from congress proceedings.

Expert Review: Isavuconazole’s pharmacokinetic profile, broad-spectrum antifungal activity, and clinical trial data make this new triazole a welcome addition to the armamentarium.

**Keywords:** isavuconazole, isavuconazonium sulfate, antifungal agent, triazole, aspergillosis, mucormycosis

# 1 Introduction

Invasive mould diseases are a persistent healthcare problem for immunocompromised patients (1, 2). *Aspergillus* spp. are the most common filamentous fungi identified. However, less common filamentous fungi are increasingly recognized. Morbidity and mortality remains high despite advances in antifungal therapy. Diagnostic tests are challenging in immunocompromised patients making the distinction between diseases caused by *Aspergillus* spp. and other filamentous fungi, such as Mucorales somewhat challenging (3-5).

There are few drugs available for the treatment of invasive aspergillosis and mucormycosis, and each has significant limitations. Amphotericin B formulations have been available for many decades. However, the toxic effects of amphotericin B restrict its clinical use in spite of its broad-spectrum antifungal activity (6). First and second generation triazoles have increased the available therapeutic options, but in general are characterised by variable pharmacokinetics, toxicity, resistance, and drug-drug interactions that all complicate therapy (7). Treatment with a broad-spectrum antifungal agent may minimize delays in the provision of effective antifungal therapy, which are often detrimental to clinical outcomes (8-12).

Isavuconazole is the most recent triazole to be licensed and provides some potential advantages over older compounds. Isavuconazole is administered as the water-soluble prodrug, isavuconazonium sulfate. A recent clinical trial suggests that isavuconazole is non-inferior to voriconazole for the treatment of invasive mould disease and has comparable efficacy to amphotericin B-treated historical control groups for treatment of mucormycosis. The *in vitro* antifungal spectrum of activity is broad (13). Isavuconazole displays linear PK up to dosages of 600 mg/day and has fewer drug-drug interactions than other triazoles (14). Herein, we review the *in vitro*, *in vivo* and clinical trial data to support the use of isavuconazole for treatment of invasive mould diseases. We suggest the potential roles for isavuconazole for the treatment of invasive aspergillosis and mucormycosis.

## 1.1 Compound

The triazole class of antifungal agents was introduced in the 1980s (15). There are substantial differences in the structure of the side-chains of both imidazoles and triazoles. Both classes are orally bioavailable. The triazoles are first-line agents for the treatment of serious and life-threatening infections caused by pathogenic yeasts and moulds. Voriconazole is a first-line agent for the treatment of invasive aspergillosis and can be used for prophylaxis. Posaconazole is mostly used for antifungal prophylaxis, but is also indicated for patients with invasive aspergillosis who are refractory to amphotericin B or itraconazole or in patients who are intolerant of these agents.

Isavuconazole (Astellas Pharma Inc, Cresemba**®** [isavuconazonium sulfate] 2015, http://www.astellas.us/docs/cresemba.pdf) is administered as a water-soluble pro-drug, isavuconazonium sulfate. This new triazole was recently licensed in the US and EU for the treatment of invasive aspergillosis and mucormycosis (13, 16, 17). In Europe, the license for mucormycosis is for patients in whom amphotericin B is not appropriate. Isavuconazole has demonstrated potent to moderate *in vitro* activity when tested against *Aspergillus* spp., organisms of the Mucorales order, *Candida* spp., *Cryptococcus* spp., dimorphic, and other rare yeast and mould pathogens (13, 18-34). Clinically, isavuconazole demonstrated non-inferiority versus voriconazole, which was recently established in a large phase 3 randomized, controlled clinical trial for the primary treatment of invasive aspergillosis. The primary endpoint was all-cause mortality in the intention to treat population (ITT), which included all patients who received blinded study drug (35). In an open-label study, efficacy as measured by all-cause mortality in patients for the treatment of invasive mucormycosis was comparable to patients treated with amphotericin B formulations in a matched-case control population (36).

Isavuconazole displays linear pharmacokinetics, is available in both i.v. and oral formulations, with high oral bioavailability of the latter, and is generally well tolerated in patients (37). The i.v. formulation does not require cyclodextrin and both i.v. and oral isavuconazole can be safely used in patients with varying degrees of renal impairment. Isavuconazole undergoes oxidative metabolism, but the magnitude of drug-drug interactions is less than other triazoles. Collectively, these features facilitate the use of isavuconazole in a group of patients for whom drug therapy is always complicated.

## 1.2 Pharmaceutical Class

### 1.2.1 Mode of Action and Spectrum of activity

Triazoles block the cytochrome P450 dependent membrane protein, lanosterol 14-α-demethylase, which inhibits the synthesis of ergosterol, the protein responsible for maintaining the integrity of fungal cell membranes (6). The structure of the compound and its active moiety is shown in **Figure 1 (37)**. The *in vitro* activity of isavuconazole has been studied against a large number of medically important fungal pathogens, ranging from common yeasts to rare fungi (13, 18-34). **Table 1** provides an overview of *in vitro* studies that have estimated the activity of isavuconazole against *Aspergillus* spp. and organisms of the Mucorales order. The MIC90 values for *Aspergillus* spp. generally range from 0.25 to 2 mg/L, except for *A. niger*, which tends to have an MIC90 values 1-2 dilution steps higher than the upper range of the other species. For Mucorales organisms, MIC90 values range from 1-16 mg/L and MIC50 values range from 0.25-8 mg/L.

### 1.2.2 Resistance

* 1. Two *in vitro* studies have evaluated the activity of isavuconazole against well-characterized *A. fumigatus* isolates with *cyp*51A mutations. In the first study, isavuconazole was tested alongside amphotericin B, voriconazole, posaconazole, and itraconazole against 40 clinical isolates collected between 1989 and 2008 collected from the Canada, Denmark, France, and UK (38). All MICs were determined using CLSI M38-A2 methodology. Thirty-one of the 40 isolates had alterations in the *cyp*51A sequence at the positions M220 (n = 9), G54 (n = 6), G138/Y431/G434/G448 (n = 5), L98 (n = 3), and other mutations (n = 8). The remaining 9 were wild-type organisms. Isavuconazole MICs had the highest degree of correlation with those for voriconazole (Spearman’s correlation coefficient 0.885, P <0.001). The activity of isavuconazole is not affected by alterations in the G54 region and retained variable activity for strains with alterations in the M220 mutation. As for the other mutations, isavuconazole MICs are more likely to be raised in strains of *A. fumigatus* with reduced susceptibility to other triazoles, and tended to mirror changes in voriconazole susceptibility. A second study with the primary focus to establish epidemiological cut-off values includes 10 strains with *cyp*51A mutations. Similar patterns of activity are seen with isavuconazole retaining activity for G54 isolates and variable activity against M220 mutations and reduced susceptibility to isolates with TR34/L98H alterations (26).
  2. The expression of CDR genes (*CRD1*, *CDR2*, and *CgCDR1*) in *Candida* spp. increase isavuconazole MICs by 2- to 32-fold, similar to posaconazole (POS). Unlike fluconazole and voriconazole, *MDR1* or *FLU1* transporters do not affect isavuconazole MICs. *ERG11* mutations increased isavuconazole MICs by one- to eight-fold, which was a lower increase than that observed for fluconazole, itraconazole and voriconazole (21).

Clinical interpretive breakpoints were established by EUCAST for *Aspergillus fumigatus* (susceptible ≤ 1 mg/L, resistant > 1 mg/L), *Aspergillus terreus* (susceptible ≤ 1 mg/L, resistant > 1 mg/L), and *Aspergillus nidulans* (susceptible ≤ 0.25 mg/L, resistant > 0.25 mg/L) (20, 39). Only the breakpoints for *A. fumigatus* were established based on a substantial set of data including PK, microbiological, and clinical trial data. However, clinical data for both *A. terreus* and *A. nidulans* were sparse. No breakpoints have been established for organisms of the Mucorales order as PD targets have not been established for these organisms for isavuconazole or other drugs. The clinical correlation of MIC values to outcome has not been fully established for these organisms (3). Mean plasma concentrations reported in patients with IA are 3.9 mg/L (35, 40). The CLSI Antifungal Subcommittee and FDA have not established clinical breakpoints for isavuconazole.

## 2. Pharmacology

The prodrug is cleaved by plasma esterases in the blood or by hydrolysis in the gastrointestinal tract (16). The prodrug is not detectable after approximately 1.25 hours from the start of the infusion and ultimately represents <1% of the total AUC of isavuconazole. The inactive cleavage product remains detectable for up to 8 hours after the start of an i.v. infusion (14, 41, 42).

*In vitro* metabolism studies suggest isavuconazole is a substrate of CYP3A4 and CYP3A5 and less prominently uridine diphosphate-glucuronosyltransferases (UGT). In humans, isavuconazole is predominantly metabolised via CYP3A4/5 with subsequent fecal elimination (37). Isavuconazole is a mild-moderate inducer of CYP3A4, mild inducer of CYP2B6, and mild inhibitor of P-gp, OCT1/OCT2 and MATE1. Metabolites of isavuconazole, which undergo glucuronidation, exhibit mild indirect inhibitory effects on substrates of UGT (16, 17). Strong inducers and inhibitors of CYP3A4 should not be co-administered with isavuconazonium sulfate.

The absence of cyclodextrin in the intravenous formulation coupled with hepatic metabolism provides a potential therapeutic option for patients with renal impairment. Isavuconazonium sulfate does not prolong the QTc interval; rather it shortens the QTc interval in a concentration-dependent manner in healthy volunteer studies (37). Dose adjustments are not required in patients with renal or mild to moderate hepatic impairment (16, 17, 42, 43).

*In vivo* rat tissue distribution studies using radiolabeled prodrug have been performed (44). After administration of a relatively low dose (3 mg/kg), distribution is extensive and highest at 0.5 hours after the dose. The tissues with highest concentrations of isavuconazole are the adrenal cortex and the liver. The lowest concentrations are observed in the eye and lens. By 8 hours post-dose, the tissue concentrations decline by a factor of five. Excretion is nearly complete by 144 hours and occurs mainly from the bile/feces (80%) and 20% in the urine. The only tissues with measurable levels by 144 hours are the adrenal glands and the liver.

Following a single oral dose of [cyano-C14] prodrug isavuconazonium sulfate, approximately 46.1% of the total sample radioactivity was recovered in feces after 600 h. Isavuconazole is highly protein bound (>99%) and the volume of distribution is large (~450 L), which suggests extensive tissue distribution (40). The terminal half-life is approximately 130 hours (14). These pharmacokinetic properties allow for once-daily dosing after a 2 day loading regimen.

### Drug Interactions

An extensive array of drug-drug interaction studies have been conducted with isavuconazonium sulfate as part of the clinical development program. Many of these studies have only been presented in abstract form, and are also available in the briefing materials posted on the FDA website following the Advisory Committee meeting in January 2015. While isavuconazole demonstrates typical triazole CYP3A4 interactions, the magnitude of those interactions appears to be somewhat less than other imidazoles and triazoles. Isavuconazole is a sensitive substrate for CYP3A4 and use with other strong inducers and inhibitors is not recommended. Co-administration with ketoconazole in healthy volunteers leads to an increase in isavuconazole Cmax and AUC of 9% and 422%, respectively (45). However, in the case of mild to moderate CYP3A4 substrates (e.g. midazolam and sirolimus), the increase in exposure is only 2-fold as compared to a 10-fold increase with concomitant use of voriconazole (46-48). In addition, there are no significant changes to the exposure of the following concomitant medications when tested with isavuconazole: caffeine (1A2), repaglinide (2C8), warfarin (2C9), omeprazole (2C19), and dextromethorphan (2D6). Interaction studies, with bupropion (2B6) leads to a 42% reduction in bupropion exposures. The US prescribing information highlights the impact of isavuconazole co-administration on other drugs as well (16). Specifically, exposures of the following drugs are increased when co-administered with isavuconazonium sulfate: atorvastin, cyclosporine, sirolimus, tacrolimus, midazolam, mycophenolate mofetil, and digoxin. Exposures to the following drugs are decreased when co-administered with isavuconazonium sulfate: lopinavir/ritonavir and bupropion. It is recommended that these drugs be monitored when taking them concomitantly with isavuconazonium sulfate.

### Pharmacokinetics

The pharmacokinetic (PK) characteristics of isavuconazole have been reported for healthy volunteers and patients in a phase 2 clinical trial conducted in neutropenic patients with acute myeloid leukemia (AML) (14, 49). The key data from these studies are included in **Table 2**. The results from the phase 1 and 2 studies suggest linear PK. A population PK model has been fitted to data from patients with invasive aspergillosis enrolled in a phase III clinical trial (SECURE study) that were treated with isavuconazonium sulfate. These data have been combined with PK obtained from nine healthy volunteer studies (40). Dosing in the single-dose and multiple-dose phase 1 studies ranged from 40 mg to 400 mg. The phase 3 clinical trial dosing includes a loading regimen of 200 mg every 8 hours (q8) for the first 48 hours followed by 200 mg once daily. The population PK analyses show a significant relationship between Asian ethnicity and clearance, as well as body mass index and disease status (i.e. healthy volunteer or patients with invasive mould disease) on volume of distribution. The mean clearance is 2.4 L/h and 1.5 L/h in the Caucasian and Asian subjects, respectively. A covariate evaluation of the subject type (healthy volunteer versus patients) on clearance did not reveal any significant relationship. Simulated steady state AUC**0-24** for the healthy volunteer and patient population following administration of the clinical dosing regimen used in the phase 3 clinical trial shows comparable mean values (**Table 2**). The inter-subject variability in AUC is approximately 60% in the patient group. In patients, the average trough level is 3.9 mg/L, which exceeds the majority of the MIC90 values for target pathogens.

## 3. Non-Clinical Pharmacology

The pharmacodynamics (PD) of isavuconazole for the treatment of invasive aspergillosis has been studied in several experimental models. *In vivo* studies demonstrate potent, dose-dependent activity of isavuconazole against *Aspergillus* spp. at clinically relevant exposures (50, 51). *In vivo* dose fractionation studies suggest that the total drug AUC:MIC is the pharmacodynamic (PD) index that best links isavuconazole exposure to efficacy (50, 52, 53). PD targets that establish the threshold values of total AUC/MIC that correlates with the outcome in experimental models range from 11.4 to 503 for *A. fumigatus* (52, 54, 55). In each model, *in vivo* efficacy is achieved for isolates with MICs up to 2 mg/L regardless of the presence of resistance mechanisms.

The *in vivo* efficacy of isavuconazole against experimental mucormycosis in mice is comparable to the efficacy of liposomal amphotericin B (LAmB) (56). Neutropenic mice treated with isavuconazonium sulfate at a dose of 215 mg/kg, three times daily has significantly (P <0.05) higher 21-day survival rates compared with placebo-treated controls (70% versus 10%). Isavuconazonium sulfate is as effective as LAmB (15 mg/kg, once-daily i.v.) for treating pulmonary mucormycosis infections in neutropenic mice. After 21 days, the survival rates for isavuconazole-, LAmB-, and placebo-treated mice were 65%, 40%, and 15%, respectively. In addition, decreases in lung and brain fungal burden are similar between the isavuconazonium sulfate-treated and LAmB-treated mice and significantly better than placebo-treated mice. No formal PK-PD studies have been conducted in the setting of mucormycosis for isavuconazole. This is a gap in knowledge for all Mucorales-active agents.

## 4. Clinical Trials

### 4.1 Invasive Aspergillosis (SECURE)

#### 4.1.1 Study Design

In the SECURE clinical trial a total of 516 patients were randomized and receive either isavuconazole or voriconazole (n=258 per group) (35). Randomization was stratified by geographic region, allogeneic hematopoietic stem cell transplant (HSCT), and active malignancy. The enrollment period spread over a six-year period (2007-2013). However, there was a nearly 2-year suspension in the trial because of unanticipated non-clinical toxicology studies and other licensing activities. The maximum treatment duration was 84 days. Key inclusion criteria included: age 18 years and older with possible, probable or proven invasive mould disease, as defined by the MSG/EORTC criteria (57). Mycological evidence that was required for diagnostic criteria of invasive mould disease included culture or direct microscopy or cytology of tissue revealing fungal elements suggestive of mould, but also positive galactomannan (GM) defined as a single optical density value of ≥ 0.7 or two consecutive values of ≥ 0.5. Key exclusion criteria include evidence of hepatic dysfunction or renal dysfunction.

All-cause mortality through day 42 in the intent-to-treat (ITT) population was the primary endpoint with a pre-specified non-inferiority margin of 10%. The ITT population included all randomized patients who received at least one dose of study drug (either isavuconazole or voriconazole). An independent Data Review Committee (DRC) blinded to both the treatment assignment and the treating investigator's outcome assessment also reviewed the data to adjudicate the clinical, radiological, and mycological outcomes for each patient at the end of therapy, day 42, and day 84. A key secondary endpoint was overall response as assessed by the independent DRC at the end of treatment in the modified ITT population (mITT). The mITT includes the subset of ITT patients with proven or probable invasive mould disease, as determined by the DRC.

#### 4.1.2 Results

The ITT population was comprised of 258 patients in each group. Table 1 of the primary manuscript provides a full description of the demographics and baseline characteristics of the two groups, which were well matched. Over 80% of the study population had an underlying hematological malignancy and approximately 70% had active malignancy at baseline. A total of 63% and 68% of the isavuconazole and voriconazole groups were neutropenic at baseline, respectively. Other risk factors for invasive fungal infection included the use of T-cell immunosuppressants in 43% and 42% and use of corticosteroids in 19% and 15% or the isavuconazole and voriconazole treated groups, respectively. While baseline renal impairment was an exclusion criterion, a small percentage of patients in each group had eGFR-MDRD < 60 mL/min/1.73 m2 (8% and 13%, respectively) at baseline.

The breakdown of patients by degree of evidence of disease and mycological criteria used to confirm disease is shown in **Table 3**. The two groups are relatively similar. However, more isavuconazole patients had probable disease and more voriconazole patients had possible disease.

The mITT populations consisted of 143 isavuconazole treated patients and 129 voriconazole treated patients with proven and probable invasive mould disease. Of the 34% isavuconazole and 30% voriconazole treated patients diagnosed with invasive aspergillosis in this population, *A. fumigatus* is the most commonly isolated organism followed by *A. flavus*. A total of 50% and 53% of the isavuconazole and voriconazole treated patients, respectively, in the mITT had galactomannan as the only mycological criterion.

The primary objective was met. Isavuconazole is non-inferior to voriconazole based on all-cause mortality through day 42 in the ITT population [19% vs. 20%; treatment difference (isavuconazole-voriconazole): -1%; 95% CI -7.8% to 5.7%]. Several sensitivity analyses were undertaken to demonstrate the robustness of the results and each reveal a consistent outcome supporting the primary conclusion. The key secondary endpoint of overall response at the end of therapy in the mITT population demonstrated similar results between the two groups [35% vs. 36%, treatment difference (voriconazole-isavuconazole): 1.6%; 95% CI -9.3% to 12.6%].

The isavuconazole group had significantly fewer hepatobiliary disorders, eye disorders, and skin or subcutaneous tissue disorders, and significantly fewer drug-related adverse events. In addition, there were fewer permanent discontinuations because of treatment emergent adverse events and fewer drug-related events causing permanent discontinuation in the isavuconazole group.

The significance of this study is the robustness of the results both within the study and consistency with prior voriconazole trials. Day 42 and Day 84 all-cause mortality are similar to the voriconazole arm in a previous trial that compared voriconazole with amphotericin B deoxycholate (58). However, in light of the lack of activity for organisms of the Mucorales order, non-linear PK, higher intersubject and intrasubject variability in serum concentrations, and differential safety profile displayed in the SECURE trial, isavuconazole appears to be a useful addition to the antifungal agents that can be used for the treatment of invasive mould disease. Similar to the Herbrecht trial, the large majority of the patients enrolled in the SECURE trial had hematologic conditions, limiting the understanding of the use of isavuconazole in patients with other underlying conditions (58).

Exposure-response analyses for efficacy and safety have been described in abstract form at the time of this review. Currently, there is no suggestion of any observable relationship between drug exposure and either efficacy and toxicity (59, 60). The implications of this finding for routine therapeutic drug monitoring remains unclear at this stage.

### 4.2 Invasive Mucormycosis: VITAL

#### 4.2.1 Study Design and Results

The clinical trial that supported the approval of isavuconazonium sulfate for the treatment of invasive mucormycosis was an open-label trial that enrolled renally-impaired patients with invasive aspergillosis, and other patients with invasive mucormycosis, dimorphic, and other rare filamentous fungi and yeasts (37, 61). The isavuconazole dosing regimen was similar to the SECURE trial; however, there was no restriction regarding the use of iv or oral formulations. The maximum treatment duration was 180 days. The efficacy endpoints included all-cause mortality at days 42 and 84, and overall response adjudicated by the DRC at the end of therapy. Overall response was adjudicated by the independent DRC based on pre-specified definitions of response for clinical, mycological and radiological assessments. The study enrolled 146 patients who received at least one dose of isavuconazonium sulfate of whom 37 were treated for proven or probable invasive mucormycosis (mITT Mucorales population). An additional nine patients were not included in the mITT population either because of a possible infection (n=1) or mixed fungal infections (n=8). Each case was reviewed by an independent DRC to confirm the diagnosis and adjudicate outcomes. Of the 37 patients, 21 had primary infection, 11 were refractory to prior systemic antifungal therapy, and 5 were intolerant to prior antifungal therapy. The majority of patients had proven infection (86.5%) with a smaller number having probable infection (13.5%). A summary of the underlying disease characteristics is found in **Table 4**. The majority of patients had an underlying hematologic malignancy and were neutropenic (ANC <500/mm3).

The median age was 50 years and 81.1% were male. Over 67% were white, 43.2% were from the United States, and 43.2% from other regions, which included Brazil, India, Israel, Lebanon, Mexico, Russia, South Korea, and Thailand. The median duration of therapy was 84 days (range 2-882 days). The primary reasons that patients discontinued isavuconazonium sulfate treatment were death (29.7%) followed by adverse events or intercurrent illness (16.2%).

The most common causative agents were mucormycetes (not otherwise specified, NOS)(35.1%), *Mucor* spp. (18.9%), *Rhizopus oryzae* (18.9%), and *Rhizomucor* spp. (13.5%). Invasive mucormycosis was most commonly found in a non-lower respiratory tract disease (LRTD) body site such as sinus (n=16), eye (n=7), central nervous system (n=6), bone (n=5), muscle (n=3), GI tract (n=2), kidneys (n=2) liver (n=2), skin (n=2), and spleen (n=1) in 41% of Mucorales patients. LRTD plus another organ were diagnosed in 32% of patients while 27% had LRTD only. A total of 30% had disseminated disease.

**Table 5** shows the results for each endpoint. All-cause mortality through Day 42 and 84 were 37.8% and 43.2%, respectively. A total of 31.4% of patients experienced a successful overall response. Of note, 28.6% of the patients that failed therapy had stable disease by the EOT.

Comparisons were made to several sets of data including historical literature and a prospective registry (Fungiscope). The Fungiscope registry was utilized to match each primary therapy Mucorales patient enrolled in the VITAL study with cases from the Registry. The latter patients were primarily treated with amphotericin B formulations. The primary matching criteria included severity of infection (with or without central nervous system involvement or disseminated infection), underlying hematologic malignancy, and surgical resection or debridement. The matching was conducted only on the VITAL Mucorales cases that received isavuconazole for primary therapy (n=21) and there was at least one control available for each VITAL patient.

Historically, the data consistently shows that, without treatment, mortality is nearly 100% (10, 62, 63). In addition, Chamilos and colleagues demonstrates that delay in amphotericin B based therapy by more than 6 days leads to 2-fold increase in mortality at day 84 (82.9%) compared with early treatment (48.6%) for a population of 70 hematological malignancy patients. The FDA and Sponsor briefing materials also describe a meta-analysis of these three papers (37, 61). All of these data plus the VITAL mortality results are compared in **Figure 2**. The figure illustrates the similarity of the mortality rates across the different studies. Despite the limitations of comparing across separate uncontrolled literature reviews and patient registries, the mortality rates are strikingly similar and there is a clear treatment effect compared with the untreated population.

## 5. Expert Commentary

Isavuconazole is the newest antifungal to be approved for the treatment of invasive aspergillosis and invasive mucormycosis. The data from a large clinical trial demonstrates isavuconazole to be non-inferior to voriconazole for the treatment of invasive mould disease. The results of the study provide support for its use of isavuconazole for patients with invasive mould disease. Importantly, the data demonstrating the efficacy in the treatment of invasive mucormycosis, while limited, support the use of isavuconazole in this patient population. The efficacy of isavuconazole against invasive mucormycosis is especially useful for cases when there is a degree of diagnostic uncertainty (as there often is). Consistent with other compounds with activity against organisms of the Mucorales order, the spectrum of activity is incomplete. Therefore, more information related to *in vivo* efficacy as well as clinical outcome data for different species will be required and take some time to accrue.

Isavuconazole is well tolerated. In keeping with other imidazoles and triazoles, hepatotoxicity may be an issue with isavuconazole although the incidence appears lower than voriconazole. The potential for QT shortening has also been reported. The clinical significance of this phenomenon is unknown, but patients with familial short QT syndromes should not use isavuconazole. There does not appear to be a clinical correlate to the electrocardiographic findings of shortening of the QTc. The list of potential drug interactions is similar to other triazole agents. Nevertheless, the strength of some of these interactions appears to be less for isavuconazole, which may make use in the critically ill patients somewhat easier.

The pharmacokinetics of isavuconazole are linear and less variable than other imidazoles and triazoles. The long half-life allows for once a day dosing and the oral formulation is 99% bioavailable in healthy volunteer studies. This along with the absence of any food effect provides an option for longer-term consolidation therapy. At the current time there is no relationship between drug exposure and the probability of either clinical response or toxicity. The absence of any relationship makes any argument for routine therapeutic drug monitoring somewhat difficult although this may change with the accrual of more information and real world experience.

Isavuconazole has some defining features and will be a welcome addition to the current armamentarium of systemic antifungal agents.

## 6. Five-Year View

As more clinical experience with this new drug emerge, it is expected that we will learn more detailed information about how this drug behaves under real-life conditions. Additional clinical studies will be helpful in the future to investigate if isavuconazole has promise in infections caused by other important fungi, such as rare yeasts and other moulds. A large phase 3 study comparing isavuconazole to caspofungin has recently completed in the treatment of invasive candidiasis and candidemia did not meet its primary endpoint. It will be important to better understand these data as they emerge.

## 7. Key Issues

* Isavuconazonium sulfate, the prodrug of the active moiety isavuconazole, is the newest systemic antifungal of the triazole class available for use.
* Data from a large phase 3 clinical trial demonstrated that isavuconazole was non-inferior to voriconazole for all-cause mortality through Day 42 in the setting of invasive aspergillosis and other filamentous fungi.
* Comparison of a small subset of patients with invasive mucormycosis treated with isavuconazole demonstrated similar mortality results as a match-case control population from contemporary fungal registry and historical literature of patients treated with amphotericin B formulations.
* Isavuconazole displays broad-spectrum *in vitro* antifungal activity; however, with regard to resistance patterns, there does not seem to be a clear differentiation compared to other azoles.
* Isavuconazole displays linear pharmacokinetics, has both i.v. and oral formulations, with good oral bioavailability of the latter, and is generally well tolerated in patients.
* While isavuconazole demonstrates typical triazole CYP3A4 interactions, the magnitude of those interactions appears to be somewhat less than other imidazoles and triazoles.
* Currently, there is no relationship between drug exposure and the probability of either clinical response or toxicity. However, the absence of any relationship makes any argument for routine therapeutic drug monitoring somewhat difficult although this may change with the accrual of more information and real world experience.

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**Tables and Figures**

**Table 1 In Vitro Susceptibility of Isavuconazole Against *Aspergillus* spp. and Mucorales organisms**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Method#** | **Species (no. of isolates)** | **MIC (mg/L)** | | |
| **Range** | **MIC50** | **MIC90** |
| Curfs-Breuker et al, 2008 (64) | CLSI | *A. fumigatus* (n=217) | 0.25 - > 2 | 0.5 | 1 |
| non-*fumigatus A*. (n=22) | 0.063 - > 2 | 1 | 2 |
| Datta et al, 2013 (29) | CLSI | *A. lentulus* (n=15) | 0.063 – 0.5 | 0.25 | 0.25 |
| Perkhofer et al, 2009 (65) | EUCAST | *A. fumigatus* (n=32) | 0.125 - 1 | 1 | 1 |
| *A. terreus* (n=35) | 0.125 - 1 | 0.5 | 2 |
| *A. flavus* (n=16) | 0.5 - 2 | 1 | 2 |
| *A. niger* (n=13) | 0.25 - 8 | 2 | 4 |
| Pelaez et al, 2009 (66) | CLSI | *A. nidulans* (n=63) | 0.06 - 1 | 0.25 | 1 |
| Pelaez et al, 2009 (67) | CLSI | *A. terreus* (n=132) | 0.125 - 1 | 0.5 | 0.5 |
| Rudramurthy et al, 2011 (68) | EUCAST | *A. flavus* (n=20) | 0.25 - 4 | 1 | 2 |
| Guinea et al, 2008 (69) | CLSI | *A. fumigatus* (n=602) | 0.125 - 4 | 1 | 1 |
| *A. flavus* (n=34) | 0.25 - 2 | 1 | 1 |
| *A. niger* (n=32) | 0.25 - 4 | 1 | 2 |
| *A. terreus* (n=25) | 0.125 - 1 | 1 | 1 |
| Yamazaki et al, 2010 (70) | CLSI | *A. fumigatus* (n=12) | 0.1 – 0.39 | 0.2 | 0.39 |
| *A. terreus* (n=3) | 0.2 – 0.39 |  |  |
| Kathuria et al, 2014 (71) | CLSI | *A. terreus* complex(n=189) | 0.062 – 0.5 | 0.25 | 0.5 |
| CLSI | *A. hortai* (n=15) | 0.062 – 0.5 | 0.125 | 0.25 |
| CLSI | *Aspergillus* section *Terrei* complex (n=28) | 0.062 – 2 | 0.25 | 1 |
| EUCAST | *A. terreus* complex(n=189) | 0.125 - 2 | 0.5 | 1 |
| EUCAST | *A. hortai* (n=15) | 0.125 – 1 | 0.25 | 1 |
| EUCAST | *Aspergillus* section *Terrei* complex (n=28) | 0.031 – 16 | 0.5 | 1 |
| Shivaprakash, et al., 2011 (72) | CLSI | *Aspergillus flavus* (n=188) | 0.125 - 2 | 1 | 1 |
| Warn et al, 2006 (73) | CLSI | Zygomycetes (n=34) | 0.03 - 4 | 0.5 | 1 |
| Verweij et al, 2009 (74) | CLSI | *Absidia* spp. (n=80) | 0.03 - 16 | 1 | 8 |
| *Cunninghamella* spp. (18) | 0.12 – 16 | 2 | 16 |
| *Mucor* spp. (n=77) | <0.015 - >128 | 4 | 16 |
| *Rhizomucor* spp. (n=29) | 0.015 - 64 | 2 | 16 |
| *Rhizopus* spp. (n=139) | 0.12 - 32 | 1 | 4 |
| González, 2009 | CLSI | *Rhizopus arrhizus (n = 27)* | 1 - 8 | 2 | 4 |
| *Absidia corymbifera (n = 17)* | 2 - 8 | 4 | 8 |
| *Mucor circillenoides (n = 16)* | 2 - 8 | 4 | 8 |
| Kathuria, et al, 2014 (75) | CLSI | *Rhizopus arrhizus* var*. delemar* (n=25) | 0.25 - 16 | 1.5 | 8 |
| *Rhizopus arrhizus* var. *arrhizus* (n=15) | 0.5 - 4 | 1 | 3.2 |
| *R. microsporus* (n=17) | 0.125 - 4 | 1 | 2 |
| *R. stolonifer* (n=3) | 0.25 – 0.5 |  |  |
| Arendrup, et al, 2015 (76) | EUCAST (Day 1) | *Lichtheimia corymbifera* (n=12) | 0.5 - 2 | 1 |  |
| *Lichtheimia ramosa*  (n=4) | 0.125 – 0.5 | 0.25 |  |
| *Mucor circinelloides*  Group I (n=5)  Group II (n=9) | 4 – 8  1 - 16 | 8  11 |  |
| *Rhizomucor pusillus*  (n=8) | 0.5 - 1 | 0.5 |  |
| *Rhizopus microsporus*  (n=26) | 0.5 - 4 | 1 |  |
| *Rhizopus oryzae*  (n=6) | 0.125 – 0.5 | 0.25 |  |
| CLSI (Day 2) | *Lichtheimia corymbifera* (n=12) | 1 - 2 | 1 |  |
| *Lichtheimia ramosa*  (n=4) | 0.5 - 2 | 1 |  |
| *Mucor circinelloides*  Group I (n=5)  Group II (n=9) | 2 – 4  1 - 8 | 4  8 |  |
| *Rhizomucor pusillus*  (n=8) | 0.125 - 1 | 1 |  |
| *Rhizopus microsporus*  (n=26) | 0.125 - 1 | 0.5 |  |
| *Rhizopus oryzae*  (n=6) | 0.125 - 2 | 1 |  |
| Chowdhary, et al., 2015 (77) | CLSI | *Rhizopus arrhizus* var. *delemar* (n=25) | 1 – 8 | 8 | 8 |
| *Rhizopus arrhizus* var. *arrhizus* (n=22) | 0.5 - 8 | 1 | 8 |
| *Rhizopus microsporus* (n=23) | 0.5 - 8 | 2 | 4 |
| *Rhizopus stolonifer* (n=4) | 0.25 – 1 |  |  |
| *Mucor circinelloides* (n=5) | 1 – 8 |  |  |
| *Mucor ramosa* (n=1) | 8 |  |  |
| *Mucor velutinosus* (n=1) | 2 |  |  |
| *Lichtheimia ramosa* (n=7) | 0.5 - 8 |  |  |
| *Lichtheimia corymbifera* (n=6) | 2 - 8 |  |  |
| *Rhizomucor pusillus* (n=7) | 1 - 8 |  |  |
| *Rhizomucor miehei* (n=1) | 8 |  |  |
| *Cunninghamella bertolletiae* (n=3) | 8 |  |  |
| *Cunninghamella elegans* (n=1) | 8 |  |  |
| *Apophysomyces elegans (n=2)* | 0.25 – 4 |  |  |
| *Apophysomyces variabilis* (n=1) | 4 |  |  |
| *Syncephalastrum racemosum* (n=15) | 0.125 - 8 | 4 | 8 |
| EUCAST | *Rhizopus arrhizus* var. *delemar* (n=25) | 2 - 8 | 8 | 8 |
| *Rhizopus arrhizus* var. *arrhizus* (n=22) | 1 - 8 | 4 | 8 |
| *Rhizopus microsporus* (n=23) | 1 - 8 | 8 | 8 |
| *Rhizopus stolonifer* (n=4) | 0.5 – 2 |  |  |
| *Mucor circinelloides* (n=5) | 2 – 8 |  |  |
| *Mucor ramosa* (n=1) | 8 |  |  |
| *Mucor velutinosus* (n=1) | 8 |  |  |
| *Lichtheimia ramosa* (n=7) | 1 – 8 |  |  |
| *Lichtheimia corymbifera* (n=6) | 2 – 8 |  |  |
| *Rhizomucor pusillus* (n=7) | 4 – 8 |  |  |
| *Rhizomucor miehei* (n=1) | 8 |  |  |
| *Cunninghamella bertolletiae* (n=3) | 8 |  |  |
| *Cunninghamella elegans* (n=1) | 8 |  |  |
| *Apophysomyces elegans (n=2)* | 8 |  |  |
| *Apophysomyces variabilis* (n=1) | 8 |  |  |
| *Syncephalastrum racemosum* (n=15) | 1 - 8 | 4 | 8 |
| Chowdhary, et al., 2014 (78) | CLSI | *Rhizopus arrhizus* var. *delemar* (n=25) | 0.25 - 16 | 1.5 | 8 |
| *Rhizopus arrhizus* var. *arrhizus* (n=15) | 0.5 - 4 | 1 | 3.2 |
| *Rhizopus microsporus* (n=17) | 0.125 - 4 | 1 | 2 |
| *Rhizopus stolonifer* (n=3) | 0.25 – 0.5 |  |  |
| *Syncephalastrum racemosum* (n=11) | 0.125 - 8 | 1 | 8 |
| *Apophysomyces elegans* (n=2) | 0.25 |  |  |
| *Apophysomyces variabilis* (n=2) | 0.25 – 8 |  |  |
| *Lichtheimia ramosa* (n=3) | 2 – 8 |  |  |
| *Mucor*  *circinelloides*  *f. lusitanicus* (n=2) | 0.125 - 8 |  |  |
| Chakrabarti, et al., 2010 (79) | CLSI | *Apophysomyces elegans* (n=16) | 1 - 4 | 2 | 4 |

#CLSI M38-A: Clinical Laboratory and Standards Institute; EUCAST document EDef 9.2: European Committee on Antimicrobial Susceptibility Testing

**Table 2: Mean Pharmacokinetic Values from Healthy Volunteers in Phase 1 and Patients in Phase 2 and Phase 3 studies**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Phase** | **P1** | | | | **P2** | | **Population PK P3 (40)** | |
| **Subject Type** | **MD Healthy Volunteers (14)** | | | | **Proph AML (49)** | | **HV 9 studies** | **Patients with IA** |
| **Dosing Day** | 8 | | | | 7 | | Steady-state | |
| **Isavuconazole-equivalent Dose** | 100mg D1;50 mg qd; PO | 200 mg D1; 100 mg qd; PO | 100 mg D1; 50 mg; iv | 200 mg D1; 100 mg; iv | 800 mg D1; 400mg D2; 200mg qd | 1600mg D1; 800 mg D2;  400 mg qd | Doses ranging from 40 mg to 400 mg | 200 mg tid D1 and D2; 200 mg qd |
| **AUC0-24 (mg\*h/L)** | 18.1 (4.45) | 34.0 (5.70) | 12.4 (3.77) | 24.3 (5.79) | 60.1 (22.3) | 113.1 (19.6) | 92.3 (32.8) | 97.9 (57.2) |
| **Cmax (mg/L)** | 1.2 (0.215) | 2.33 (0.472) | 0.987 (0.180) | 2.52 (1.05) | 3.6 (1.0) | 8.0 (2.8) | Not reported | |
| **t1/2 (h)** | 98.4 (21.3) | 84.5 (28.3) | 93.0 (40.1) | 117.0 (17.6) | Not reported | | Not reported | |

Abbreviations: MD=multiple dose; mg=milligrams; Proph=prophylaxis; AML=acute myeloid leukemia; qd=once-daily; D=day; PO=oral administration; iv=intravenous; P1=phase 1; P2=phase 2; P3=phase 3

**Table 3 Summary of the Degree of Evidence of IFD and Mycological Criteria**

|  |  |  |
| --- | --- | --- |
| **ITT Population** | **Isavuconazole (n=258)** | **Voriconazole**  **(n=258)** |
| **Certainty of Invasive Mould Disease** | | |
| Proven | 11% | 14% |
| Probable | 44% | 36% |
| Possible | 34% | 42% |
| No IMD | 10% | 8% |
|  |  |  |
| **Mycological Criteria#** | | |
| No mycological evidence | 36% | 44% |
| Serum GM positive | 35% | 36% |
| Non-sterile cytology, direct microscopy, or culture evidence of IMD | 23% | 15% |
| Sterile-site cytology, direct microscopy, or culture evidence of IMD | 12% | 13% |
| Autopsy | <1% | 3% |

**#**A patient may have more than one mycological criterion and hence may be counted in more than one category.

Adapted from Maertens et al. 2015 (35)

**Table 4 Underlying Disease Characteristics of the Patients with Proven or Probable Mucorales Infections**

|  |  |
| --- | --- |
|  | mITT –Mucorales Group (n=37) |
| Hematological Malignancy | 59% |
| Neutropenia at baseline\* | 27% |
| Bone Marrow Transplant# | 35% |
| Diabetes Mellitus | 11% |
| Solid Organ Transplant | 8% |
| Solid Organ Malignancy | 5% |
| Other | 8% |
| Aplastic Anemia | 3% |
| No Underlying Disease Specified | 3% |

\*neutropenia = ANC <500 cells/mm3

#BMT not specified between allogeneic or autologous

Adapted from Astellas Briefing Materials (37)

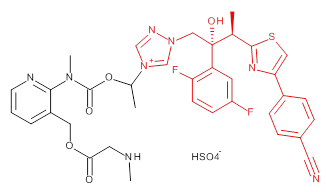
**Table 5 Efficacy Outcomes in Patients with Proven and Probable Mucorales Infection**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Primary Therapy**  **(n=21)** | **Refractory (n=11)** | **Intolerant (n=5)** | **Total**  **(n=37)** |
| All-Cause Mortality through Day 42 | 33.3% | 45.5% | 40.0% | 37.8% |
| All-Cause Mortality through Day 84 | 42.9% | 45.5% | 40.0% | 43.2% |
| Successful# Overall Response at EOT | 31.6% | 36.4% | 20.0% | 31.4% |

#Successful = Complete or partial overall response as defined by the independent DRC.

Adapted from Astellas Briefing Materials (37)

**Figure 1 Chemical Structure of the Prodrug (entire structure) and Active Drug (red portion)**

Adapted from Astellas Briefing Materials (37)

**Figure 2 Comparison of All-Cause Mortality Rates for the Mucorales Patients in the VITAL trial, Fungiscope matched-case control population, and historical literature**



† Exact binomial CIs were calculated; 95% CIs from the meta-analysis were based on normal approximation.

ISAV: isavuconazole; AMB: amphotericin B formulations

Adapted from Astellas and FDA Briefing Materials (37, 61)