Thai Food and Drug Administration (Thai FDA)
Public assessment report

New medicinal products

Cresemba® 100 mg hard capsules

Isavuconazole

E-identifier number: e6200003
Registration number: 1C 15072/63 (NC)
Approval date: 9 April 2020

Cresemba® powder for concentrate for solution for infusion 200 mg/vial

Isavuconazole

E-identifier number: e6200004
Registration number: 1C 15073/63 (NC)
Approval date: 9 April 2020

Applicant: Pfizer (Thailand) Limited

Product team leader:	Worasuda Yoongthong
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Start of the procedure:	25 January 2019
Date of this report:	21 December 2020

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Administrative information

Invented name of the medicinal product:	CRESEMBA เครสเซมบา
INN (**or common name**) **of the active substance**(**s**):	Isavuconazole (as isavucozonium sulfate) ไอซาวูโคนาโซล
Applicant:	Pfizer (Thailand) Limited
Applied indication(**s**):	CRESEMBA is indicated in adults for the treatment of • Invasive aspergillosis • Mucomycosis in patients for whom amphotericin B is inappropriate
Pharmaco-therapeutic group (**ATC Code**):	(J02)
Pharmaceutical form(**s**) **and strength**(**s**):	100 mg capsule, hard; 200 mg/vial powder for concentrate for solution for infusion

Declarations

This application includes an Active Substance Master File (ASMF):

☐ Yes ☐ No

☒ Not applicable

☐ The assessor confirms that proprietary information on, or reference to, third parties (e.g. ASMF holder) or products are not included in this assessment, including the Product Information, unless there are previous contracts and/or agreements with the third party(ies).

☐ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

Whenever the above box is un-ticked please indicate section and page where confidential information is located (including the Product Information document) here:

1. Recommendation

Based on the review of the data and the Applicant's response to the list of questions (LOQs) on quality, safety, efficacy, Thai FDA considers that the application for CRESEMBA indicated in adults for the treatment of

- Invasive aspergillosis
- Mucomycosis in patients for whom amphotericin B is inappropriate

is approvable provided that the applicant commits to perform risk management plan as post authorisation measures to be reported back to Thai FDA within predefined timeframes. A preliminary list of such post-authorisation measures is in section 5.1 of this report.

2. Executive summary

2.1. Problem statement

Invasive aspergillosis is a life-threatening infection that is seen predominantly in immunocompromised patients. Patients at greatest risk are those with prolonged neutropenia related to antineoplastic chemotherapy or hematopoietic stem cell transplantation (HSCT), those receiving immunosuppressants following solid organ transplants, advanced HIV infection and those given high doses of corticosteroids.

The transmission of fungal spores to the human host is via inhalation and Aspergillus primarily affects the lungs, causing 4 main syndromes: allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing Aspergillus pneumonia (also termed chronic necrotizing pulmonary aspergillosis [CNPA]), aspergilloma, and invasive aspergillosis. The majority of human illness is caused by *Aspergillus fumigatus* and *Aspergillus niger* and, less frequently, by *Aspergillus flavus* and *Aspergillus clavatus*. *Aspergillus* may hematogenously disseminate beyond the lungs and the CNS, cardiovascular system, and other tissues may be infected as a result.

Invasive aspergillosis is treated with systemic antifungal agents, such as polyenes (Amphotericin B), mould active triazoles (voriconazole, itraconazole, posaconazole) and echinocandins (caspofungin, micafungin, and anidulafungin). Certain conditions of invasive aspergillosis warrant consideration for surgical resection of the infected focus. Despite the current available antifungal therapies (AFTs) for invasive aspergillosis IFD is still associated with high mortality rates (30-40% in treated and 95% in untreated patients).

Mucormycosis is extremely rare and refers to several different diseases caused by infection with fungi in the order of Mucorales. Rhizopus species are the most common causative organisms. *Mucoraceae* are ubiquitous fungi that are commonly found in soil and in decaying matter. *Rhizopus* can be found in moldy bread. Most humans are exposed to these organisms on a daily or weekly basis. The major route of infection is via inhalation of conidia; other routes include ingestion and traumatic inoculation. They rarely cause disease because of the low virulence of the organisms; instead, they mainly affect immunocompromised patients. Patients with uncontrolled diabetes mellitus, especially with ketoacidosis, are at high risk. Patients with cancer—especially those who are neutropenic and receiving broad-spectrum antibiotics—as well as individuals receiving immunosuppressive agents—including oral or intravenous steroids and tumor necrosis factor (TNF)–alpha blockers—are at risk. In addition, hematologic cancer patients with opportunistic herpetic infections (e.g., cytomegalovirus) and graft versus host disease are at increased risk.

Most mucormycosis infections are life-threatening. Severe infection of the facial sinuses, which may extend into the brain, is the most common presentation. Pulmonary, cutaneous, and gastrointestinal (GI) infections are also recognized. Rhinocerebral disease causes significant morbidity in patients who survive, because treatment usually requires extensive, and often disfiguring, facial surgery.

Surviving mucormycosis requires rapid diagnosis and aggressive coordinated medical and surgical therapy. Successful mucormycosis treatment requires correction of the underlying risk factor(s), antifungal therapy with liposomal amphotericin B, and aggressive surgery.

Still mucormycosis carries a mortality rate of 50-85%. The mortality rate associated with rhinocerebral disease is 50-70%. Pulmonary and gastrointestinal (GI) diseases carry an even higher mortality rate, because these forms are typically diagnosed late in the disease course. Disseminated disease carries a mortality rate that approaches 100%. Cutaneous disease carries the lowest mortality rate (15%).

2.2. About the product

Isavuconazonium sulphate is a water-soluble triazole antifungal agent and the prodrug of the active moiety isavuconazole. Isavuconazole demonstrates a fungicidal effect by blocking the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14 alpha demethylase responsible for the conversion of lanosterol to ergosterol. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane.

CRESEMBA is indicated in adults for the treatment of

- Invasive aspergillosis
- Mucormycosis in patients for whom amphotericin B is inappropriate

CRESEMBA is approved by several stringent regulatory authorities include USA and EU.

2.3. The development programme/compliance with Thai FDA guidance/scientific advice

Not applicable

2.4. General comments on compliance with GMP, GLP, GCP

GMP Clearance of Overseas Pharmaceutical Manufacturer: GMP clearance letters approve SwissCo Services AG, Almac Pharma Services Limited and Baxter Pharmaceutical Solutions LLC.

GLP/GCP: The information stated in the dossier that non-clinical studies and clinical studies were complied with GLP and GCP and already assessed by EMA and acceptable.

2.5. Type of application and other comments on the submitted dossier

- Product type: New medicinal product
- Application type: Stand-alone application
- Review method: Abbreviated assessment through unredacted assessment report from EMA

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented in two pharmaceutical forms:

a) powder for concentrate for solution for infusion containing 200 mg isavuconazole as active substance per vial (corresponding to 372.6 mg isavuconazonium sulfate). It is administered by intravenous infusion after reconstitution with 5.0 ml of water for injection and further dilution with 250 ml of 0.9% sodium chloride solution or 5% dextrose solution and

b) hard capsules containing 100 mg isavuconazole as active substance corresponding to 186.3 mg isavuconazonium sulfate.

Other ingredients of the powder for concentrate for solution for infusion are: mannitol and sulfuric acid, as described in section 6.1 of the SmPC.

Other ingredients of the hard capsules are: capsule contents: magnesium citrate (anhydrous), microcrystalline cellulose, talc, anhydrous colloidal silica, stearic acid; Capsule shell: hypromellose, water, red iron oxide (E172), titanium dioxide (E171), gellan gum, potassium acetate, disodium edetate, sodium laurylsulfate; Printing ink: shellac, propylene glycol, potassium hydroxide, black iron oxide (E172), as described in section 6.1 of the SmPC.

Cresemba powder for concentrate for solution for infusion is available in Type I glass vial with a teflon-coated butyl rubber stopper and an aluminium/plastic flip-off seal, as described in section 6.5 of the SmPC.

Cresemba hard capsules is available in Alu/Alu blisters, as described in section 6.5 of the SmPC.

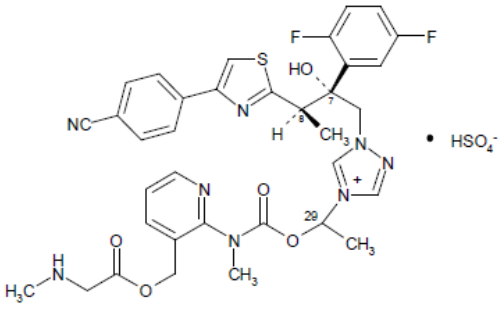
3.1.2. Active Substance

General Information

Nomenclature

International non-proprietary name (INN) (modified):	Isavuconazonium sulfate
Chemical names (IUPAC):	1-{(2R,3R)-3-[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl}-4-[(1RS)-1-({methyl[3-({[(methylamino)acetyl]oxy}methyl)pyridin-2-yl]carbamoyl}oxy)ethyl]-1H-1,2,4-triazol-4-ium monosulfate
CAS No.:	946075-13-4

Chemical Structure:



Molecular Formula: $C_{35}H_{35}F_2N_8O_5S \cdot HSO_4$

Molecular Weight: 814.84

Molecular Weight of Active Moiety (isavuconazole): 437.47

Stereochemistry: Drug substance has three chiral centers at C7 (*R*), C8 (*R*), and C29 (*R/S*). Drug substance is a mixture of two epimers. After administration both epimers are rapidly converted to the active moiety, isavuconazole.

3.1.3. Finished Medicinal Product [Hard Capsule]

1. Description and Composition of the Drug Product

Isavuconazonium sulfate capsules are hard capsules containing 186.3 mg isavuconazonium sulfate corresponding to 100 mg isavuconazole (active moiety BAL4815). The capsules have a Swedish Orange (reddish-brown color) body and a white cap. The capsules are imprinted with "C" (cap) and "100" (body) in black ink.

The composition of isavuconazonium capsules is described in Table 2.3.P-1 indicating their reference quality standard and functions. The composition of capsule shell is listed Table 2.3.P-2 and Table 2.3.P-3 and the composition of ink is listed Table 2.3.P-4. All components are tested in accordance with the current requirements of the compendia or legislation.

Composition of Isavuconazonium Capsules

Components
Isavuconazonium sulfate
Magnesium citrate, anhydrous
Cellulose, microcrystalline
Talc
Silica, colloidal anhydrous
Stearic acid
Capsule (size #0 elongated)
Ink (10A2 Black)

Isavuconazonium sulfate capsules are packaged in aluminum / aluminum blisters with desiccant.

3.1.4. Finished Medicinal Product [Powder for Concentrate for Solution for Infusion]

1. Description and Composition of the Drug Product

Isavuconazonium sulfate powder for concentrate for solution for infusion is a sterile, product containing 372.6 mg isavuconazonium sulfate, corresponding to 200 mg isavuconazole, per vial. It is administered by intravenous infusion after reconstitution with 5.0 mL of water for injection (WFI) and further dilution with 0.9% sodium chloride solution or 5% dextrose solution.

Unit Composition of Isavuconazonium Sulfate Powder for Concentrate for Solution for Infusion

Component
Isavuconazonium sulfate
Mannitol
Sulfuric acid
Nitrogen

3.2. Non clinical aspects

3.2.1. Pharmacology

An overview of the Primary Pharmacodynamics and Safety Pharmacology studies conducted with isavuconazole is presented in [Table 1].

Table 1. Primary Pharmacodynamics and Safety Pharmacology Studies Conducted with Isavuconazole

Type of Study	Animal Species	Study No
Primary pharmacodynamics studies [Module 5.3.5.4]		
hERG current	hERG transfected HEK293 cells	9766-PT-0001
Central Nervous System, Respiratory and Cardiovascular Systems, Autonomic Nervous System and Smooth Muscle, Renal System, Gastrointestinal System	Various species	9766-PT-0002
Sodium, potassium, and calcium currents	Several transfected cell lines	9766-PT-0003
Receptor/enzyme screen	*In vitro*	TBC

HEK: human embryonic kidney; hERG: human ether-á-go-go-related gene

1. Primary Pharmacodynamics

Isavuconazonium sulfate is the water-soluble prodrug of the active triazole isavuconazole, an antifungal with activity against a wide range of pathogenic fungi. Isavuconazole inhibits the cytochrome P450 (CYP) dependent lanosterol-14α-demethylase in yeasts and moulds.

Isavuconazole has *in vitro* antifungal activity against *Aspergillus* spp with Minimum Inhibitory Concentration (MIC90) ranging from 1-2 mg/L. The activity against *A. fumigatus* may be less affected by mutations in the *CYP51A* gene of the target enzyme at codons G54 and M220, compared with codons TR_{34}/L98H.

Isavuconazole also showed *in vitro* activity against the rare moulds, Rhizomucor and Rhizopus (MIC90:4-16 mg/L) as well as against *Candida* spp. Isavuconazole activity was unaffected by mutations in the Multi Drug Resistance 1 (MDR1) or Fluconazole resistance 1 (FLU1) transporter genes. The MIC90 values of isavuconazole against *C. neoformans* and *C. gattii* ranged from 0.0086 to 0.25 mg/L.

In vivo, isavuconazonium reduced tissue fungal burden and/or increased the survival rate in animal models of *Aspergillus* spp, *R. oryzae*, or *Candida* spp fungal infections. The pharmacodynamic parameter AUC/MIC correlated best with treatment outcome. *In vivo* and *in vitro* dynamic models utilizing both wild-type and isolates with elevated MICs or well-characterized mutations in the target gene demonstrated that efficacy could be optimized by increasing the isavuconazole concentrations.

In conclusion, isavuconazole has a broad spectrum of *in vitro* activity against *Aspergillus*, spp, several species of *Mucorales*, and *Candida* spp. Administration of isavuconazonium in animal models of fungal infection showed *in vivo* efficacy against these same pathogens. These data suggest that isavuconazonium could have therapeutic benefit for the treatment of patients with systemic fungal infections.

2. Secondary Pharmacodynamics and Safety Pharmacology

Central Nervous System: Isavuconazonium prolonged pentobarbital sleep duration in mice (30 mg/kg; human equivalent dose 0.39-fold the clinical maintenance dose of 200 mg/day isavuconazole). It has been reported in literature, that azole compounds prolong pentobarbital-induced sleep duration secondary to inhibitory effects on CYP isozymes which would slow the metabolism of pentobarbital [Study Report 9766-PT-0002]. As this effect on pentobarbital-induced sleep duration was secondary to the CYP inhibition, it is not considered a relevant central nervous system (CNS) finding for humans. Isavuconazonium had no effect on body temperature nor spontaneous locomotion in mice.

Cardiovascular System: Isavuconazole inhibited the human ether-á-go-go-related gene potassium current with an IC_{50} of 5.82 µM (34-fold the unbound C_{max} at the clinical maintenance dose of 200 mg/day isavuconazole). A second *in vitro* ion channel study confirmed this finding but also showed that isavuconazole inhibited the L-type calcium channel (hCav1.2) with an IC_{50} of 6.57 µM (38-fold the unbound C_{max} at the clinical maintenance dose of 200 mg/day isavuconazole).

Intravenous administration of isavuconazonium to monkeys at human equivalent doses up to 2.2-fold the clinical maintenance dose of isavuconazole resulted in transient and reversible decreases in systolic and diastolic blood pressure during the infusion period. In addition, an increase in heart rate was noted for the highest dose tested.

Respiratory System: No effect on respiratory rate or blood pH.

Renal System: No effect on electrolyte and water excretion.

GI and Autonomic Nervous Systems: No effect on GI transport, however, *in vitro*, isavuconazonium accentuated acetylcholine induced contraction of the guinea pig ileum but had no effect on histamine or barium chloride induced contraction.

***In vitro* pharmacology screen**: In the receptor/enzyme screen (CEREP Safety Screen 44) with isavuconazole sulfate (BAL4815-002) at a concentration of 20 µM, the only ion channels and receptor where any relevant inhibition or stimulation (> 50%) were noted were the Na^+ (77.9%) and Ca^{2+} (52.8%) channels and the androgen receptor AR (h) (54.3%). The effects on Na^+ and Ca^{2+} channels are consistent with *in vitro* safety pharmacology observations summarised above. The slightly increased inhibition of the androgen receptor AR (h) did not demonstrate any androgen-related toxicity or symptoms of an anti-androgenic effect.

3.2.2. Pharmacokinetics

1. Absorption and General Pharmacokinetics

The studies presented here consist of studies in rats and cynomolgus monkeys [Table 2]. Plasma concentrations of isavuconazonium (prodrug), isavuconazole (active moiety), and BAL8728 (inactive cleavage product) were measured after single and repeated administrations in rats and cynomolgus monkeys. Blood and plasma concentrations of radioactivity were measured after single administration in rats and cynomolgus monkeys. The effect of food intake was studied in cynomolgus monkeys.

Table 2. Absorption and General Pharmacokinetic Studies with Isavuconazonium

Type of Study	Animal Species	Administration Method	Study No
Single dose; Blood and plasma radioactivity levels	SD Rat	IV bolus, oral gavage	[9766-ME-1029]
Single dose; Blood and plasma radioactivity levels	Cynomolgus monkey	IV bolus, oral gavage	[9766-ME-1017]
Single dose; Isavuconazonium, isavuconazole, and BAL8728 plasma levels	SD Rat	IV bolus, oral gavage	[9766-ME-0013]
Single dose and effect of food intake; Isavuconazonium, isavuconazole, and BAL8728 plasma levels	Cynomolgus monkey	IV bolus, oral gavage	[9766-ME-0017]
Repeated doses; Blood and plasma radioactivity levels	SD Rat	Oral gavage	[9766-ME-1020]
Repeated doses; Isavuconazonium, isavuconazole, and BAL8728 plasma levels	SD rat	IV infusion (2 h)	[9766-ME-0015]
Repeated doses; Isavuconazole and BAL8728 plasma levels	SD rat	Oral gavage	[9766-ME-0009]
Repeated doses; Isavuconazonium, isavuconazole, and BAL8728 plasma levels	Cynomolgus monkey	IV infusion (2 h)	[9766-ME-0007]
Repeated doses; Isavuconazole plasma level	Cynomolgus monkey	Oral gavage	[9766-ME-0014]

After a single-dose intravenous bolus administration, isavuconazonium was rapidly converted to the active moiety, isavuconazole (BAL4815), and the inactive cleavage product (BAL8728). In rats and cynomolgus monkeys, the elimination half-life ($t_{1/2}$) of isavuconazole after intravenous dosing was 5.07 and 9.84 h, respectively. Plasma clearance of isavuconazole was low and its distribution was large in monkeys. After a single-dose oral administration, isavuconazonium was not detected in the plasma, suggesting a rapid conversion of isavuconazonium in the intestinal tract, and/or by a high first-pass metabolism in the intestine and liver as well as plasma. The C_{max} of isavuconazole was observed at 2-3 h after oral dosing. The relative oral bioavailability of isavuconazole was 61.9% in rats and 86.9% in monkeys, suggesting a good oral absorption. Additionally, the inactive cleavage product (BAL8728) was not detected in the plasma of monkeys, and detectable levels of the inactive cleavage product were only reported in rats with limited data points. In cynomolgus monkeys, oral administration of isavuconazonium with food reduced AUC of isavuconazole by 19%, C_{max} by 51%, and delayed t_{max} from 3.33 to 5.00 h.

Repeated-dose oral and intravenous toxicokinetic studies in rats and cynomolgus monkeys demonstrated that the AUC of isavuconazole were almost dose-proportional and there were no indications of drug accumulation. A gender difference in AUC of isavuconazole was observed in rats (females > males), but not in cynomolgus monkeys.

2. Distribution

The distribution studies consist of studies in albino and pigmented rats and in cynomolgus monkeys [Table 3]. *In vitro* studies for plasma protein binding were performed for mice, rats, guinea pigs, rabbits, cynomolgus monkeys, and humans.

Table 3. Distribution Studies with Isavuconazonium

Type of Study	Animal Species	Administration Method	Study No
Single dose; Radioactivity level in tissues	SD rat	IV bolus	[9766-ME-0025]
Single dose; Radioactivity level in tissues	Long Evans rat (pigmented)	oral gavage	[9766-ME-1014]
Repeated doses; Radioactivity level in tissues	SD rat	IV bolus and oral gavage	[9766-ME-1020]
Plasma and brain concentrations of isavuconazole	Wistar Rat	Oral gavage	[9766-ME-0049]
Placental transfer	SD rat	IV bolus	[9766-ME-1019]
Plasma protein binding	ICR mouse, SD rat, Wistar rat, Hartley guinea pig, Himalayan rabbit, cynomolgus monkey, and human	*In vitro*	[9766-ME-1011]
Blood/plasma ratios of radioactivity	SD rat and cynomolgus monkey	IV bolus and oral gavage	[9766-ME-1029, 9766-ME-1017]

The tissue distribution in albino rats was investigated by quantitative whole-body autoradiography (QWBA) after intravenous dosing of 14C/3H-labeled isavuconazonium chloride. Isavuconazole-related radioactivity was widely distributed in all organs with levels generally higher than those found in plasma and there was no evidence of tissue-specific retention. The tissue distribution in pigmented rats was also investigated by QWBA after oral dosing of [cyano-14C] isavuconazonium sulfate and intravenous dosing of [pyridinylmethyl-14C] isavuconazonium sulfate. No affinity for melanin by isavuconazole-related radioactivity was confirmed, but the affinity was indicated by BAL8728-related radioactivity.

Repeat dosing of [cyano-14C] isavuconazonium did not lead to accumulation of radioactivity in tissues. The highest radioactivity was consistently measured in the liver and adrenal gland.

After intravenous administration of [cyano-14C] isavuconazonium or [pyridinylmethyl-14C] isavuconazonium to pregnant rats, the drug-derived constituents from both isavuconazole and BAL8728 crossed the placental barrier.

In vitro plasma protein binding of isavuconazole was nearly constant in the range of 0.2 to 20 µg/mL: 98.7%-99.1% in mice, 97.3%-97.9% in rats, 96.4%-97.2% in guinea pigs, 97.3%-98.0% in rabbits, 99.0% in cynomolgus monkeys, and 99.2%-99.4% in humans. The unbound fraction was lowest in humans. These differences do not impact the species comparison.

3. Metabolism

Using plasma, urine, bile, or feces samples from rats, cynomolgus monkeys, and humans, metabolite profiling and identification or elucidation of metabolites were conducted [Table 4]. Also, *in vitro* metabolism studies were performed using liver microsomes, hepatocytes, or plasma.

Table 4. Metabolism Studies with Isavuconazonium

Type of Study	Animal Species	Administration Method	Study No
In vitro metabolism (plasma)	SD rat, cynomolgus monkey, and human	*In vitro*	[9766-ME-0004]
In vitro metabolism (plasma)	SD rat, cynomolgus monkey, and human	*In vitro*	[9766-ME-0005]
In vitro metabolism (plasma)	Rabbit and dog	*In vitro*	[9766-ME-0037]
In vitro metabolism (liver microsomes and hepatocytes)	SD rat, cynomolgus monkey, and human	*In vitro*	[9766-ME-0021]
In vitro metabolism (liver microsomes and hepatocytes)	Rat	*In vitro*	[9766-ME-0032]
In vitro metabolism (liver microsomes)	Mouse, rat, rabbit, dog, cynomolgus monkey, and human	*In vitro*	[9766-ME-0035]
In vivo metabolism (plasma, urine, and bile)	SD rat	IV bolus and oral gavage	[9766-ME-1030]
In vivo metabolism (plasma, urine, and bile)	Cynomolgus monkey	IV bolus and oral gavage	[9766-ME-1018]
In vivo metabolism (plasma)	SD rat	IV infusion	[9766-ME-1034]
In vivo induction of drug-metabolizing enzymes	SD rat	IV infusion	[9766-ME-0011]
In vivo induction of drug-metabolizing enzymes	Cynomolgus monkey	IV infusion	[9766-ME-0010]

Isavuconazonium was quantitatively converted to the active moiety, isavuconazole, with a $t_{1/2}$ < 2 min in rat, rabbit, cynomolgus monkey, and human plasma *in vitro*. In contrast, the conversion of isavuconazonium to isavuconazole in dog plasma was less extensive (< 20% in 5 min) and slower than was seen for other test species. Conversion of isavuconazonium to isavuconazole in rat, cynomolgus monkey, and human plasma was completely inhibited by the addition of an esterase inhibitor (1 mmol/L paraoxon), suggesting the involvement of plasma esterases in this process. Isavuconazonium is a 1:1 racemic mixture of 2 diastereomers derived from an asymmetric carbon atom in the prodrug moiety. Both diastereomers were rapidly ($t_{1/2}$ < 2 min) converted to isavuconazole in rat, cynomolgus monkey, and human plasma with small (about 2-fold) differences in the conversion rates between 2 diastereomers.

In the *in vitro* metabolism studies with liver microsomes and hepatocytes, isavuconazole was metabolized to a small extent to a mono-oxidative metabolite that was then conjugated. The *in vitro* metabolic pattern was similar in cynomolgus monkeys and humans. All toxicological species were qualified as suitable by the presence of all human metabolites in the test species and the absence of human specific metabolites.

Plasma, urine, bile or feces samples from rats, cynomolgus monkeys, and humans following intravenous or oral administration of [cyano-^{14}C] isavuconazonium or [pyridinylmethyl-^{14}C] isavuconazonium were used to identify metabolites. Chemical structures of a total of 77 metabolites were estimated based on various analytical methods. In plasma, isavuconazole was the main component derived from [cyano-^{14}C] isavuconazonium in all species tested including humans. In rats, M7 (carboxylic acid form of destriazole isavuconazole) was also the main component. In contrast, M4 (cleavage metabolite of the carbamoyl group from BAL8728) was the main component derived from [pyridinylmethyl-^{14}C] isavuconazonium in all species tested including humans. BAL8728 was also detected as the minor component in all species. The exposures of isavuconazole and M4, which were more than 10% of total drug-related materials in human plasma from [cyano-^{14}C] isavuconazonium and [pyridinylmethyl-^{14}C] isavuconazonium, respectively, were covered in one of the species used in toxicology studies (rat or cynomolgus monkey).

At toxicological doses (30 or 60 mg/kg, intravenous), induction of CYP3A and CYP2B in female rats and that of CYP2B in male and female cynomolgus monkeys was observed.

4. Excretion

The excretion studies were conducted in rats and cynomolgus monkeys [Table 5].

Table 5. Excretion Studies with Isavuconazonium

Type of Study	Animal Species	Administration Method	Study No
Excretion of radioactivity into urine and feces	Wistar rat	IV bolus and oral gavage	[9766-ME-0012]
Excretion of radioactivity into urine and feces	Cynomolgus monkey	IV bolus and oral gavage	[9766-ME-1017]
Excretion of radioactivity into urine and bile	Wistar rat	IV bolus	[9766-ME-0022]
Excretion of radioactivity into urine and bile	Cynomolgus monkey	IV bolus and oral gavage	[9766-ME-1017]
Entero-hepatic circulation	SD rat	Intraduodenal injection	[9766-ME-1029]
Excretion into milk	SD rat	IV bolus	[9766-ME-1019]

In the mass balance studies after intravenous and oral administrations of [$^{14}C/^{3}H$] isavuconazonium to rats, or [cyano-^{14}C] isavuconazonium and [pyridinylmethyl-^{14}C] isavuconazonium to cynomolgus monkeys, the main elimination pathway of radioactivity for isavuconazole-related materials in rats was excretion in feces, but in monkeys, radioactivity was excreted at almost equal levels in the urine and feces. In contrast, the main elimination pathway of radioactivity for BAL8728-related materials in rats and monkeys was excretion in urine.

In rats, enterohepatic circulation of radioactivity for both isavuconazole- and BAL8728-related materials was observed.

After intravenous administration of [cyano-^{14}C] isavuconazonium and [pyridinylmethyl-^{14}C] isavuconazonium to lactating rats, isavuconazonium-derived constituents, especially isavuconazole-derived ones, were excreted into milk. Therefore, it is expected also to be present in human milk.

5. Pharmacokinetic Drug Interactions

The pharmacokinetic drug interaction study was conducted in mice [Table 6].

Table 6. Pharmacokinetic Drug Interactions Study with Isavuconazonium

Type of Study	Animal Species	Administration Method	Study No
Interaction with Maalox® and isavuconazole, food effect	NMRI mouse	Oral gavage	[9766-ME-0048]

In mice, the potential interaction between isavuconazole and Maalox® was evaluated; AUC of isavuconazole was similar with or without administration of Maalox.

3.2.3. Toxicology

Studies in the early phase of development were conducted with the isavuconazonium chloride salt, while those in the late phase were conducted with the sulfate salt. There was no difference in systemic exposure after administration of either salt form. The purity of the isavuconazonium drug substance ranged from 74.1% to 99.3%. Impurities necessary for safety qualification (> 0.15%) were evaluated in the toxicology studies since these impurities were present in the drug substance used for general toxicology and genotoxicity studies.

Toxicity studies were also conducted with active moiety isavuconazole, inactive cleavage product, as well as on starting materials (BAL16173, BAL17699 and BAL17702), a manufacturing intermediate (BAL17478), and drug substance impurities (BAL19714, BAL19715, BAL31264, and BAL31265).

All pivotal studies have been performed in accordance with ICH and local guidelines.

1. Single-Dose Toxicity

Single dose oral and intravenous administration studies with isavuconazonium were conducted in rats and cynomolgus monkeys [Table 7]. The oral LD50 values in male and female rats were estimated at 1024 mg/kg and 708 mg/kg respectively (Study Report [9766-TX-0001]). In the cynomolgus monkey, a single oral dose of 2000 mg/kg resulted in the death of 1/2 male animals (LD50; Study Report [9766-TX-0002]).

After IV administration, the LD50 values in rat were estimated at 10.2 mg/kg in males and 9.8 mg/kg in females at an infusion rate of 1 mL/min, and >20 mg/kg in both sexes after intravenous administration at an infusion rate of 0.1 mL/min (see Study Report [9766-TX-0001]). A similar finding with toxicity depending upon the speed of administration was observed in cynomolgus monkeys. A single intravenous bolus injection of isavuconazonium at a dose of 64 mg/kg was lethal to monkeys (2/2 animals) (see Study Report [9766-TX-0002]), while a 2-h intravenous infusion at a dose of 120 mg/kg resulted in a 50% mortality rate. The implication of this finding for humans is that isavuconazonium should not be rapidly infused clinically.

Table 7. Single Dose Toxicity Studies with Isavuconazonium

Species and Strain	Salt form of the test article	Method of Administration	Doses (mg/kg)	GLP Compliance	Study No
Rat/SD	Chloride	Oral gavage IV	0, 500, 1000, 2000 (oral) 0, 5, 10, 20 (IV, 1 mL/min) 10, 20, 40 (IV, 0.1 mL/min)	Yes	[9766-TX-0001]
Cynomolgus monkey	Chloride	Oral gavage IV bolus IV infusion (2 h)	500, 1000, 2000 (oral) 4, 8, 16, 32, 64 (IV bolus) 90, 120 (IV infusion)	Yes	[9766-TX-0002]

2. Repeat-Dose Toxicity

Repeat dose toxicity assessments with oral gavage administration of isavuconazonium were conducted in mice (up to 13 weeks), rats (up to 26 weeks), and cynomolgus monkeys (up to 39 weeks). Intravenous infusion of isavuconazonium was administered to rats and cynomolgus monkeys (both up to 6 weeks) [Table 8]. Exposures to the active moiety, isavuconazole, relative to the human exposure at the clinical maintenance dose of 200 mg/day isavuconazole are presented in [Table 9].

Table 8. Repeat-dose Dose Toxicity Studies with Isavuconazonium

Species and Strain	Salt Form of the Test Article	Method of Administration	Duration of Dosing	Doses (mg/kg)†	GLP Compliance	Study No
Mouse/CD1	Sulfate	Oral gavage	2 weeks	0, 30, 90, 180	No	[9766-TX-0004]
Mouse/CD1	Sulfate	Oral gavage	13 weeks	0, 30, 90, 300	Yes	[9766-TX-0005]
Rat/Wistar	Chloride	Oral gavage	2 weeks	0, 30, 90	Yes	[9766-TX-0014]
Rat/SD	Chloride	IV infusion (2 h)	2 weeks	0, 10, 30, 60	Yes	[9766-TX-0006]
Rat/Wistar	Chloride	IV infusion (2 h)	2 weeks	0, 10, 60/30	Yes	[9766-TX-0007]
Rat/Wistar	Sulfate	IV infusion (24 h)	2 weeks	0, 60	Yes	[9766-TX-0008]
Rat/SD	Chloride	Oral gavage	4 weeks	0, 10, 30, 90	Yes	[9766-TX-0013]
Rat/Wistar	Sulfate	IV infusion (2 or 4 h)	6 weeks	0, 10, 20, 40/30	Yes	[9766-TX-0009]
Rat/SD	Sulfate	Oral gavage	13 weeks	0, 10, 30, 90	Yes	[9766-TX-0015]
Rat/SD	Sulfate	Oral gavage	26 weeks	0, 10, 30, 90	Yes	[9766-TX-0016]
Cynomolgus Monkey	Chloride	IV infusion (2 h)	2 weeks	0, 10, 30, 60	No	[9766-TX-0010]
Cynomolgus Monkey	Chloride	IV infusion (2 h)	2 weeks	0, 10, 30, 60	Yes	[9766-TX-0011]
Cynomolgus monkey	Chloride	Oral gavage	4 weeks	0, 10, 30, 90	Yes	[9766-TX-0017]
Cynomolgus Monkey	Sulfate	IV infusion (2 or 4 h)	4 or 6 weeks	0, 10, 20, 40	Yes	[9766-TX-0012]
Cynomolgus monkey	Sulfate	Oral gavage	13 weeks	0, 10, 20, 40	Yes	[9766-TX-0018]
Cynomolgus monkey	Sulfate	Oral gavage	39 weeks	0, 10, 20, 40	Yes	[9766-TX-0019]

†The NOAEL (No-observed-adverse-effect level) is underlined.

Table 9. Compilation of Systemic Exposure Data of Isavuconazole at NOAEL and LOAEL (Pivotal Studies)

Study No.	Species/ Study Duration	Dose (mg/kg)	Sex (M/F)	C_{max} (ng/mL)		AUC_{24} (ng·h/mL)		Remarks	C_{max} (last dose)	AUC (last dose)
				First Dose	Last Dose	First Dose	Last Dose		Fold compared to Maintenance Dose†	
[9766-TX-0009]	Rat, 6-week, 2 or 4-hour IV	20 (NOAEL)	M	718	1180	NA	NA	NOAEL based on marked irritation at infusion site and premature death	0.16	NA
			F	1075	1440	NA	NA		0.19	NA
		40/30 (LOAEL)	M	2152	2730$	NA	NA		0.36	NA
			F	1584	1761¥	NA	NA		0.24	NA
[9766-TX-0012]	Monkey, 6-week, 2-hour IV	10 (NOAEL)	M	1850	2610	13900	13600	NOAEL based on intolerance at infusion site and increased neutrophils	0.35	0.11
			F	1800	2150	13300	13600		0.29	0.11
		20 (LOAEL)	M	3360	4460	37600	31100		0.59	0.26
			F	3990	15300	34300	56100		2.04	0.46
[9766-TX-0015]	Rat, 13-week, po	30 (NOAEL)	M	762	1810	7080	10500	NOAEL based on liver hypertrophy	0.24	0.09
			F	2000	2620	21200	21900		0.35	0.18
		90 (LOAEL)	M	5170	3580	48800	25200		0.48	0.21
			F	5700	8380	80100	56900		1.12	0.47
[9766-TX-0016]	Rat, 26-week, po	10 (NOAEL)	M	746*	497	3330*	2770	NOAEL based on liver hypertrophy and ptyalism	0.07	0.02
			F	1130*	1300	8730*	11500		0.17	0.09
		30 (LOAEL)	M	2100*	1780	15200*	12600		0.24	0.10
			F	2720*	7890	38300*	35400		1.05	0.29
[9766-TX-0018]	Monkey, 13-week, po	20 (NOAEL)	M	2630	3070	26100	24300	NOAEL based on liver and adrenal hypertroph	0.41	0.20
			F	3720	2170	30400	24100		0.29	0.20
		40 (LOAEL)	M	6980	7360	89000	94600		0.98	0.78
			F	6890	7570	82700	89900		1.01	0.74
[9766-TX-0019]	Monkey, 39-week, po	20 (NOAEL)	M	3480*	2840	33100*	36000	NOAEL based on increased liver and adrenal weight;	0.38	0.30
			F	3910*	2580	45600*	30400		0.34	0.25
		40 (LOAEL)	M	7070*	6700	100000*	87800		0.89	0.72
[9766-CL-0017]	Human	200 mg/day	M/F		7499‡		121402‡		1.00	1.00
		600 mg/day	M/F		20028‡		352805‡		2.67	2.91

*C_{max} and AUC for 26-week rat and 39-week monkey of week 13;$ C_{max} on Day 28; ¥ C_{max} on Day 14. †Maintenance dose: 200 mg/day isavuconazole, study 9766-CL-0017; ‡ day 13 steady state

F: Female; IV: intravenous; LOAEL: Lowest-observable-adverse-effect; M: Male; MD: maximum dose; NA: Not applicable; NOAEL: No-observed-adverse-effect level; po: oral.

C_{max} and AUC values refer to isavuconazole (active drug)

3. Liver

In the sub-acute and chronic toxicity studies, administration of isavuconazonium was associated with increased liver weight and/or hepatocellular hypertrophy in mice (Study Report [9766-TX-0004]), rats (Study Reports [9766-TX-0006], [9766-TX-0009], [9766-TX-0013], [9766-TX-0015], [9776-TX-0016]), and monkeys (Study Reports [9766-TX-0011], [9766-TX-0012], [9766-TX-0017], [9766-TX-0018], [9766-TX-0019]). Increasing the duration of administration was not associated with increased severity of the findings.

Since isavuconazonium is a prodrug that is rapidly metabolized in plasma to its active moiety isavuconazole, and an inactive cleavage product, an assessment was made to determine if these hepatic findings were due to either isavuconazole or its inactive cleavage product. Oral administration of isavuconazole, for 4 or 2 weeks to rats and monkeys, respectively, was associated with hepatic changes observed with the prodrug isavuconazonium (Study Reports [9766-TX-0020, 9766-TX-0021]). Conversely, intravenous administration of the inactive cleavage product for 2 weeks to rats was not associated with hepatic changes (Study Report [9766-TX-0022]). These data suggest that the hepatic findings observed with isavuconazonium were due to the active moiety, isavuconazole.

Increased liver weight and centrilobular hepatocellular hypertrophy in rats and monkeys are common histological changes associated with enzyme induction in animals, which is considered adaptive and not injurious [Greaves, 2012]. Intravenous administration of isavuconazonium to rats or monkeys was associated with an increase in liver weight and increases in CYP enzyme activity (Study Reports [9766-ME-0010, 9766-ME-0011]. Histological findings of hepatocellular hypertrophy were also noted in the toxicity studies. Together, these data support the conclusion that the increase in liver weights and hepatocellular hypertrophy was not a toxicological finding but rather related to pharmacological induction of hepatocellular enzymes similar to that seen with other azole compounds [Suzuki et al, 2000]. As such, these data support the conclusion that isavuconazonium poses little or no risk for mediating hepatic injury to patients.

4. Thyroid

Repeated dose administration of isavuconazonium or isavuconazole was associated with an increase in thyroid weights that were associated with thyroid follicular cell hypertrophy in rats (Study Reports [9766-TX-0013, 9766-TX-0015, and 9766-TX-0016]). As with the liver findings, increases in thyroid weights were observed following repeated dosing with the active moiety, isavuconazole (Study Report [9766-TX-0020]) but were not altered following the administration of the inactive cleavage product (Study Report [9766-TX-0022]), supporting the hypothesis that the thyroid findings associated with the administration of isavuconazonium were mediated by systemic exposure to isavuconazole.

As indicated above, isavuconazonium induces liver microsomal enzymes, and in rats, long-term exposure to agents that induce these enzyme pathways result in a chronic stimulation of the thyroid. This chronic stimulation of the thyroid results in increased thyroid weight and follicular cell hypertrophy, which are considered to be secondary to the hyper stimulation [Curran 1991]. These changes are commonly reversible; in addition, it should be noted that the recovery period in the 26-week rat study was relatively short, at only 4 weeks. These findings are specific to rodents, which lack thyroid hormone-binding globulin [Wu and Farrelly, 2006; Klaunig, 2013[and the rat is therefore not considered an appropriate species for a meaningful human risk prediction [Greaves 2012].

Unlike in rats, administration of isavuconazonium or isavuconazole to monkeys was not associated with an increase in thyroid weights or with thyroid follicular cell hypertrophy (Study Reports [9766-TX-0011, 9766-TX-0012, 9766-TX-0017, 9766-TX-0018, 9766-TX-0019, 9766-TX-0021]). In addition, after administration of isavuconazole to monkeys daily for 2 weeks, there were no histopathological findings in this organ (Study Report [9766-TX-0021]), further supporting the conclusion that this is a rat specific

finding.

In summary, isavuconazole induces liver microsomal enzymes and in rats, long-term exposure to agents that induce these enzyme pathways, results in a chronic stimulation of the thyroid. This chronic stimulation of the thyroid results in increased thyroid weight and follicular cell hypertrophy. These findings are specific to rodents which lack thyroid hormone-binding globulin [Klaunig, 2013]. Support for this interpretation comes from the observation that isavuconazonium administration to monkeys daily for up to 39 weeks had no effect on either thyroid weights or histology. Therefore, the effects of isavuconazonium and its active moiety, isavuconazole, on the thyroid are not considered relevant to humans and, as such, poses no discernible clinical risk.

5. Adrenal

Repeated administration of isavuconazonium to monkeys resulted in increases in or a trend towards increases in adrenal weights and/or vacuolation/hypertrophy of adrenocortical cells (Study Reports [9766-TX-0010, 9766-TX-0011, 9766-TX-0017, 9766-TX-0018, 9766-TX-0019]). The increase in adrenal weights were reversible at the end of the recovery period (Study Reports [9766-TX-0018, 9766-TX-0019]). The adrenal changes, which are observed with azole anti-fungal agents, are thought to result from CYP induction (CYP2B as observed in male and female cynomolgus monkeys) [Harvey and Sutcliffe, 2010; You, 2004]. Despite enlarged vacuolated adrenal cortical cells and increased adrenal weight in the cynomolgus monkey studies, no atrophic or necrotic lesions were observed. The clinical significance of the preclinical adrenal findings is unclear.

6. Administration Site Reactions

Vascular and perivascular irritation and inflammation were observed following repeated dose intravenous administration of isavuconazonium to both rats and cynomolgus monkeys (Study Reports [9766-TX-0006, 9766-TX-0007, 9766-TX-0008, 9766-TX-0009, 9766-TX-0010, 9766-TX-0011, 9766-TX-0012]). In these species, the vascular findings were dose or duration limiting (Study Reports [9766-TX-0007, 9766-TX-0012]) and were attributable to methodological limitations such as repeated percutaneous injections into peripheral veins.

7. Genotoxicity

Genotoxicity of isavuconazole was investigated in the studies listed in Table 10.

Table 10. Studies on the Genotoxicity of Isavuconazonium

Type of Study	Species and Strain	Salt Form of the Test Article	Method	Doses (mg/kg)	GLP	Study No
Ames	*S.typhimurium*	Chloride	*in vitro*	0, 0.316 to 1000 mcg/plate	Yes	[9766-TX-0023]
Mouse lymphoma	Mouse Lymphoma L5178Y $tk^{+/-}$ cells	Chloride	*in vitro*	0, 5 to 140 mcg/mL	Yes	[9766-TX-0027]
In vivo micronucleus	Rat/Wistar	Chloride	IV bolus	0, 6.25, 12.5, 25	Yes	[9766-TX-0030]

Genotoxicity of isavuconazonium was assessed in the bacterial reverse mutation assay (Ames and Ames II assays; Study Reports [9766-TX-0023, 9766-TX-0024, 9766-TX-0025, 9766-TX-0026]), mouse lymphoma cell thymidine kinase assay (Study Reports [9766-TX-0027, 9766-TX-0028, 9766-TX-0029]) and in the rat bone marrow micronucleus test (Study Report [9766-TX-0030]). In the bacterial reverse mutation assay, isavuconazonium showed no discernible genotoxic potential while in the mouse lymphoma cell thymidine kinase assay, marginal increases in mutant colonies were noted only at cytotoxic concentrations. In order to further assess the genotoxic potential, the *in vivo* rat micronucleus test was performed. First, a dose range finding study was performed which concluded that the intravenous administration of isavuconazonium at a dose of 25 mg/kg was the maximum tolerated non-lethal dose that could be administered. Administering this dose (25 mg/kg) to rats did not result in an increase in the incidence of micronuclei in polychromatic erythrocytes indicating no discernible genotoxic potential for isavuconazonium. By extension, these data also showed no discernible genotoxic potential for isavuconazole or for the inactive cleavage product.

Since the active moiety, isavuconazole, contains an azole ring that has been associated with genotoxic potential, an additional bacterial reverse mutation study was performed only on the active moiety (Study Report [9766-TX-0031]). In that study, none of the tester strain of bacteria showed an increase in revertant colonies indicating that isavuconazole had no discernible mutagenic potential. Finally, as confirmation of this response, isavuconazole was also assessed for genotoxic potential in the mouse lymphoma cell thymidine kinase assay. Here too, isavuconazole showed no discernible genotoxic potential (Study Report [9766-TX-0032]). These data directly show that neither isavuconazonium nor isavuconazole had discernible genotoxic potential. The *in vivo* data indirectly showed that the inactive further supported by the fact that the structure of the inactive cleavage product had no genotoxic alerts by Deductive Estimation of Risk from Existing Knowledge (DEREK) analysis.

8. Carcinogenicity

Carcinogenicity studies for isavuconazonium sulfate have not yet been completed

9. Reproductive and Developmental Toxicity

Reproductive and developmental toxicity of isavuconazonium was investigated in studies to examine effects on fertility and early embryonic development, embryo-fetal development, and pre- and postnatal development including maternal function [Table 11].

Table 11. Studies on the reproductive and developmental toxicity of isavuconazonium

Type of Study	Species and Strain	Salt form of test article	Method	Duration of Dosing	Doses (mg/kg)	GLP	Study No
Fertility and early embryonic development	Rat/Wistar	Sulfate	Oral gavage	M: 4 weeks prior to mating F: 2 weeks prior to mating through GD6	0, 10, 30, 90	Yes	[9766-TX-0049]
Embryo-fetal development	Rat/Wistar	Chloride	Oral gavage	GD6 to GD17	0, 6, 30, 150	No	[9766-TX-0051]
Embryo-fetal development	Rat/Wistar	Chloride	Oral gavage	GD6 to GD17	0, 6, 30, 150	Yes	[9766-TX-0052]
Embryo-fetal development	Rabbit/ Himalayan	Chloride	Oral gavage	GD6 to GD18	0, 10, 30, 60	No	[9766-TX-0054]
Embryo-fetal development	Rabbit/ Himalayan	Chloride	Oral gavage	GD6 to GD18	0, 10, 20, 45	Yes	[9766-TX-0055]
Pre and postnatal development	Rat/Wistar	Sulfate	Oral gavage	GD6 to LD20	0, 10, 30, 90	Yes	[9766-TX-0056]
Dose-range	Rabbit/ Himalayan	Chloride	Subcutaneous	2 weeks	0, 45, 90	No	[9766-TX-0053]
Dose-range	Rat/Wistar	Chloride	Subcutaneous	GD6 to GD17	0, 6, 30, 60, 90, 150	No	[9766-TX-0050]

GD: gestation day; GLP: Good Laboratory Practice; LD: lactation day.

Isavuconazonium administration at maternal systemic exposures 0.2-fold the human systemic exposure at the maintenance dose of 200 mg/day isavuconazole, induced skeletal abnormalities and variations in the rat (Study Report [9766-TX-0052]). In rabbits, a visceral variation and a skeletal abnormality were reported following the oral administration of isavuconazonium to the maternal animals at a dose of 45 mg/kg per day (0.1-fold the human systemic exposure at the maintenance dose of 200 mg/day) (Study Report [9766-TX-0055]). No maternal toxicity or effects on reproductive parameters were observed in either rats or rabbits indicating that the findings were not associated with the maternal health condition. In order to rule out the possibility that these fetal findings were due to the inactive cleavage product, rats were administered the cleavage product (BAL8728) at a dose of 50 mg/kg per day during the period of organogenesis (Study Report [9766-TX-0057]). At this maternally lethal dose, there were no fetal findings reported, indicating that the isavuconazole moiety was responsible for the fetal skeletal findings.

Preclinical teratogenicity has been reported with azole anti-fungal agents including fluconazole, itraconazole, and ketoconazole [Amaral and Nunes, 2009; Tiboni et al, 2006; Tiboni and Giampietro, 2005]. This effect was extended to humans in a review by Carey et al (2009), who indicated that high dose regimens of fluconazole were associated with craniofacial birth defects. Although preclinical studies with other azole antifungal agents showed teratogenic effects involving craniofacial, palate, and limb formation, the isavuconazonium associated skeletal findings appeared to be limited to zygomatic arch fusion, rudimentary cervical rib (unilateral and bilateral), and additional ossification of the fourth lumbar vertebral arch (Study Report [9776-TX-0052]). Azoles are known to interact with several isoforms of mammalian CYP enzymes, some of which play fundamental roles in embryonic development. It is hypothesized that these interactions result in the teratogenic effects of azoles [Marotta and Tiboni, 2010]. Based on the preclinical findings of skeletal anomalies in both rats and rabbits at systemic exposures below that of the human systemic exposures, it is concluded that isavuconazonium, as a member of the azole class of antifungal agents, has the potential to adversely affect human embryo-fetal development.

No drug-related changes were observed in sperm morphology, motility, viability and counts in SD male rats dosed with isavuconazonium in a 2-week intravenous infusion study at doses up to 60 mg/kg isavuconazonium (infusion speed 12.5 mL/kg/h for 2 h/day) (Study Report [9766-TX-0006]).

10. Juvenile Animals

The toxicity profile of isavuconazonium sulphate in juvenile animals was investigated in rats [Table 12].

Table 12. Studies in Juvenile Animals with Isavuconazonium

Type of study	Species and strain	Salt form of test article	Method	Duration of dosing	Doses (mg/kg)	GLP	Study No
Dose range finding	Rat/SD	Sulfate	Oral gavage	14 days (from 4 days old)	0, 10, 30, 90	No	[9766-TX-0065]
Dose range finding	Rat/SD	Sulfate	Oral gavage	13 weeks (from 4 days old)	0, 10, 30, 90	Yes	[9766-TX-0066]

GLP: Good Laboratory Practice.

In juvenile animals given oral (gavage) doses of 10, 30 or 90 mg/kg, dose-related toxicity was observed after 2 or 13 weeks dosing [Study Nos. 9766-TX-0065, and 9766-TX-0066, respectively] in the liver (increased weights and centrilobular hepatocellular) and thyroid gland (increased weights and follicular cell hypertrophy) in both sexes. In addition, in the 13-week study, there was some evidence of anemia and prolongation of activated partial thromboplastin time, but only in females. In the 13-week study, after the 2-week recovery period, the treatment-related changes had completely or partially resolved, demonstrating reversibility. The toxicity profile observed in juvenile animals after 13 weeks of dosing was comparable to that observed in adults after IV and oral administration studies of between 2 and 13 weeks [Study Nos. 9766-TX-0006, 9766-TX-0009, 9766-TX-0013, and 9766-TX-0015], and after 26 weeks of oral dosing [Study No. 9776-TX-0016].

Table 13. Systemic Exposure Data of Isavuconazonium, isavuconazole and the cleavage product at NOAEL in 13 week Juvenile Study

Study No.	Species/ Study Duration	Analyte	Dose (mg/kg)[2]	Sex (M/F)	C_{max} (ng/mL)			AUC_{24} (ng·h/mL)		
					Day 1	Day 6	Week 13	Day 1	Day 6	Week 13
[9766-TX-0066]	Rat (Juvenile)[1]/ 13-week	Isavuconazonium (BAL8557)	10 (NOAEL)	M	2.465	NA	0.000	2.465	NA	0.000
				F	3.910	NA	0.000	3.910	NA	0.000
			30	M	28.70	NA	0.000	88.77	NA	0.000
				F	36.60	NA	0.000	101.3	NA	0.000
			90	M	169.3	34.10	0.000	670.7	70.47	0.000
				F	197.8	41.42	0.000	640.5	94.28	0.000
		Isavuconazole (BAL4815)	10 (NOAEL)	M	459.6	NA	652.4	5552	NA	5963
				F	451.9	NA	1306	5557	NA	12580
			30	M	1837	NA	2110	24700	NA	19560
				F	1775	NA	3004	26010	NA	32300
			90	M	7850	3160	3956	122300	46450	44230
				F	8784	3248	5675	12500	49020	54110
		Cleavage product (BAL8728)	10 (NOAEL)	M	153.1	NA	571.7	1073	NA	2900
				F	213.0	NA	371.6	1633	NA	946.4
			30	M	971.0	NA	1608	5723	NA	7709
				F	907.3	NA	1301	6504	NA	3396
			90	M	2781	1386	3399	29770	6011	19460
				F	2699	1001	2214	17680	4737	7542

[1] Animals were 4 days old when first dose was given
[2] Dose given as isavuconazonium
NOAEL: No-observed-adverse-effect level (refers to dose of BAL8557); po: oral.

11. Safety Pharmacology

Effect of isavuconazole on ion channel currents was studied and resulted in a dose-related inhibition of the hERG potassium channel current with an IC_{50} of 5.82 mcM, which was 34-fold higher than the non-protein bound C_{max} at the clinical maintenance dose of 200 mg/day. This finding was qualitatively confirmed in a subsequent study where isavuconazole inhibited the hERG potassium channel current with an IC_{50} of 19.44 mcM (113-fold higher than the non-protein bound C_{max} at the clinical maintenance dose of 200 mg/day). Isavuconazole also inhibited hCav1.2, hKvLQT1/hminK, hNav1.5 (tonic), and hNav1.5 (phasic) ion channel currents with IC_{50} values of 6.57, 24.02, 20.36, and 14.87 mcM, respectively. Of these, the effects on the hCav1.2 ion channel may have clinical relevance as this effect was consistent with the observed QT interval shortening noted in the clinical TQT study. The effects of isavuconazole on the other ion channels were not considered clinically relevant due to the high concentrations needed to inhibit the ion channels (87- to 140-fold higher than the non-protein bound C_{max} at the clinical maintenance dose of 200 mg/day). The remaining ion channels evaluated (hKIR2.1, h/KIR3/1/3.4, KIR6.2/SUR2A, hKv1.5, and hKv4.3/KChiP2.2) were not inhibited by isavuconazole at concentrations up to 30 mcM.

In the receptor/enzyme screen (CEREP Safety Screen 44) with isavuconazole sulfate (BAL4815 002) tested at a concentration of 20 µM, the only ion channels and receptor where any relevant inhibition or stimulation (> 50%) was noted were for the Na^+ (77.9%) and Ca^{2+} (52.8%) channels, and the androgen receptor AR (h) (54.3%). The effects on Na^+ and Ca^{2+} channels are consistent with *in vitro* safety pharmacology observations summarised above. The slightly increased inhibition of the androgen receptor AR (h), as seen in studies with ketoconazole [Eil 1992], was not found to translate into the signs of androgen deficiency, which was reported for ketoconazole. Results from the nonclinical safety studies in rats and primates with isavuconazole did not show any evidence of androgen related toxicity. In addition, clinical studies did not suggest an association between treatment with isavuconazole and symptoms of an anti-androgenic effect.

Data obtained from the general pharmacology study showed that isavuconazonium has little or no effect on the cardiovascular, respiratory, renal, GI, and CNS as well as autonomic nervous systems.

12. Other Toxicity Data

Other Toxicity Studies

The effect of accidental ocular exposure was evaluated in rabbits where it was shown that minimal eye irritation was seen following instillation in the conjunctival sac at concentrations of 5 or 10 mg/mL (Study Report [9766-TX-0058]). These concentrations are at least 667-fold higher than the human C_{max} at the maintenance dose of 200 mg/day isavuconazole and, as such, suggest that the systemic levels achieved following oral or intravenous administration of isavuconazonium should pose little risk of eye irritation (5 mg/mL divided by human C_{max} of 7.499 µg/mL). Further support for this conclusion comes from the rat and monkey repeated dose studies where opthalmalogic assessments showed no indication of ocular toxicity (Study Reports [9776-TX-0016 and 9766-TX-0019]). The data support the conclusion that isavuconazonium poses little risk for eye irritation or injury in the clinical setting. In the manufacturing setting, appropriate safety measures should be used to prevent eye contact with isavuconazonium.

Isavuconazonium will be available for both oral and intravenous administration. As such, *in vitro* hemolysis assessments are necessary and in those studies, it was observed that hemolysis of human blood cells could be induced by isavuconazonium at concentrations at least 1 mg/mL (Study Report [9766-TX-0060]). However, because these concentrations are at least 133-fold higher than the human C_{max} at the maintenance dose of 200 mg/day isavuconazole, it is unlikely that the *in vivo* plasma concentrations would result in a similar outcome (1 mg/mL divided by human C_{max} of 7.499 µg/mL). Therefore, it is concluded that the risk of hemolysis is minimal.

As isavuconazonium was shown to absorb light in the UV wavelength range (250 to 320 nm, an *in vitro* assessment of phototoxicity was performed (Study Report [9766-TX-0061]). Isavuconazonium showed no *in vitro* phototoxicity, leading to the conclusion that it has no discernible phototoxicity potential. Although no phototoxicity study was conducted with isavuconazole, as its UV-spectra are comparable with isavuconazonium, isavuconazole is also not considered to be phototoxic. This is further supported by the absence of signs of phototoxicity or photosensitisation in clinical studies.

Impurities

Twelve identified impurities may occur in the drug substance at NMT $\geqslant$0.15%. The safety of these impurities has been evaluated by their presence in the batches used in the repeated-dose and reproduction toxicity studies. These impurities have also been evaluated for genotoxic potential. BAL19714 showed an alert for genotoxicity by DEREK analysis. It was positive in a bacterial reverse mutation assay (Ames II test) with the positive response being more prominent in the absence than in presence of metabolic activation. The proposed limit of 100 ppm of this impurity in the drug substance is agreed by Thai FDA, following the approach of the ICH guideline M7 on mutagenic impurities, At the proposed maintenance dose of 372.6 mg isavuconazonium sulfate per day ($\approx$200 mg isavocunazole), the limit of 100 ppm would lead to a daily intake of 37 µg of this impurity. This intake is lower than the calculated acceptable intakes of 200 µg of a genotoxic impurity if the treatment is administered no longer than 6 months and 100 µg if administered no longer than 12 months.

A mutagenic potential was also identified for BAL17699 and BAL17478. These compounds are limit controlled to <1 ppm and, as such would result in administration of less than the threshold for concern (TTC) level of 1.5 µg/day.

The impurities BAL20019, BAL30655, BAL19875 and BAL20027 showed no structural alert for mutagenicity in DEREK analyses. Based on this information, it is concluded that these impurities can be considered to be non-mutagenic (class 5).

The impurity BAL8728 is identical to metabolite M5, which generated by the cleavage of isavuconazonium by plasma esterases to isavuconazole. This impurity had no genotoxic alerts in the DEREK analysis.

The impurities BAL30145, BAL31265 and BAL4815 are qualified by the toxicity studies impurity profile of toxicological batches used in the repeated-dose and reproduction toxicity studies.

Other impurities in the drug substance include BAL16173 and BAL17702, which are starting materials, and the drug substance impurities BAL19715 (chloromethyl-pyridine impurity of BAL8557), BAL31264, BAL31265, diisopropylurea and 2-butenal. The proposed limits of these impurities in the drug substance have been adequately justified and were agreed by Thai FDA.

3.2.4. Discussion on non-clinical aspects

The results of pharmacology and pharmacokinetics profile have been presented in a satisfactory manner.

The carcinogenicity studies of isavuconazonium sulfate have not yet been completed. The protocols of Study [B-7854] and [B-7855] are submitted. The studies have started since late April 2017. The result of toxicology besides carcinogenicity is satisfy.

3.2.5. Conclusion on non-clinical aspects

Based on the information in dossier, the non-clinical part of isavuconazonium sulfate is acceptable and appropriate.

The remaining concern on carcinogenicity missing data, the applicant is requested to submit the complete carcinogenicity studies report as post-approval.

3.3. Clinical aspects

3.3.1. Tabular Listing of All Clinical Studies

Table 1 Tabular Listing of All Clinical Studies: Completed

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Mass Balance Studies								
PK	9766-CL-0016	Evaluate the PK of [cyano-^{14}C]BAL8557 including routes of excretion and extent of metabolism, identify metabolic profile of BAL4815 in plasma, urine and/or feces, and evaluate safety/tolerability	Phase 1, open-label, one-period, single-dose, mass balance study	radiolabeled BAL8557: 200 mg administered po	7	Healthy male volunteers	Single dose, study release on days 22-29	Completed; Full
PK	9766-CL-0050	Evaluate the PK of [^{14}C]BAL8728 and BAL4815 including routes of excretion and extent of metabolism, identify metabolic profile of BAL8728 in plasma, urine and/or feces, and evaluate safety/tolerability	Phase 1, open-label, one-period, single-dose, mass balance study	radiolabeled BAL8557: 200 mg administered *iv*, 1 hour infusion	6	Healthy male volunteers	Single dose, study release on days 4-9	Completed; Full
Biopharmaceutic Studies								
BA	WSA-CP-010 (9766-CL-0010)/ Germany	BA, safety/tolerability	Phase 1, randomized, open-label, 2-treatment crossover study	IZs, equivalent to ISA: 400 mg oral capsule; fasted IZs, equivalent to ISA: 400 mg *iv* over 2 hr; fasted	14	Healthy male volunteers	Single dose each treatment followed by a 42-day washout period between crossover	Completed; Full
BA, FE	9766-CL-0013 (BAP00382)/ Switzerland	PK, FE, BA (Isavuconazole hydrochloride capsules or liquid concentrate) and safety/tolerability	Phase 1, randomized, open-label, parallel-group study	ISA HCL: 400 mg; fasted; oral capsule ISA HCL: 400 mg; fed; oral capsule ISA HCL: 400 mg; fasted; liquid concentrate (oral) ISA HCL: 400 mg fed; liquid concentrate (oral)	Capsule fasted: 6 Capsule fed: 6 Liquid concentrate fasted: 7 Liquid concentrate fed: 5	Healthy male volunteers	Single dose	Completed; Full
FE	WSA-CP-019 (9766-CL-0015)/ Germany	FE, PK, safety/tolerability	Phase 1, randomized, open-label, 2-treatment crossover study	IZs, equivalent to ISA: 400 mg oral capsule; fed - fasted or fasted - fed	26	Healthy male volunteers	Single dose each crossover period, 42-day washout between treatments	Completed; Full
Human Pharmacokinetic Studies (SAD and MAD)								
PK	WSA-CP-001 (9766-CL-0001)/ Switzerland	PK, safety/tolerability, SAD	Phase 1, randomized, double-blind, placebo-controlled, single ascending dose study	IZc, equivalent to ISA, or Placebo: 100, 200 or 400 mg, oral capsule; fasted	IZc: 15 Placebo: 8	Healthy male volunteers	Single dose	Completed; Full
PK	WSA-CP-002 (9766-CL-0002)/ Germany	PK, safety/tolerability, SAD	Phase 1, randomized, double-blind, placebo-controlled, single ascending dose study	IZc, equivalent to ISA, or Placebo: 40, 80 or 160 mg; iv (1-h infusion); fed	IZc: 18 Placebo: 6	Healthy male volunteers	Single dose	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	WSA-CP-003 (9766-CL-0003)/ Germany	PK, 24-hr urinary ratio of 6-beta-hydroxycortisol/cortisol over time and safety/tolerability, MAD	Phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose study	IZc, equivalent to ISA, or Placebo: 200 mg loading dose plus 100 mg maintenance dose (qd) or 100 mg loading dose plus 50 mg maintenance dose (qd) oral capsule; fasted IZc, equivalent to ISA, or Placebo: 200 mg loading dose plus 100 mg maintenance dose (qd) or 100 mg loading dose plus 50 mg maintenance dose (qd); iv (1-h infusion); fasted	IZc (po): 12 IZc (iv): 12 Placebo (po): 4 Placebo (iv): 4	Healthy male volunteers	IZc capsule (qd) for 21 days (days 1 to 21) or iv for 14 days (days 1 to 14)	Completed; Full

Human Pharmacokinetic Studies (Special Populations - Intrinsic Factors)								
PK	9766-CL-0041/ US	PK, safety/tolerability by age and sex	Phase 1, open-label, single-dose, parallel group study	IZs, equivalent to ISA: 200 mg oral capsule	48 Non-elderly: 24 (M 12, F 12) Elderly: 24 (M 12, F 12)	Healthy non-elderly and elderly male and female volunteers	Single dose	Completed; Full
PK	WSA-CP-008 (9766-CL-0008)/ Hungary	PK and safety/tolerability in hepatic impairment (oral vs iv), and metabolism of lidocaine to MEGX	Phase 1, open-label, single-dose, parallel group study	IZs, equivalent to ISA: 100 mg oral capsule IZs, equivalent to ISA: 100 mg iv over 2 h Lidocaine hydrochloride : 1 mg/kg (iv) (3-min infusion)	48 (16 healthy, 16 mild and 16 moderate hepatic impairment)	Healthy male and female volunteers and subjects with mild to moderate hepatic impairment due to liver cirrhosis caused by alcohol abuse	Single dose	Completed; Full
PK	WSA-CP-018 (9766-CL-0014)/Ukraine	PK and safety/tolerability in hepatic impairment (oral vs iv) and metabolism of lidocaine to MEGX	Phase 1, open-label, single-dose, parallel group study	IZs, equivalent to ISA: 100 mg oral capsule IZs, equivalent to ISA: 100 mg iv (2-h infusion Lidocaine hydrochloride 1 mg/kg iv (3-min infusion)	48 Healthy: 16 Subjects with mild liver cirrhosis: 16 Subjects with moderate liver cirrhosis: 16	Healthy volunteers and subjects with mild to moderate hepatic impairment due to liver cirrhosis caused by chronic hepatitis B and/or C	Single dose	Completed; Full
PK	9766-CL-0018	**Part 1**: Evaluate effect of ESRD on PK of BAL4815 and BAL8728 relative to subjects with normal renal function, establish if BAL4815 and BAL8728 are dialyzable and safety/tolerability **Part 2**: Evaluate effect of mild, moderate and severe renal impairment on PK of BAL4815 and BAL8728, and evaluated safety/tolerability relative to healthy subjects with normal renal function	Phase 1, open-label, 2-part, parallel group study comparing effect of renal impairment on PK and safety/tolerability of ISA	IZs, equivalent to ISA: 200 mg iv, infused over 1 hour	49 Part 1: 20 Healthy: 9 Subjects with ESRD: 11 Part 2: 29 Healthy: 8 Subjects with Renal Impairment: 21	Healthy volunteers with normal renal function, ESRD, and mild, moderate and severe renal impairment	**Part 1**: Single dose on day 1 of Part 1, and on day 15 for ESRD subjects. Study period of 18 days **Part 2**: Single dose on day 1 of 13-day study period	Completed; Full
PK	9766-CL-0038	Evaluate PK and safety/tolerability of BAL4815 and BAL8728 after single dose and steady-state administration of IZs in healthy Chinese subjects	Phase 1, open-label, single dose (crossover) and multiple dose study of safety and PK of IZs in healthy Chinese volunteers	**Part 1**: IZs, equivalent to ISA: 200 mg po or iv on day 1 of each treatment period (crossover design) **Part 2**: IZs, equivalent to ISA: 200 mg tid for 2 days followed by qd for 10 days administered po or iv	36 **Part 1**: 12 iv to po: 6 po to iv: 6 **Part 2**: 24 iv: 12 po: 12	Healthy Chinese volunteers	**Part 1**: Single dose on day 1 of each 15-day study period (crossover design) followed by a 2-week washout. **Part 2**: IZs administration for first 12 days of 26-day study period	Completed; Full
Human Pharmacokinetic Studies (Drug-drug Interactions)								
PK/DDI	WSA-CP-005 (9766-CL-0005)/The Netherlands	DDI and safety/tolerability of IZs and ketoconazole or rifampicin	Phase 1, open-label, multiple-dose sequential dosing study	Ketoconazole: 200 mg (qd) on days 36-71; oral tablet Rifampin: 600 mg (qd) on days 36-71; oral tablet IZs, equivalent to ISA: 400 mg on day 1 and 100 mg on days 2-14; 400 mg on day 44 and 100 mg on days 45-57; oral capsule	52 (IZs + ketoconazole 26; IZs + rifampin 26)	Healthy male volunteers	IZs (qd) for 2 weeks followed by a 3-week washout period, then a 36-day treatment period (days 36-71) including co-administration of ketoconazole or rifampin with IZs (days 44-57)	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	WSA-CP-006 (9766-CL-0006)/US	DDI, PD (PT and PT AUC) and safety/tolerability of IZs and warfarin	Phase 1, open-label multiple-dose, sequential dosing study	Warfarin: 10 mg (qd) on days 1 and 29; oral tablet IZs, equivalent to ISA: 400 mg on day 9 and 100 mg qd on days 10-36; oral capsule	12	Healthy male volunteers	Single dose of warfarin followed by a 1-week washout period, then a 28-day treatment period (days 9 to 36)	Completed; Full
PK/DDI	WSA-CP-007 (9766-CL-0007)/ Germany	DDI and safety/tolerability of IZs and tacrolimus or cyclosporine	Phase 1, open-label multiple-dose sequential dosing study	Tacrolimus: 5 mg on days 1 and 22; oral capsule Cyclosporine: 300 mg on days 1 and 22; oral capsule IZs, equivalent to ISA: 400 mg on day 8 and 100 mg (qd) on days 9-27; oral capsule	52 (IZs + cyclosporine 26; IZs + tacrolimus 26)	Healthy male volunteers	Single dose cyclosporine or tacrolimus followed by a 1-week washout period, and a 20-day treatment period (days 8 to 27)	Completed; Full
PK/DDI	WSA-CP-009 (9766-CL-0009)/ Germany	DDI and safety/tolerability of IZc and ketoconazole, indinavir or cyclosporine	Phase 1, open-label, single-dose, sequential dosing crossover study	Group A: IZc, equivalent to ISA: 400 mg on days 1 and 36; oral capsule Ketoconazole: 200 mg on day 36; oral tablet Group B: Indinavir: 800 mg on days 1 and 15; oral capsule IZc, equivalent to ISA: 400 mg on day 15; oral capsule Group C: Cyclosporine: 300 mg on days 1 and 15; oral capsule IZc, equivalent to ISA: 400 mg on day 15; oral capsule	36 (IZc + ketoconazole 12; IZc + indinavir 12; IZc + cyclosporine 12)	Healthy male volunteers	Single dose each treatment (day 1) followed by 5-week washout, co-administration of IZc and ketoconazole for one day (day 36) or 2-week washout, co-administration of IZc with indinavir or cyclosporine for 1 day (day 15)	Completed; Full
PK/DDI	WSA-CP-011 (9766-CL-0011)/ France	DDI and safety/tolerability of IZs and omeprazole, and detectable presence of IZs and cleavage product (BAL8728) in urine at steady state	Phase 1, open-label, multiple-dose, single sequence study	Omeprazole: 40 mg on days 1 and 23; oral capsule IZs, equivalent to ISA: 200 mg tid on days 9-10, 200 mg qd on days 11-23; oral capsule	27	Healthy male volunteers	Single dose of omeprazole on day 1 followed by 1-week washout, 15-day treatment period (days 9 to 23) including co-administration of omeprazole and IZs on day 23	Completed; Full
PK/DDI	WSA-CP-012 (9766-CL-0012)/ Germany	DDI and safety/tolerability of IZs and sirolimus	Phase 1, open-label multiple-dose, sequential dosing study	Sirolimus: 1 mg on days 1 and 35; oral tablet IZs, equivalent to ISA: 200 mg tid on days 22-23; 200 mg qd on days 24-44; oral capsule	26	Healthy male volunteers	Single dose of sirolimus followed by 3-week washout, 23-day treatment period (days 22 to 44)	Completed; Full
PK/DDI	9766-CL-0020/US	DDI and safety/tolerability of IZs and sirolimus	Phase 1, open-label, sequential dosing study	Sirolimus: 2 mg on days 1 and 26; oral tablet IZs, equivalent to ISA: 200 mg tid on days 22-23, and 200 mg qd on days 24-34; oral capsule	22	Healthy volunteers	Single dose on day 1 followed by a 21-day washout period, then a 13-day treatment period (days 22-34) including co-administration of sirolimus and IZs on day 26	Completed; Full
PK/DDI	9766-CL-0021/US	DDI and safety/tolerability of IZs and tacrolimus	Phase 1, open-label, sequential dosing study	Tacrolimus: 5 mg on days 1 and 20; oral capsule IZs, equivalent to ISA: 200 mg tid on days 16-17, and 200 mg qd on days 18-28; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 15-day washout, then a 13-day treatment period (days 16-28) including co-administration of tacrolimus and IZs on day 20	Completed; Full
PK/DDI	9766-CL-0022/US	DDI and safety/tolerability of IZs and cyclosporine	Phase 1, open-label, sequential dosing study	Cyclosporine: 300 mg on days 1 and 15; oral capsule IZs, equivalent to ISA: 200 mg tid on days 11-12, and 200 mg qd on days 13-18; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 10-day washout, then an 8-day treatment period (days 11-18) including co-administration of cyclosporine and IZs on day 15	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	9766-CL-023/ US	DDI and safety/tolerability of IZs and midazolam	Phase 1, open-label, sequential dosing study	Midazolam: 3 mg on days 1 and 12; syrup (oral) IZs, equivalent to ISA: 200 mg tid on days 3-4 and 200 mg qd on days 5-13; oral capsule	23	Healthy volunteers	Single dose of midazolam syrup on day 1, followed by a 1-day washout period, then a 10-day treatment period (days 3 to 13) including co-administration of midazolam and IZs on day 12	Completed; Full
PK/DDI	9766-CL-0024/ US	DDI and safety/tolerability of IZs and prednisone	Phase 1, open-label, sequential dosing study	Prednisone: 20 mg on days 1 and 9; oral tablet IZs, equivalent to ISA: 200 mg tid on days 5-6, and 200 mg qd on days 7-10; oral capsule	21	Healthy volunteers	Single dose on day 1, followed by a 4-day washout, then a 6-day treatment period (days 5-10) including co-administration of prednisone and IZs on day 9	Completed; Full
PK/DDI	9766-CL-0025/ US	DDI and safety/tolerability of IZs and digoxin	Phase 1, open-label, sequential dosing study	Digoxin: 0.5 mg on days 1 and 19; oral tablet IZs, equivalent to ISA: 200 mg tid on days 15-16, and 200 mg qd on days 17-26; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 14-day washout, then a 12-day treatment period (days 15-26) including co-administration of digoxin and IZs on day 19	Completed; Full
PK/DDI	9766-CL-0027/US	DDI and safety/tolerability of IZs and methadone	Phase 1, open-label, sequential dosing study	Methadone: 10 mg on days 1 and 20; oral tablet IZs, equivalent to ISA: 200 mg tid on days 16-17, and 200 mg qd on days 18-28; oral capsule	23	Healthy volunteers	Single dose on day 1, followed by a 15-day washout, then a 13-day treatment period (days 16-28) including co-administration of methadone and IZs on day 20	Completed; Full
PK/DDI	9766-CL-0030/US	DDI and safety/tolerability of IZs and MMF	Phase 1, open-label, sequential dosing study	MMF: 1 g on days 1 and 13; oral tablet IZs, equivalent to ISA: 200 mg tid on days 9-10, and 200 mg qd on days 11-16; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 7-day washout, then an 8-day treatment period (days 9-16) including co-administration of MMF and IZs on day 13	Completed; Full
PK/DDI	9766-CL-0031/US	DDI and safety/tolerability of IZs and EE and NE	Phase 1, open-label, sequential dosing study	Oral Contraceptive: 35 mcg EE and 1 mg NE on days 1 and 13; oral tablet IZs, equivalent to ISA: 200 mg tid on days 9-10, and 200 mg qd on days 11-16; oral capsule	24	Healthy postmenopausal female volunteers	Single dose on day 1, followed by an 8-day washout, then an 8-day treatment period (days 9-16) including co-administration of oral contraceptive and IZs on day 13	Completed; Full
PK/DDI	9766-CL-0033/US	DDI, PD and safety/tolerability of IZs and warfarin	Phase 1, open-label, sequential dosing study	Warfarin: 20 mg on days 1 and 20; oral tablet IZs, equivalent to ISA: 200 mg tid on days 16-17, and 200 mg qd on days 18-28; oral capsule	21	Healthy volunteers	Single dose on day 1, followed by an 15-day washout, then an 13-day treatment period (days 16-28) including co-administration of warfarin and IZs on day 20	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	9766-CL-0035/US	DDI and safety/tolerability of IZs and LPV and RTV	Phase 1, randomized, open-label, two-part, 3-arm parallel group study	**Part 1, Arm 1**: IZs, equivalent to ISA: 100 mg tid on days 1-2 and 100 mg qd on days 3-13; oral capsule **Arm 3**: IZs, equivalent to ISA: 100 mg tid on days 1-2 and 100 mg qd on days 3-13; oral capsule LPV/RTV: 400/100 mg bid on days 1-13; oral tablet **Part 2, Arm 1**: IZs, equivalent to ISA: 200 mg tid on days 1-2 and 200 mg qd on days 3-13 oral capsule **Arm 2**: LPV/RTV: 400/100 mg bid on days 1-12 and 400/100 mg qd on day 13; oral tablet **Arm 3**: IZs, equivalent to ISA: 200 mg tid on days 1-2 and 200 mg qd on days 3-13; oral capsule LPV/RTV: 400/100 mg bid on days 1-13; oral tablet	**Part 1:** **Arm 1**: IZs 6 **Arm 3**: IZs + LPV/RTV: 7 **Part 2:** **Arm 1**: IZs 18 **Arm 2**: LPV/RTV: 19 **Arm 3**: IZs + LPV/RTV: 18	Healthy volunteers	Treatment period days 1-13	Completed; Full
PK/DDI	9766-CL-0040/US	DDI and safety/tolerability of IZs and ketoconazole	Phase 1, randomized, open-label, two-arm, parallel group study	**Arm 1**: IZs, equivalent to ISA: 200 mg on day 1; oral capsule **Arm 2**: IZs, equivalent to ISA: 200 mg on day 4; oral capsule Ketoconazole: 200 mg bid on days 1-24; oral tablet	**Arm 1:** IZs: 12 **Arm 2:** IZs + ketoconazole: 12	Healthy volunteers	**Arm 1:** Single dose day 1 **Arm 2:** Treatment for 24 days (days 1-24) including co-administration of IZs and ketoconazole on day 4	Completed; Full
PK/DDI	9766-CL-0042/US	DDI and safety/tolerability of IZs and DXM	Phase 1, randomized, open-label, sequential dosing study	DXM: 30 mg on days 1 and 10; oral capsule IZs, equivalent to ISA: 200 mg tid on days 6-7, and 200 mg qd on days 8-12; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by 5-day washout, then a 7-day treatment period (days 6-12) including co-administration of DXM and IZs on day 10	Completed; Full
PK/DDI	9766-CL-0043/US	DDI and safety/tolerability of IZs and atorvastatin	Phase 1, randomized, open-label, sequential dosing study	Atorvastatin: 20 mg on days 1 and 12; oral tablet IZs, equivalent to ISA: 200 mg tid on days 8-9, and 200 mg qd on days 10-15; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 7-day washout, then an 8-day treatment period (days 8-15), including co-administration of atorvastatin and IZs on day 12	Completed; Full
PK/DDI	9766-CL-0044/US	DDI and safety/tolerability of IZs and bupropion	Phase 1, randomized, open-label, sequential dosing study	Bupropion: 100 mg on days 1 and 15; oral tablet IZs, equivalent to ISA: 200 mg tid on days 8-9, and 200 mg qd on days 10-20; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 7-day washout, then a 13-day treatment period (days 8-20), including co-administration of bupropion and IZs on day 15	Completed; Full
PK/DDI	9766-CL-0051	DDI and safety/tolerability of IZs and metformin	Phase 1, open-label, sequential dosing study	Metformin: 850 mg po on days 1 and 8 IZs, equivalent to ISA: 200 mg tid po on days 4-5, and 200 mg qd po on days 6-9	24	Healthy volunteers	Single dose on day 1, followed by a 3-day washout, then a 6-day treatment period (days 4-9), including co-administration of Metformin and IZs on day 8	Completed; Full
PK/DDI	9766-CL-0052	DDI and safety/tolerability of IZs and MTX	Phase 1, open-label, sequential dosing study	MTX: 7.5 mg po on days 1 and 8 IZs, equivalent to ISA: 200 mg tid po on days 4-5, and 200 mg qd po on days 6-9	24	Healthy male volunteers	Single dose on day 1, followed by a 3-day washout, then a 6-day treatment period (days 4-9), including co-administration of MTX and IZs on day 8	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	9766-CL-0053	DDI and safety/tolerability of ISA and repaglinide and caffeine	Phase 1, open-label, sequential dosing study	Repaglinide: 0.5 mg on day 1, and 0.5 mg on day 14; oral tablet Caffeine: 200 mg on day 3, and 200 mg on day 16; oral tablet IZs, equivalent to ISA: 200 mg tid on days 5 and 6, and 200 mg qd on days 7-17; oral capsule	24	Healthy volunteers	Single dose of repaglinide on day 1, followed by a single dose of caffeine on day 3, followed by IZs administration (tid on days 5 and 6 and qd on days 7-17) including co-administration of repaglinide with IZs on day 14 and of caffeine with IZs on day 16	Completed; Full
PK/DDI	9766-CL-0054	DDI and safety/tolerability of ISA and esomeprazole	Phase 1, randomized, open-label, 2-arm parallel group study	**Arm 1**:IZs, equivalent to ISA: 200 mg tid on days 1 and 2, and 200 mg qd on days 3, 4 and 5; oral capsule **Arm 2**: Esomeprazole 40 mg qd days 1-10; oral capsule IZs, equivalent to ISA: 200 mg tid on days 6 and 7, and 200 mg qd on days 8, 9 and 10; oral capsule	24 **Arm 1**: IZs: 12 **Arm 2**: esomeprazole + IZs: 12	Healthy volunteers	**Arm 1**: IZs on days 1 to 5 (tid on days 1 and 2, qd on days 3-5) **Arm 2**: Single dose of esomeprazole on days 1 to 10 including co-administration with IZs on days 6 and 7 (tid) and on days 8, 9 and 10 (qd)	Completed; Full
Human Pharmacodynamic Studies								
PD/PK	WSA-CP-004 (9766-CL-0004)/ The Netherlands	PK, safety/tolerability, and cardiac repolarization using QTcI	Phase 1, randomized, double-blind, placebo- and active-controlled, parallel group, multiple-dose study	**IZs, equivalent to ISA, or Placebo:** 400, 300 and 200 mg (qd) on days 4, 3 and 6, respectively; 100 mg qd on days 7-10; 300, 250 and 200 mg (qd) on days 12, 13 and 14, respectively; and 150 mg (qd) on days 15-18; oral capsule **IZs, equivalent to ISA, or Placebo:** 100 and 150 mg (qd) on days 11 and 19, respectively; iv (1 h) **Moxifloxacin:** 400 mg (qd) on day 1; oral capsule	82 IZs + Moxifloxacin: 41 Placebo + Moxifloxacin: 41	Healthy volunteers	Single dose moxifloxacin followed by 2-day washout period, 2 consecutive treatments 8 days each (days 4 to 19)	Completed; Full
PD/PK	9766-CL-0017/ US	PK, safety/tolerability and QTcF	Phase 1, randomized, double-blind, placebo- and active-controlled, parallel group study	**Group 1**: IZs, equivalent to ISA: 200 mg tid on days 1-2, and 200 mg qd on days 3-13, oral capsule **Group 2**: IZs, equivalent to ISA: 200 mg tid on day 1-2, and 600 mg qd on day 3-13; oral capsule **Group 3**: Placebo: tid on days 1-2, and qd on days 3-13; oral capsule **Group 4**: Placebo: tid on days 1-2, and qd on days 3-12; oral capsule Moxifloxacin: 400 mg on day 13, oral tablet	161 **Group 1**: IZs 41 **Group 2**: IZs 40 **Group 3**: Placebo 40 **Group 4**: Placebo + Moxifloxacin 40	Healthy volunteers	13 days	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human (Patient) PK and Efficacy and Safety Studies								
E/S	WSA-CS-001 (9766-CL-0101)/ South Africa	DDI and safety/tolerability and relapse rate of IZc and fluconazole in EC	Phase 2, randomized, multicenter, double-blind, parallel group study	**Group A:** IZc, equivalent to ISA: 200 mg on day 1, 50 mg qd on day 2 to EOT; oral capsule **Group B:** IZc, equivalent to ISA: 400 mg on day 1, 400 mg on days 7, 14, 21; oral capsule **Group C:** IZc, equivalent to ISA: 400 mg on day 1, 100 mg (qd) on day 2 to EOT; oral capsule **Group D:** fluconazole: 200 mg on day 1, 100 mg (qd) on day 2 to EOT; oral capsule	IZc: 122 (Group A 40, Group B 40, Group C 42) Fluconazole (Group D): 38	Male and postmenopausal female patients with uncomplicated EC	Single dose of IZc or fluconazole for at least 14 days of treatment (days 1 to EOT), or a single dose of IZc (day 1) with a 5-day washout period between the next doses (days 7, 14 and 21)	Completed; Full
E/S	WSA-CS-002 (9766-CL-0102)/ Germany	PK, efficacy and safety/tolerability of 2 escalating dose regimens of IZs in patients with neutropenia who are undergoing chemotherapy for AML	Phase 2, randomized, open-label, sequential group comparison of 2 dose levels of IZs	**Low Dose:** IZs, equivalent to ISA: 400/200/200 mg on day 1 and 200/200 mg on day 2 and 200 mg/day to EOT; iv **High Dose:** IZs, equivalent to ISA: 800/400/400 mg on day 1 and 400/400 mg on day 2 and 400 mg/day to EOT; iv	IZs: 23 (Low dose: 11; High dose: 12)	Male and female patients > 18 years old undergoing therapy for AML	Up to 28 days	Completed; Full
E/S	WSA-CS-003 (9766-CL-0103)	Efficacy and safety of IZs (po vs iv)	Phase 3, open-label study of IZs	IZs, equivalent to ISA: (iv and po): 200 mg (q8h) on days 1-2 and 200 mg (q12h) on day 3 to EOT	146 patients (59 with renal impairment, 87 with no renal impairment)	Male and female patients ≥ 18 years old with IA and renal impairment or with IFD caused by rare moulds, yeasts or dimorphic fungi	Up to 180 days (additional duration allowed in amendment 4)	Completed; Full
E/S	WSA-CS-004 (9766-CL-0104)	Efficacy and safety of IZs (iv and po) vs VRC (iv and po)	Phase 3, randomized, double-blind noninferiority study of IZs vs VRC	IZs, equivalent to ISA: (iv and po): 200 mg (q8h) on days 1-2 and 200 mg (q12h) on day 3 to EOT or VRC: 6 mg/kg iv (q8h) on day 1, 4 mg/kg iv (q8h) on day 2, 4 mg/kg iv (q12h) or 200 mg po (q12h) on day 3 to EOT	516 (SAF) ISA: 257 VRC: 259	Male and female patients ≥ 18 years old with IA	Up to 84 days	Completed; Full

BAL8728: inactive cleavage product; DDI: drug-drug interaction; DXM: dextromethorphan; EC: esophageal candidiasis; EE: ethinyl estradiol; EOT: end of treatment; E/S: efficacy and safety; ESRD: end stage renal disease; FE: food effect; HV: healthy volunteers; ISA: isavuconazole; ISA HCL: isavuconazole hydrochloride; IZc: isavuconazonium hydrochloride; IZs: isavuconazonium sulfate; LPV: lopinavir; MAD: multiple ascending dose; MEGX: monoethylglycinexylidide; MMF: mycophenolate mofetil; NE: norethindrone; PD: pharmacodynamics; PK: pharmacokinetics; PT: prothrombin time; PT AUC: prothrombin time area under the curve; RTV: ritonavir; SAD: single ascending dose; SAF: safety population.

3.3.2. Pharmacokinetics

Following intravenous administration, isavuconazonium is rapidly and quantitatively converted to the active moiety isavuconazole and its cleavage product BAL8728 by enzymatic hydrolysis. After oral administration, isavuconazonium predominantly undergoes chemical hydrolysis in the gastrointestinal lumen and is not detected in plasma. The oral bioavailability of isavuconazole was 98%, and the oral formulation of isavuconazole can be used in place of the intravenous formulation at any time with or without food.

Isavuconazole is highly protein bound (> 99%), primarily to albumin, and is extensively distributed throughout the body, with a mean volume of distribution of approximately 450 L in healthy subjects and patients. Isavuconazole clearance in healthy subjects and patients was low (mean 2.4 L/hr), consistent with a long mean terminal half-life of approximately 130 hours.

1. Enantiomer interconversion

Isavuconazonium contains three chiral centers. The compound exists as a racemate (1:1) of two diastereomers (designated F1 and F2) in the solid state. Both diastereomers are converted to the same active moiety, isavuconazole. *In vitro*, there were small differences in the hydrolysis rate between the diastereomers in human plasma (mean t1/2 of 1.3 and 0.65 min for F1 and F2, respectively), but these differences are unlikely to significantly affect the pharmacokinetic profiles of the active drug, isavuconazole. During the cleavage process, the stereochemistry at both chiral centers of isavuconazole remains intact. Isavuconazole is a single enantiomer with 7R, 8R.

2. Absorption and exposure

2.1. Isavuconazole after intravenous and oral administration

After intravenous administration, exposure to the active moiety isavuconazole increased approximately dose-proportionally, with maximum plasma concentration (C_{max}) reached 1 hour after single and multiple dosing. After oral administration of single and multiple doses, isavuconazole generally reached C_{max} in 2 to 3 hours. For both routes of administration, isavuconazole concentrations were generally measurable in plasma for at least 480 hours post-dose. The mean absolute bioavailability of isavuconazole after a single oral dose of isavuconazonium sulfate (equivalent to 400 mg isavuconazole) was 98%, demonstrating complete absorption.

2.2. Isavuconazonium and BAL8728 after intravenous administration

Following intravenous administration of isavuconazonium, maximum plasma concentrations of the inactive cleavage product BAL8728 and the prodrug were detectable during infusion, and declined rapidly following the end of administration. Isavuconazonium concentrations were below the lower limit of quantification within 1.25 hours after the start of a 1-h infusion.

After intravenous administration, BAL8728 concentrations were quantifiable in some subjects up to 8 hours after the start of infusion, with mean tmax values being reached towards the end of infusion. The total exposure of BAL8728 (based on AUClast) was approximately 1.3% of that of isavuconazole after intravenous administration.

2.3. Isavuconazonium and BAL8728 after oral administration

The inactive cleavage product BAL8728 was undetectable in plasma, or close to the LLOQ in plasma, of healthy subjects after oral administration of isavuconazonium. No significant concentrations of the prodrug isavuconazonium or the inactive cleavage product BAL8728 were detectable in plasma after oral administration.

3. Distribution

Isavuconazole is extensively distributed, with a steady-state volume of distribution (V_{ss}) of approximately 450 L after intravenous administration. Isavuconazole is highly (> 99%) protein-bound, predominantly to albumin.

4. Metabolism

In vitro studies demonstrated that isavuconazonium in blood is rapidly hydrolyzed to isavuconazole by esterases, predominately by butyrylcholinesterase. Isavuconazole is a sensitive CYP3A substrate.

Following single doses of [cyano-14C] isavuconazonium and [pyridinylmethyl-14C] isavuconazonium in humans, a number of minor metabolites were identified in addition to the active moiety isavuconazole and the inactive cleavage product BAL8728. Except for the active moiety, no individual metabolite was observed with an AUC > 10% of the parent.

In vivo studies indicated that CYP3A4, CYP3A5, and subsequently uridine diphosphate-glucuronosyltransferases (UGT) are involved in the metabolism of isavuconazole.

5. Elimination

Isavuconazonium is eliminated by chemical hydrolysis and/or plasma esterases to isavuconazole and BAL8728. The isavuconazonium half-life was not estimated in pharmacokinetic studies because isavuconazonium plasma concentrations were essentially undetectable after oral administration, and typically only quantifiable during the infusion interval. Once the infusion was stopped, isavuconazonium plasma concentrations decreased rapidly and were generally undetectable within 30 minutes post-infusion. BAL8728 had a terminal half-life of approximately 1 hour after intravenous administration.

Isavuconazole plasma concentrations declined in a biphasic manner after both oral and intravenous administration of isavuconazonium. Additional peaks in plasma concentrations were often observed in the declining phase of individual isavuconazole plasma concentration-time profiles, with these secondary peaks usually occurring about 6 to 12 hours post-dose, typically coinciding with a meal or snack. The population mean half-life of isavuconazole was approximately 130 hours for both routes of administration across a range of isavuconazonium doses, suggesting that the elimination process of isavuconazole is not dependent on dose or administration route. Isavuconazole has a low clearance of approximately 2.4

L/h, which represents < 10% of liver plasma flow; the hepatic extraction ratio of isavuconazole must therefore be low, in agreement with the observed high oral bioavailability of isavuconazole.

6. Excretion

Following a single oral solution dose of [cyano-14C]-labeled isavuconazonium sulfate (target 200 mg eq. of isavuconazole) in study 9766-CL-0016, a mean of 46.1% of the administered radioactive dose was recovered in feces, and 45.5% was recovered in urine through the last collection interval. Most (81.6%) of the administered radioactivity was recovered in the first 312 hours post-dose. The overall mean recovery of radioactivity in urine and feces samples was 91.6% over the 600-hour study, with recovery in individual subjects ranging from 86.3% to 96.7%.

Isavuconazole accounted for the majority of the radioactivity in feces (33% up to 144 hours postdose). The majority of the [cyano-14C]-radioactivity recovered in urine was excreted as metabolites of isavuconazole. In studies 9766-CL-0002 and 9766-CL-0018, renal excretion of isavuconazole itself was less than 1% of the dose administered.

BAL8728 is primarily eliminated by metabolism and renal excretion of the metabolites. Following intravenous administration of [pyridinylmethyl-14C] isavuconazonium sulfate, 95% of the total radioactive dose was excreted in the urine; the major form of urine radioactivity was the oxidative carbamate cleavage metabolite M4 (56% of total dose). In study 9766-CL-0018, renal elimination of intact BAL8728 was less than 1% of the total dose administered.

7. Dose proportionality

The dose proportionality of isavuconazole exposure after oral and intravenous administration of isavuconazonium was explored in several studies in both healthy subjects and patients. The data indicate that there are no relevant deviations from dose proportionality in isavuconazole plasma exposure for either route of administration.

In the second thorough QTc study 9766-CL-0017 in healthy subjects, AUC_{tau} at 600 mg/day was 2.9-fold higher than at 200 mg/day. C_{max} at 600 mg/day was 2.7-fold higher than at 200 mg/day and t_{max} was 1 hour later at the higher dose.

No major deviations from dose-proportionality were observed in patients with uncomplicated esophageal candidiasis in study 9766-CL-0101, who received either a high dose regimen (400 mg eq. on Day 1 followed by 100 mg eq. per day from Day 2 up to Day 21; n=13) or low dose regimen (200 mg eq. on Day 1 followed by 50 mg eq. per day from Day 2 up to Day 21; n=12) of oral isavuconazonium chloride. The GMR for dose-normalized AUC_{tau} and C_{max} were 90% and 85%, respectively, on Day 1, and 116% and 124%, respectively, on Day 14. None of the 90% CIs for the ratios fell entirely within the bioequivalence intervals of 80% to 125%; this may be due to the small sample size and high variability.

Approximately dose-proportional pharmacokinetics of isavuconazole were also observed in patients undergoing chemotherapy for acute myeloid leukemia in study 9766-CL-0102, who received either a high dose regimen (800/400/400 mg eq. Day 1, 400 mg eq. b.i.d. Day 2, and 400 mg eq. Day 3 up to Day 28; n=12) or low dose regimen (400/200/200 mg eq. Day 1, 200 mg eq. b.i.d. Day 2, and 200 mg eq. Day 3 up to Day 28; n=11) of intravenous isavuconazonium sulfate. The GMR for dose-normalized AUCtau and C_{max} on Day 7 was 98% (90% CI: 78%-122%) and 107% (90% CI: 82%-139%), respectively.

8. Accumulation and time-dependency

Assessment of isavuconazole predose trough concentrations in study 9766-CL-0003 indicates that near steady-state conditions of isavuconazole are achieved within 14 days of once daily oral and intravenous dosing of isavuconazonium. This is consistent with an apparent terminal half-life of approximately 130 hours. Mean isavuconazole AUC increased approximately 4- to 5-fold at steady state after once-daily administration relative to single-dose data after maintenance doses of 50 and 100 mg. This estimation is based on a comparison of mean dose-normalized AUC24 on Day 1 and Day 14 (IV)/21 (oral) and assumes approximately dose-proportional pharmacokinetics. Isavuconazole C_{max} was approximately 2- to 3-fold higher at steady state than after a single dose. The prodrug cleavage product BAL8728 did not accumulate after once-daily intravenous doses of isavuconazonium.

To achieve steady-state isavuconazole concentrations more quickly and ensure adequate exposure to treat infection, a loading dose regimen was used in the Phase 3 studies. With the Phase 3 dose regimen (200 mg q8h for 48 hours followed by 200 mg daily), isavuconazole predose plasma concentrations were

predicted to be at or near steady-state on Day 3 with trough levels of approximately 3 µg/mL, which is above the targeted MIC values of 1 to 2 µg/mL.

The time dependency of isavuconazole pharmacokinetic parameters (measured as the ratio of AUC_{tau} at steady state to AUC_{inf} after a single dose) has not been formally assessed in a dedicated study. Based on between-study comparisons of single-dose AUC_{inf} and multiple-dose AUC_{tau} of isavuconazole, there appeared to be no major changes in (apparent) clearance with time following once-daily oral or intravenous dosing of isavuconazonium. Single-dose AUC_{inf} and multiple-dose AUC_{tau} of isavuconazole were comparable after 100 mg eq. single and multiple doses for both routes of administration.

9. Intersubject and intrasubject variability

After oral and intravenous administration to healthy subjects in study 9766-CL-0010 of a single dose of isavuconazonium sulfate, corresponding to isavuconazole 400 mg orally or as a 2-h infusion, intersubject variability in isavuconazole C_{max} was low after both oral (21%) and intravenous (13%) administration. Intersubject variability in isavuconazole AUC_{inf} was moderate (%CV of 37%), and similar for both routes of administration, suggesting that variability in isavuconazole pharmacokinetics is mainly due to differences in disposition.

Based on population pharmacokinetics in patients, intersubject variability for AUC (%CV of 58%) and intrasubject variability (%CV of 45%) were moderate.

10. Special populations

10.1. Patients and healthy subjects

No relevant differences were observed between the clearance of patients and healthy subjects.

10.2. Age, gender

The C_{max} and AUC of isavuconazole following a single oral dose (200 mg eq.) in elderly subjects (≥ 65 years) were similar to those in younger healthy subjects (18 to 45 years) and in female and male healthy subjects. Elderly female subjects exhibited the highest AUC_{inf} values compared with non-elderly females and elderly males. The demographics of these groups was unbalanced; elderly females were essentially Asians, in contrast to the other groups. The increased exposure in elderly females can be attributed to ethnicity rather than to age or gender. No differences in AUC_{inf} were observed between elderly and non-elderly males. Based on the safety profile and pharmacokinetic/pharmacodynamic relationship for antifungal activity of isavuconazole, the differences were not considered clinically significant, and no dose adjustments are required based on age or sex.

The pharmacokinetics of isavuconazole in pediatric patients have not been evaluated.

Population pharmacokinetic modeling was able to adequately describe the isavuconazole plasma concentrations, and was able to determine the effect of age and sex on the pharmacokinetics of isavuconazole. Results indicated that only elderly female subjects had higher exposure than non-elderly subjects due to reduced clearance.

10.3. Race

The population pharmacokinetic analysis of Chinese and healthy Western subjects from Europe, who were predominantly Caucasian, revealed that the nearly 50% higher exposure seen in Chinese subjects compared to Western subjects was essentially due to a reduction in total systemic clearance. Neither BMI nor age played a role in the observed differences. Based on the safety profile and pharmacokinetic/pharmacodynamic relationship for the antifungal activity of isavuconazole, the differences are not considered to be clinically significant; no dose adjustment is required.

10.4. Hepatic impairment

After a single 100 mg dose of isavuconazole was administered to 32 patients with mild (Child-Pugh Class A) hepatic insufficiency, and 32 patients with moderate (Child-Pugh Class B) hepatic insufficiency (16 intravenous and 16 oral patients per Child-Pugh Class), the geometric least squares mean systemic exposure (AUC) increased 64% in the Child Pugh Class A group, and 84% in the Child-Pugh Class B group relative to 32 age- and weight-matched healthy subjects with normal hepatic function. Geometric least squares mean plasma concentrations (C_{max}) were 2% lower in the Child-Pugh Class A group, and 30% lower in the Child-Pugh Class B group.

The population pharmacokinetic evaluation of isavuconazole in healthy subjects and patients with mild and moderate hepatic dysfunction demonstrated that subjects in the mild and moderate hepatic impairment population had 40% and 48% lower isavuconazole clearance values, respectively, than healthy subjects (clearance 2.54 L/hr). As the risk of lack of efficacy with a lower dose is considered greater than the risk of adverse reactions with the standard dose, it is recommended that the standard isavuconazole loading and maintenance dose regimen be used for patients with mild to moderate hepatic impairment, i.e., no dose adjustment is necessary in patients with mild to moderate hepatic impairment.

Isavuconazole has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

10.5. Renal impairment

A population pharmacokinetic analysis in study 9766-PK-0002 of isavuconazole in healthy subjects, and patients with mild, moderate and severe renal impairment and with end-stage renal disease (ESRD), showed that there were no clinically relevant differences in the concentration-time profile of the targeted population.

From the non-compartmental analysis of study 9766-PK-0002, the geometric least squares mean AUC ratios of isavuconazole in patients with mild, moderate or severe renal impairment are similar to those of healthy subjects, which indicates that the decrease in renal clearance in patients with mild, moderate and severe renal impairment had no significant impact on the overall clearance of isavuconazole. In patients with ESRD, the pharmacokinetic parameters of isavuconazole were influenced by the experimental conditions of dosing, either pre- or post-dialysis, that influence intravascular volume, such as intercompartmental fluid shifts (hemodilution postdialysis and hemoconcentration during dialysis). When these intravascular shifts are taken into account, the pharmacokinetics of isavuconazole in ESRD patients do not appear to be significantly altered. Highly-protein-bound (> 99%) isavuconazole is not readily dialyzable, and less than 1% of the administered isavuconazonium dose in the form of isavuconazole was recovered in dialysate fluid. Dialysis is not expected to have any appreciable effects on the pharmacokinetics of isavuconazole (9766-CL-0018).

No dose adjustment is required in patients with mild, moderate or severe renal impairment, or in patients with ESRD. Isavuconazole is not readily dialyzable and extracorporeal therapy cannot be used to treat an overdose.

10.6. Gastric pH, smoking, alcohol consumption

Co-administration of steady-state esomeprazole (40 mg daily for 10 days) with steady-state isavuconazole resulted in a 7.6% increase in AUC_{tau} and a 4.8% increase in the C_{max} of isavuconazole compared to isavuconazole alone. These findings indicate that concomitant medications that alter the gastric pH (including proton-pump inhibitors, H2-receptor antagonists, and antacids) do not significantly affect the pharmacokinetics of isavuconazole.

The effect of smoking and alcohol consumption on isavuconazole exposure has not been evaluated.

11. Drug-drug interaction studies

Drug interaction studies were conducted to investigate the effect of co-administered drugs on isavuconazole and the effect of isavuconazole on the pharmacokinetics of co-administered drugs.

11.1. Effect of other drugs on the pharmacokinetics of isavuconazole

Isavuconazonium sulfate is rapidly and quantitatively converted to the active moiety isavuconazole by plasma esterases. While esterase inhibitors may slow the conversion of isavuconazonium to the active moiety, the conversion of isavuconazonium to isavuconazole is so rapid that esterase inhibitors are unlikely to have a clinically relevant effect.

Isavuconazole is a sensitive substrate of CYP3A. CYP3A inhibitors or inducers may alter the plasma concentrations of isavuconazole. Isavuconazole is a moderate inhibitor of CYP3A, and a mild inhibitor of P-glycoprotein (P-gp) and Organic Cation Transporter 2 (OCT2).

11.1.1. Strong CYP3A inhibitors

The geometric least squares mean C_{max} of isavuconazole was increased by approximately 9% and AUC_{inf} by approximately 422% when isavuconazole was administered as a single 200 mg oral dose after multiple twice daily 200 mg oral doses of ketoconazole. Co-administration of isavuconazole and ketoconazole is contraindicated.

When twice-a-day, multiple dose lopinavir/ritonavir (400/100 mg) was given in combination with multiple doses of isavuconazole (200 mg/day), the AUCtau and C_{max} of isavuconazole increased by 96% and 74%, respectively, compared to isavuconazole alone. The geometric least squares mean AUCtau and C_{max} for lopinavir decreased by 27% and 23%, respectively, and for ritonavir decreased by 31% and 33%, respectively, when compared to lopinavir/ritonavir alone. Multiple-dose lopinavir/ritonavir is a moderate inhibitor of the sensitive CYP3A substrate, isavuconazole. Multiple-dose isavuconazonium is a weak inhibitor of both lopinavir and ritonavir. No modification of the isavuconazole dose or the lopinavir/ritonavir dose is recommended when the drugs are co-administered.

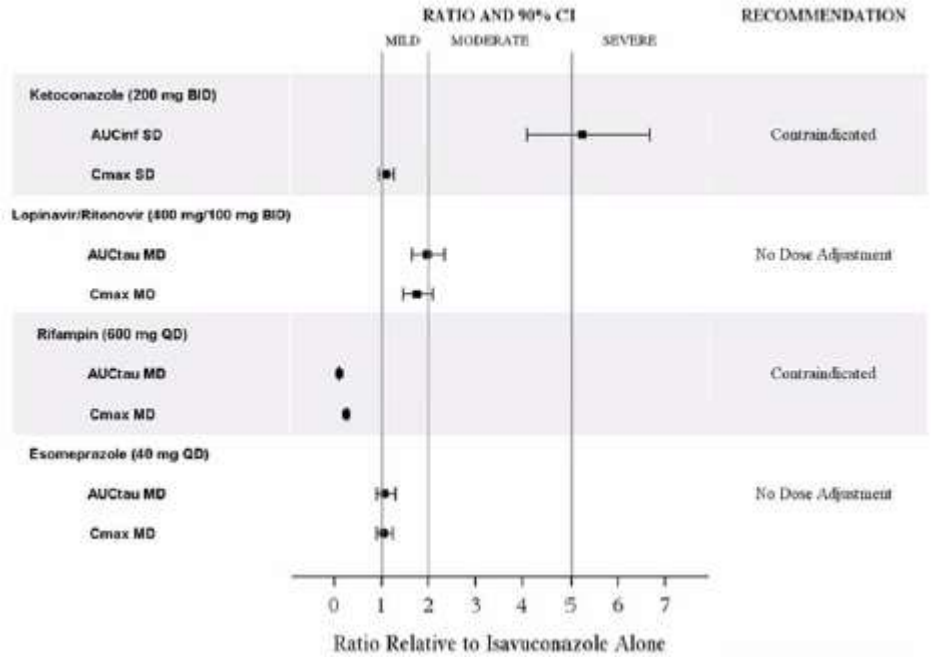
11.1.2. Strong CYP3A inducers

Repeated doses of rifampin (600 mg/day) decreased mean C_{max} and AUC_{tau} of isavuconazole by 75% and 90%, respectively.

Concomitant use of isavuconazonium with strong CYP3A inducers (e.g., rifampin, rifapentin, phenytoin, carbamazepine, long-acting barbiturates such as phenobarbital and St. John's wort, high-dose ritonavir) or moderate inducers (efavirenz, nafcillin and etravirine) is contraindicated. Co-administration with mild inducers such as aprepitant, prednisone and pioglitazone should be avoided while isavuconazole plasma concentrations may decrease.

The effect of ketoconazole, lopinavir/ritonavir, rifampin, and esomeprazole on the pharmacokinetics of isavuconazole are shown in Figure 1.

Figure 1 Effect of other drugs on the pharmacokinetics of isavuconazole



11.3. Effect of isavuconazole on the pharmacokinetics of other drugs

In vitro, isavuconazole is an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT isoenzymes and P-gp, BCRP and OCT2-mediated drug transports. *In vitro*, isavuconazole is also an inducer of CYP1A2, CYP3A4/5, CYP2B6, CYP2C8 and CYP2C9.

The effect of isavuconazole on the pharmacokinetics of co-administered drugs were studied after single and multiple doses of isavuconazole in healthy subjects.

11.3.1. CYP3A substrates

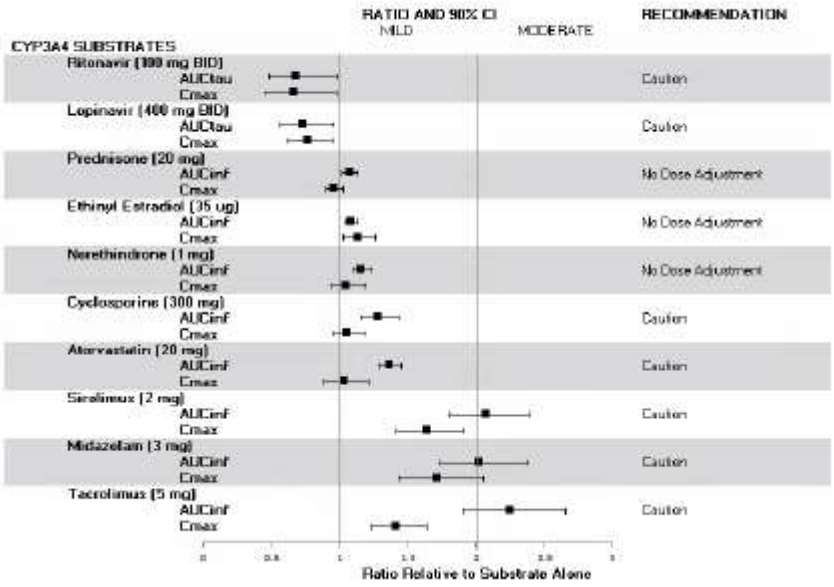
Isavuconazole, at the therapeutic dose of isavuconazonium, increased the systemic exposure of sensitive CYP3A substrates midazolam, sirolimus and tacrolimus approximately 2-fold; isavuconazole can therefore be considered a moderate inhibitor of CYP3A.

Multiple doses of isavuconazole at the recommended clinical dose increased the C_{max} and AUC of midazolam (clinical dose) by 72% and 103%, respectively, sirolimus (clinical dose) by 65% and 84%, and tacrolimus (clinical dose) by 42% and 125%.

Caution is advised if isavuconazonium is co-administered with CYP3A substrates such as the immunosuppressants tacrolimus, sirolimus and ciclosporin. Appropriate therapeutic drug monitoring and dose adjustment may be necessary during co-administration

The effects of isavuconazole on the CYP3A substrates ritonavir, lopinavir, prednisone, ethinyl estradiol, norethindrone, ciclosporin, atorvastatin, sirolimus, midazolam and tacrolimus are show in Figure 2. No dose adjustment is necessary for lopinavir/ritonavir, midazolam, atorvastatin, and oral contraceptives comprised of ethinyl estradiol and norethindrone when given concurrently with isavuconazole.

Figure 2 Effect of isavuconazole on pharmacokinetics of CYP3A4 substrates



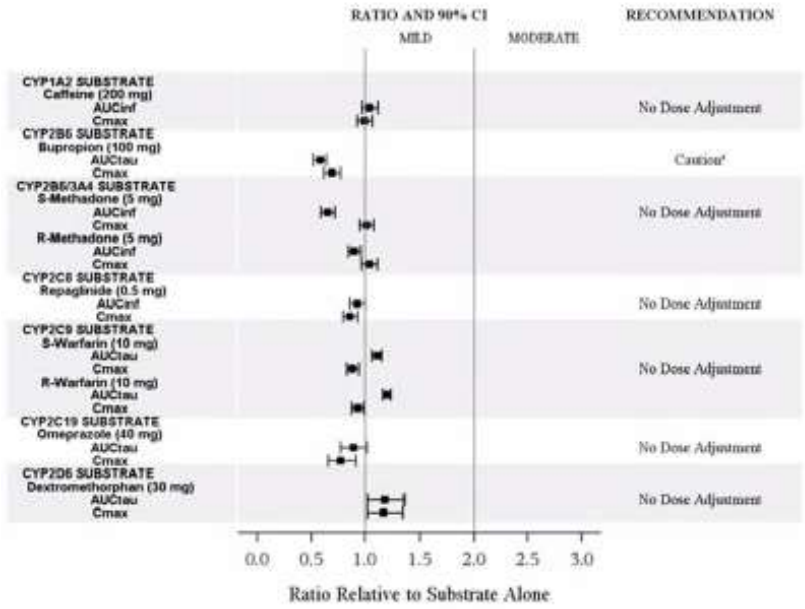
Caution: Appropriate therapeutic drug monitoring and dose adjustment of tacrolimus, sirolimus and ciclosporin may be necessary when co-administered with isavuconazole. No dose adjustment is required for lopinavir/ritonavir, but careful monitoring is recommended for any occurrence of lack of anti-viral efficacy. No dose adjustment is required for atorvastatin, but monitoring of adverse reactions typical of statins is advised. No dose adjustment is required for midazolam, but careful monitoring of clinical signs and symptoms is recommended, and dose reduction if required.

11.3.2. Other CYP substrates

Isavuconazonium is a weak inducer of CYP2B6 *in vivo*. Co-administration of isavuconazonium (200 mg eq. isavuconazole once per day orally) with bupropion resulted in decreased AUC_{inf} and C_{max} by 42% and 31%, respectively, compared with bupropion alone. Caution is advised if isavuconazonium is co-administered with CYP2B6 substrates, especially narrow therapeutic index drugs such as cyclophosphamide.

The effects of isavuconazole on the pharmacokinetics of other CYP substrates such as caffeine, bupropion, methadone, repaglinide, warfarin, omeprazole, and dextromethorphan are presented in Figure 3. No dose adjustment is necessary for these compounds when given concurrently with isavuconazole.

Figure 3 Effect of isavuconazole on pharmacokinetics of other CYP substrates



Caution[1]: Isavuconazole decreased the systemic exposure of bupropion. Caution is advised if isavuconazonium is co-administrated with CYP2B6 substrates, especially narrow therapeutic index drugs such as cyclophosphamide.

11.3.3. UGT substrates

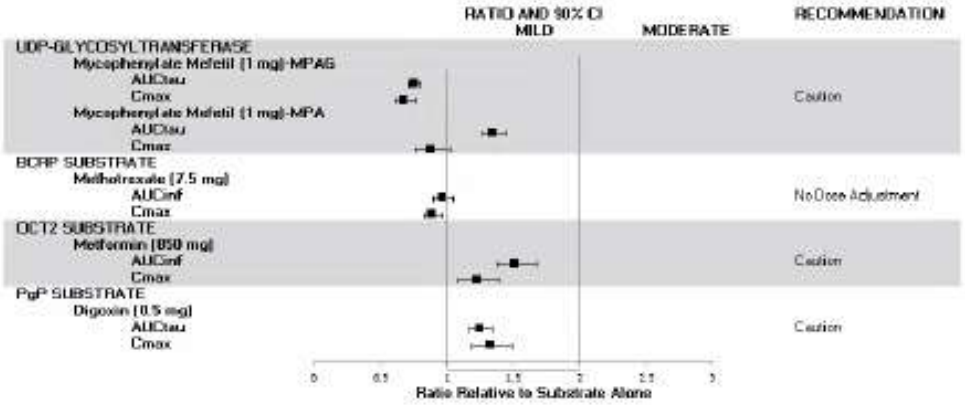
Co-administration of multiple doses of isavuconazonium (200 mg eq. isavuconazole once per day orally) with mycophenolate mofetil (MMF) increased the AUC_{inf} of the active moiety mycophenolic acid (MPA) by 35%, and decreased the C_{max} by 11%, compared to MMF alone (study 9766-CL-0030). The AUC_{inf} and C_{max} of the glucuronide metabolite of MPA (MPAG), decreased by 24% and 32%, respectively. Due to the unclear association between MPA pharmacokinetics and MPA-related toxicity, no specific recommendation regarding dose alterations of MPA when used with isavuconazonium can be made. Patients receiving isavuconazole concurrently with MMF should be monitored for MPA-related toxicities.

11.3.4. Transporter substrates

Co-administration of isavuconazonium (200 mg eq. isavuconazole once per day orally) with the P-gp substrate digoxin resulted in a 33% increase in C_{max} and a 25% increase in AUC_{inf} (9766-CL-0025) compared to digoxin alone. In patients receiving isavuconazonium concurrently with digoxin, serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. Other drugs with a narrow therapeutic range that are substrates for P-gp, such as colchicine and dabigatran etexilate, may require dose adjustment when administered concomitantly with isavuconazonium.

The effects of isavuconazole on the pharmacokinetics of UGT and transporter substrates such as MMF, methotrexate, metformin and digoxin are shown in Figure 4. No dose adjustment is necessary for methotrexate when given concurrently with isavuconazole.

Figure 4 Effect of isavuconazole on the pharmacokinetics of UGTs and transporters



Caution: Due to the unclear association between MPA pharmacokinetics and MPA-related toxicity, no specific dose recommendation can be made. Patients receiving isavuconazole concurrently with MMF should be monitored for MPA-related toxicities. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. Metformin dose reduction might be necessary.

BCRP: breast cancer resistance protein; MMF: mycophenolate mofetil; MPA: mycophenolic acid; OCT2: organic cation transporter 2; P-gp: P-glycoprotein; UDP: uridine diphosphate.

3.3.3. Pharmacodynamics

Pharmacodynamics: thorough QT evaluation

There was no evidence of QTc prolongation by any correction formula (individual, Bazett's or Fridericia's).

For both isavuconazonium doses in study 9766-CL-0017 (200 mg eq. and 600 mg eq. isavuconazole), a shortening of the QTcF interval was observed at all time points. The largest shortening occurred at 2 hours for both doses (isavuconazole 200 mg eq.: −13.10 msec [90% CI: −17.07, −9.13]; isavuconazole 600 mg eq.: −24.56 msec [90% CI: −28.71, −20.41]).

Isavuconazole inhibited the L-type calcium channel (hCav1.2) with an IC_{50} of 6.57 mcM (38-fold the human non-protein bound C_{max} at the clinical maintenance dose of 200 mg/day). This ion channel finding is consistent with the QTcF interval shortening reported in the clinical thorough QT study.

Primary pharmacology

Aspergillus spp.

Using CLSI methodology to test 1,717 worldwide isolates of Aspergillus the isavuconazole MIC_{50} and MIC_{90} were 0.5 and 2 mg/L, respectively (range 0.06 to 32 mg/L). Using EUCAST methodology to test 1,563 isolates the MIC_{50} and MIC_{90} were 1 and 2 mg/L, respectively (range 0.004 to 16 mg/L), see below table:

Table 2 MICs of isavuconazole against *Aspergillus* spp.

Species	Method	Isolates (n)	MIC parameter (mg/L)				
			MIN	MAX	MIC_{50}	MIC_{90}	GM
All	CLSI	1,717	0.06	32	0.5	2	0.65
	EUCAST	1,563	0.004	16	1	2	0.75
A. fumigatus	CLSI	875	0.12	8	1	1	0.79
	EUCAST	434	0.12	16	1	1	0.8
A. flavus	CLSI	145	0.12	16	1	4	0.89
	EUCAST	233	0.12	4	1	2	1.1
A. niger	CLSI	101	0.12	32	1	2	0.97
	EUCAST	222	0.25	16	2	4	2.24
A. terreus	CLSI	432	0.06	32	0.25	1	0.39
	EUCAST	431	0.06	8	0.5	4	0.65
A. nidulans	CLSI	85	0.12	16	0.5	1	0.39
	EUCAST	206	0.004	8	0.12	0.5	0.19

In a study of isavuconazole using CLSI and EUCAST methodologies, DNA sequencing identified 189 *A. terreus* complex, 15 *A. hortai* and 30 falling in the *Aspergillus terrei* complex. Against all isolates, isavuconazole had a CLSI MIC_{90} of 0.5 mg/L and a EUCAST MIC_{90} of 1 mg/L.

Acquired azole resistance in *Aspergillus* is relatively uncommon, except for fluconazole, and usually involves one or more mutational events in the gene encoding CYP51A. In addition, the CDR1B efflux transporter is associated with non-CYP51A-mediated itraconazole resistance in *Aspergillus fumigatus*. Other mechanisms have been identified in *Candida* species (efflux pumps, over-expression of altered CYP51A and bypass pathways). Little is known about resistance mechanisms in other fungal species.

Sixteen laboratory-derived isavuconazole-resistant mutants did not have point mutations in the CYP51A or CYP51B gene and showed no or a slight variation in the expression profile of the four efflux pump genes (MDR1-4). All of the resistant mutants showed cross-resistance with at least one of itraconazole and voriconazole. There was no clear evidence that acquired isavuconazole resistance reduced fitness in non-clinical infection models.

Aspergillus fumigatus (40) with CYP51A mutations conferring azole resistance were tested against isavuconazole using the CLSI methodology. The strains included 31 with alterations in their CYP51A sequence at M220 (n=9), G54 (n=6), G138/Y431/G434/G448 (n=5), L98 (n=3) and other mutations (n=8). The remaining nine strains were allocated to the group for wild-type CYP51A sequence.

All had MICs > 8 mg/L for itraconazole MICs, of which 77% (24/31) and 68% (21/31) had raised MICs of posaconazole and voriconazole, respectively. The isavuconazole MIC ranges of the CYP51A-mutated and wild type isolates were 0.5–>8 and 0.5–2 mg/L, respectively. Strains with alterations L98H, G138C, Y431C, G434C and G448S showed elevated MICs to all triazoles including isavuconazole.

Isavuconazole MICs showed the highest degree of correlation with those for voriconazole (Spearman's correlation coefficient 0.885, p <0.001). Isavuconazole MICs were more likely to be raised in strains of *A. fumigatus* with reduced susceptibility to other triazoles, and tended to mirror changes in voriconazole susceptibility. There was no correlation between MICs for isavuconazole and ampB (-0.165, p <0.307).

In a study of *A. fumigatus* isolates with various CYP51A mutations strains with mutations in the G54 and M220 codons had similar isavuconazole MICs to the wild-type isolates. Among the G54 and M220 mutants 10/80 MICs were >2 mg/L. *A. fumigatus* isolates with TR34/L98H alterations tended to have higher isavuconazole MICs (29/40 were >2 mg/L). The activity of isavuconazole against *A. fumigatus* may be less affected by mutations at codons G54 and M220 compared with TR34/L98H.

The PK/PD relationship of isavuconazole in a neutropenic murine model of invasive pulmonary aspergillosis (IPA) was examined to assess the optimal drug exposure for infection due to wild-type and CYP51 mutant isolates. A dose-response relationship was observed and higher doses were needed to achieve an antifungal effect against isolates with elevated isavuconazole MICs. The total drug AUC/MIC associated with net stasis for the CYP51 wild-type group ranged from 415-1111 whereas for isolates F14403 and F14532 (the CYP51 mutant) it was slightly lower at 361-367. For all isolates where net

stasis was achieved, the median static dose total drug AUC/MIC was 503. The 1 log10 kill total drug AUC/MIC was ~2-fold higher than the static dose PD target, with a median value of 1111. AUC/MIC was a strong predictor of observed outcome (R2 = 0.75).

The PK/PD relationship for isavuconazole was investigated in a validated dynamic in vitro model of the human alveolus using two wild-type and two mutant strains of *Aspergillus fumigatus*. The galactomannan index (GMI) was used as a quantitative biomarker to evaluate the antifungal efficacy of isavuconazole. Exposure-response relationships with a trough concentration of 0.2-0.5 mg/L were observed for green fluorescent protein (GFP) and non-GFP expressing wild types with near maximal suppression of GM release. In contrast, only the highest concentration of isavuconazole suppressed GM in the F/16216 mutant and no suppression was noted for the F/11628 mutant strain. An AUC/MIC ratio of 11.40 resulted in a 90% probability of galactomannan suppression <1.

From the two phase 3 studies, 136 baseline fungal isolates from 102 isavuconazole-treated patients (studies 9766-CL-0103 and 9766-CL-0104) and 28 baseline fungal isolates from 25 voriconazole-treated patients (study 9766-CL-0104) were tested for susceptibility to isavuconazole and other antifungal drugs. The most common genus from both studies was *Aspergillus* spp. with *A. fumigatus* (n=37, isavuconazole: studies 9766-CL-0104/9766-CL-0103; n=17 voriconazole: study 9766-CL-0104) as the most common species. Although MIC values for isavuconazole were generally similar to voriconazole MIC values, it is noted that regarding some *Aspergillus* isolates, isavuconazole MIC values of 8-32 were reported (this was irrespective of the testing method used (CLSI or EUCAST). MICs for posaconazole were in general lower, see table below:

Table 3 MIC Values for isavuconazole and Other Antifungal Drugs for Baseline Fungal Isolates from isavuconazole-Treated Patients per EUCAST Methodology from Study 9766-CL-0104 (mITT population)

Organism Genus species (No. isolates collected)	MIC †	AmB	CAS‡	ISA	POS	VOR
Aspergillus spp. (51)	MIC Range (mg/L)	0.5-32	0.12-1	0.25-32	0.25-1	0.25-32
	MIC_{50}	4	0.12	1	0.5	1
	MIC_{90}	4	0.25	2	1	4
Aspergillus flavus (9)	MIC Range (mg/L)	0.5-4	0.12-0.25	0.25-2	0.25-1	1-4
Aspergillus fumigatus (28)	MIC Range (mg/L)	2-4	0.12-1	0.25-32	0.25-1	0.25-32
	MIC_{50}	4	0.25	0.5	0.5	0.5
	MIC_{90}	4	0.25	2	1	4
Aspergillus niger (7)	MIC Range (mg/L)	1-2	0.12-0.25	1-8	0.5-1	0.5-4
Aspergillus terreus (6)	MIC Range (mg/L)	0.5-8	0.12-1	0.25-2	0.25-1	0.5-32
Aspergillus westerdijkiae (1)	MIC Range (mg/L)	32	1	4	1	32

AmB: amphotericin B; CAS: caspofungin; EUCAST: European Committee for Antimicrobial Susceptibility Testing; ISA: isavuconazole; MIC: minimum inhibitory concentration; mITT: modified intent-to-treat; POS: posaconazole; ULOQ: upper limit of quantification; VOR: voriconazole.

mITT: All ITT patients who have proven or probable invasive fungal disease as determined by the data review committee.

If a MIC value is reported as >ULOQ, then the MIC value is imputed as single two-fold dilution above the ULOQ and used in this summary.

† The MIC50 and MIC90 are not reported if the number of isolates is less than 10.

‡ Sensitivities to CAS are measured as minimum effective concentrations (MEC).

Mucorales species

MIC data were entered on a total of 374 worldwide isolates of Mucorales from 5 genera. Using CLSI methodology isavuconazole exhibited MIC_{50} and MIC_{90} values of 1–4 and 2–32 mg/L, respectively.

Table 4 MIC distributions for isavuconazole against Mucorales

Genus	Species	MIC parameter (mg/L)					
		Isolates (n)	MIN	MAX	MIC_{50}	MIC_{90}	GM
Absidia spp.	All	67	0.12	32	1	8	1.57
	A. corymbifera	44	0.12	8	1	8	1.37
	Absidia sp.	23	0.5	32	1	32	2.06
Cunninghamella spp.	All	13	0.25	32	4	32	4.45
Mucor spp.	All	68	0.12	32	4	16	3.65
	M. circinelloides	18	2	8	4	8	3.7
Rhizomucor spp.	All	18	0.12	8	1	4	1.08
	All (EUCAST)	9	2	16	16	16	10.08
Rhizopus spp.	All	134	0.12	32	1	8	1.48
	R. arrhizus	28	0.12	8	2	4	2.15
	R. microsporous	41	0.5	32	1	2	1.05
	R. oryzae	11	0.5	4	1	4	1.46
	Rhizopus sp.	52	0.12	32	1	16	1.53
	Rhizopus spp. (MFC)	14	1	32	8	32	7.61

All isolates were tested using CLSI methodology except for *Rhizomucor* spp. MFC was determined for 14 *Rhizopus* spp.

Several other studies have been conducted to determine the in vitro activity of isavuconazole. Some of the most pertinent are mentioned above. In each case it was clear that for some Mucorales the MIC_{50} values exceed the breakpoints proposed for *A. fumigatus*. Overall, isavuconazole has shown variable in vitro activity against isolates of the Mucorales order (*Absidia* spp., *Cunninghamella* spp., *Mucor* spp., *Rhizomucor* spp. and *Rhizopus* spp.), often studied in low numbers. Isavuconazole tended to be most active against *Rhizomucor* and *Rhizopus* spp. in vitro (MIC_{90}: 4–16 mg/L) and had the lowest in vitro activity against *Cunninghamella* spp. (MIC_{90}: 16–32 mg/L).

Additional MIC data on Mucorales (Arendrup 2015 and Cuenca Estrella 2015) were submitted. MICs using the EUCAST method (n=154) and CLSI method are shown in the following tables. There is a clear difference in MIC when both methods are compared, which is due to methodological differences, resulting in 1-2 dilutions higher MICs with the EUCAST method. The MIC pattern presented within the initial application is generally in line with that reported by Arendrup (2015) and Cuenca Estrella (2015), however MICs were generally higher within the initial application. With the currently recommended posology of isavuconazole, the average isavuconazole plasma trough level is approximately 4 mg/L (phase 3 clinical studies 9766-CL-0103 and 9766-CL-0104). It is therefore expected that plasma levels will be attained that are above the EUCAST MIC of only a few Mucorales species (for instance Rhizopus and Rhizomucor). Lichtheimia species are less susceptible and Mucor species are regarded not susceptible to isavuconazole. However, the clinical relevance of these MICs cannot be derived from these data only.

Table 5 Isavuconazole MIC distributions on Mucorales isolates using the EUCAST method (n=154)

Species	MIC (mg/L)								
	≤ 0.06	0.125	0.25	0.5	1	2	4	8	16
Lichtheimia corymbifera (26)	-	1	-	6	12	3	1	2	1
Lichtheimia ramosa (19)	-	1	3	3	4	4	3	1	-
Rhizomucor miehei (2)	-	-	-	-	1	1	-	-	-
Rhizomucor pusillus (18)	-	-	-	7	5	5	-	1	-
Mucor circinelloides (16)	2	-	-	1	-	1	2	7	3
Mucor circinelloides, G-I (5)	-	-	-	-	-	-	2	3	-
Mucor circinelloides, G-II (9)	-	-	-	-	1	-	1	5	2
Rhizopus arrhizus (16)	-	-	-	2	4	5	3	2	-
Rhizopus microsporus (37)	-	-	-	13	19	3	2	-	-
Rhizopus oryzae (6)	-	-	-	1	2	2	1	-	-
Percentage isolates at MIC	1.32	1.32	1.97	22	31	16	9	14	4
Cumulative percentage	1.32	2.64	4.61	26	57	73	82	96	100

Table 6 **Isavuconazole MIC distributions on Mucorales isolates using the CLSI method (n=154)**

Species	MIC (mg/L)								
	≤ 0.06	0.125	0.25	0.5	1	2	4	8	16
Lichtheimia corymbifera (26)	6	3	1	2	10	3	1	-	-
Lichtheimia ramosa (19)	6	2	1	4	3	3	-	-	-
Rhizomucor miehei (2)	-	-	1	-	-	1	-	-	-
Rhizomucor pusillus (17)	2	1	1	6	5	1	1	-	-
Mucor circinelloides (16)	6	-	1	-	3	2	3	1	-
Mucor circinelloides, G-I (5)	-	-	-	-	-	3	1	-	-
Mucor circinelloides, G-II (9)	-	-	-	-	1	-	3	5	-
Rhizopus arrhizus (16)	3	4	6	2	1	-	-	-	-
Rhizopus microsporus (37)	9	6	6	13	3	-	-	-	-
Rhizopus oryzae (6)	-	1	-	-	4	1	-	-	-
Percentage isolates at MIC	**21.1**	**11.2**	**11.2**	**18**	**20**	**8**	**7**	**4**	**0**
Cumulative percentage	**21.1**	**32.2**	**43.4**	**61**	**81**	**89**	**96**	**100**	**100**

Note: one strain of *M. circinelloides* G-I and one strain of *Rhizomucor pusillus* did not grow sufficiently at 24 h or 48 h to read an MIC.

In vivo efficacy was assessed in neutropenic and diabetic ketoacidotic (DKA) mouse models using intratracheal infection with *R. oryzae* 99-880 and treatment with isavuconazole 43, 59, and 116 mg/kg orally TID starting at 8 h for 5 days. The 116 mg/kg group had significantly ($p < 0.05$) higher 21-day survival rates vs. placebo (70% vs. 10%). Isavuconazole was as effective as LAmB in treating pulmonary mucormycosis infections with *R. oryzae* in neutropenic mice. After 21 days, the survival rates for isavuconazole-, LAmB-, and placebo-treated mice were 65%, 40%, and 15%, respectively. Isavuconazole decreased lung and brain fungal burden by approximately one log compared with the placebo group. A similar decrease in lung and brain was noted in the LAmB-treated animals.

The relevance of these animal models for the use of isavuconazole in clinical practice remains however uncertain.

In study 9766-CL-0103 19 baseline organisms of the Mucorales order were tested for susceptibility. The most common species isolates were *Rhizopus oryzae* (9), followed by *Rhizomucor pusillus* (3) and *Lichtheimia (Absidia) corymbifera* (3). Overall, isavuconazole MIC values ranged from 0.25 to 32 mg/L (CLSI and EUCAST). The EUCAST MIC range values for isavuconazole are shown in the following table.

Isavuconazole MIC values for Mucorales were considerably higher than for *Aspergillus* spp., which is considered problematic in the treatment of mucormycosis.

Table 7 **MIC Values for ISA and Other Antifungal Drugs for Baseline Isolates from the Mucorales Order per EUCAST Methodology from Study 9766-CL- 0103 (mITT)**

Organism Genus (No. isolates collected)	MIC†	AmB	CAS‡	ISA	POS	VOR
Rhizopus oryzae (9)	MIC Range (mg/L)	0.25-4	32-128	0.25-32	0.5-32	16-32
Actinomucor elegans (1)	MIC Range (mg/L) (mg/L)	2	128	4	0.5	32
Lichtheimia (Absidia) corymbifera (3)	MIC Range (mg/L)	0.25-2	32-128	8-16	0.5-1	32-64
Rhizomucor pusillus (3)	MIC Range (mg/L)	0.5-1	32-64	4- 8	1	32
Rhizopus azygosporus (1)	MIC Range (mg/L)	2	1	0.5	1	2
Rhizopus microsporus (1)	MIC Range (mg/L)	2	64	4	8	16
Mucor circinelloides (1)	MIC Range (mg/L)	2	64	32	32	16

AmB: amphotericin B; CAS: caspofungin; CLSI: Clinical and Laboratory Standards Institute; ISA: isavuconazole; MIC: minimum inhibitory concentration; mITT: modified intent-to-treat; POS: posaconazole; ULOQ: upperlimit of quantification; VOR: voriconazole.

mITT: All ITT patients who have proven or probable invasive fungal disease as determined by the data review committee.

If a MIC value is reported as >ULOQ, then the MIC value is imputed as single two-fold dilution above the ULOQ.
† The MIC_{50} and MIC_{90} are not reported if the number of isolates is less than 10.

‡ Sensitivities to CAS are measured as minimum effective concentrations (MEC).

Relationship between plasma concentration and effect

Aspergillus

Probability of target attainment analysis (PTA) was estimated for a range of MICs using Monte Carlo simulations, taking into account the mean population estimates from the best 2-compartment model with covariates. Concentration-time profiles (n=5000) were simulated to steady state based on the phase 3 regimen (200 mg q8h for 48 h and then QD). The total drug AUC/MIC values estimated in the non-clinical models ranged from 11.2 to 503 when MICs were based on CLSI methodology and from 11.4 to 24.7 when based on EUCAST methodology. The above suggested that the phase 3 regimen would suffice to treat *Aspergillus* spp. with MICs up to 1 mg/L under CLSI methodology and 2 mg/L under EUCAST methodology.

Exposure-response analyses were based on data from 232 patients with aspergillosis who were treated with isavuconazole in the phase 3 study 9766-CL-0104. Separate models were developed for mortality at day 42, DRC adjudicated overall response at EOT and DRC adjudicated clinical response at EOT for both ITT and mITT populations. Mortality was modelled as a binary outcome; the overall and the clinical responses were modelled as ordinal and also as binary responses.

AUC, concentration at steady state, concentration at day 7, concentration at day 14 and concentration after loading dose were the PK parameters analysed against efficacy endpoints. None of these primary exposure parameters were found to be statistically significant for any of the efficacy endpoints.

The applicant concluded that the absence of any relationship between exposure and response indicated that patients had plasma levels above the AUC/MIC breakpoint and factors other than exposure had a greater impact on response than exposure to isavuconazole. Modelling confirmed that in the phase 3 population, exposures were adequate to treat organisms seen in the studies. Lack of association between exposure and response would be expected if exposures exceed the AUC/MIC target for organisms within the wild type population with MIC_{90} of 1 or 2 mg/L for *Aspergillus* species.

During the procedure, EUCAST has recommended and CHMP has endorsed the following clinical breakpoints for *Aspergillus* species that were included in SmPC section 5.1:

- *Aspergillus fumigatus*: S ≤1 mg/L, R >1 mg/L
- *Aspergillus nidulans*: S ≤0.25 mg/L, R >0.25 mg/L
- *Aspergillus terreus*: S ≤1 mg/L, R >1 mg/L

S=susceptible, R=resistant

There are currently insufficient data to set clinical breakpoints for other *Aspergillus* species.

Mucorales

Positive cultures and MIC testing results were available for Mucorales from only fifteen patients. Of the patients that were infected with pathogens with MICs of ≤ 4 mg/L, 5 out of 7 (71%) had a complete/partial/stable response and in 2 out of 7 (29%) patients fungal disease progressed. Of the patients that were infected with pathogens with MICs of ≥ 8 mg/L, 2 out of 8 (25%) had a complete/partial/stable response and in 6/8 (75%) patients fungal disease progressed.

In 24/37 patients' fungal pathogens from the families of *Mucoraceae* (Genera *Actinomucor*, *Mucor*, *Rhizomucor* and *Rhizopus*), *Cunninghamellaceae* (Genus *Cunninghamella*) and *Lichtheimiaceae* (Genus *Lichtheimia* [former *Absidia*]) were identified. The most common pathogen was *Rhizopus oryzae* (7/24, 29%). Other pathogenes identified were *Mucor* NOS (5), *Rhizomucor pusillus* (4), *Lichtheimia corymbifera* (2), *Rhizopus azygosporus* (1), *Rhizopus microsporus* (1), *Rhizomucor* (1), *Mucor amphibiorum* (1), *Actinomucor elegans* (1), *Cunninghamella* (1).

From the available data, no clear relationship appears evident between fungal species and clinical outcome. In case of the patients infected with the most common identified species *Rhizopus oryzae*, 4/7 failed on isavuconazole therapy, while 2/7 cured completely and 1/7 cured partial. The four patients infected by *Rhizomucor pusillus* all failed on therapy. MICs of *Rhizomucor pusillus* identified in study 9766-CL-0103 (n=4) were considerably higher than those reported in the tables presenting the data of Arendrup (2015) and Cuenca Estrella (2015).

No recommendations for clinical breakpoints for Mucorales species were made by EUCAST.

3.3.4. Discussion on clinical pharmacology

The pharmacology profile has been presented in satisfactory manner.

The reviewer agrees with the CHMP discussion of this part:

Pharmacokinetics

The absolute bioavailability of the oral formulation is 98%. Compared to that obtained after i.v. ministration (500ml/2h) the isavuconazole Cmax after oral administration is about 22% lower, which is considered not clinically relevant. Based upon comparable exposures after oral and i.v. administration, both formulations can be interchanged. Moreover, food did not affect isavuconazole exposure, so it can be taken with or without food. A high distribution volume is observed (about 450 litres), indicating that isavuconazole is well distributed. Isavuconazole is extensively metabolized, however, it is a low clearance medicine and in plasma, exposure accounted mainly for intact drug. In addition, applying a loading dose of 200 mg t.i.d. for 2 days, followed by a maintenance dose of 200 mg q.d. resulted in a rapid achievement of steady state at day 3 and high trough levels of around and above 3 µg/ml. The trough values were above the targeted clinical MIC values of 1-2 µg/ml of especially Aspergillus. For Mucorales higher levels seems to be needed. However, a dose–response relationship for both was not identified (see section on pharmacodynamics).

Renal impairment had no influence on the pharmacokinetics of isavuconazole and as such it can be given to this patient group without a need to adjust the dose. In patients with mild and moderate hepatic impairment clearance after i.v. administration decreased by 30 and 50%, respectively, resulting in increased exposures of about 60 and 120%. After oral dosing, comparable results were observed. No dose adjustment is necessary, but an increase in AEs may be expected due to the increased exposure. There is no clinical experience in patients with severe hepatic impairment (Child-

Pugh C). Therefore the Cresemba SmPC indicates that the isavuconazole use in these patients is not recommended unless the potential benefit is considered to outweigh the risks.

With regard to interactions, the isavuconazole PK is mainly affected by inhibition and induction of CYP3A4. The strong inhibitor ketoconazole increased isavuconazole exposure more than 5-fold, and is contraindicated. The strong CYP3A4 inhibitor lopinavir/ritonavir, increased the plasma exposure of isavuconazole by about 2-fold, therefore no dose adjustment is necessary, however caution is advised. This recommendation is also applicable to other strong CYP3A4 inhibitors, as they are considered to have a similar or a less potent CYP3A4 inhibition compared to lopinavir/ritonavir. Inducers may decrease plasma exposure to a great extent. As such, strong and moderate inducers are contraindicated, and mild inducers should be avoided unless the benefit outweighs the risk. Moreover, isavuconazole mainly affect CYP3A4 substrates (increase, but also decreases observed), CYP2B6 substrates (decreases due to induction), UGT substrates (decreases due to induction), BCRP substrates (increase due to inhibition) and P-gp substrates (increases due to inhibition) resulting in warnings. In general the interaction potential is sufficient elucidated.

In comparison to voriconazole, isavuconazole is more sensitive for CYP3A4 inhibitors. However, both increase CYP3A4 substrates, but voriconazole is a strong CYP3A4 inhibitor whereas isavuconazole is a moderate inhibitor. Both increase tacrolimus levels to the same extent, i.e. about 2.2-fold. With regard to CYP2B6 and UGT substrates, isavuconazole is less favorable, as being an inducer of these substrates.

Pharmacodynamics

The mechanism of action is that of other triazoles. The selectivity ratio for isavuconazole was similar to that reported for voriconazole, indicating that it will likely have moderate inhibitory activity against the human P450 enzyme with attendant implications for the safety profile.

Aspergillus

For isavuconazole, the PD index suggested to be associated with efficacy is AUC/MIC like for most azoles. Monte Carlo simulations have shown a PTA of 95% for *Aspergillus fumigatus* with MICs that are common in the wild type isolates and below the epidemiological cut-off values. As for other azoles, the dose-response relation for isavuconazole is complex. The efficacy results of the comparative phase 3 study 9766-CL-0104 versus voriconazole are however taken into consideration.

EUCAST has recommended clinical breakpoints for *Aspergillus fumigatus*, *Aspergillus nidulans* and *Aspergillus terreus*. There are currently insufficient data to set clinical breakpoints for other *Aspergillus* species. The CHMP endorsed the EUCAST recommendations.

Mucorales

It was concluded that the available microbiological data were inadequate to support a conclusion that isavuconazole, when used at the proposed posology, is suitable for the treatment of all Mucorales species. Moreover, the data suggested that some of the genera/species may be inherently insusceptible to isavuconazole. A pathogen-specific indication was not acceptable either. Further qualifications in sections 4.4 and 5.1 in the SmPC were implemented.

The Advisor Expert Committee considered about dose adjustment in Asians due to the difference of PK profile between Asian and Caucasian population, LOQ was listed. The applicant provided a justification. The point is solved.

3.3.5. Conclusions on clinical pharmacology

Based on the information in dossier, the clinical pharmacology profile (regarding pharmacodynamics) of isavuconazonium sulfate is acceptable.

3.3.6. Clinical efficacy and safety

Two pivotal clinical trials are 9766-CL-0104 (invasive aspergillosis) and 9766-CL-0103 (mucormycosis).

Study ID	Design	Treatments	Enrolled/ Completed	Gender Mean Age (Range)	Inclusion Criteria	Primary Endpoint(s)
9766-CL-**0104** (WSA-CS-004)	Phase 3, randomized, multicentre, double-blind, non-inferiority, active controlled	Isavuconazole Loading Dose: 200 mg, IV q8h on days 1 and 2; Maintenance: 200 mg IV or oral q24h	258/118	Male: 56.2% Female: 43.8% 51.1 (17-82)	Proven, probable or possible IFD caused by *Aspergillus* species or other filamentous fungi	Crude rate of all-cause mortality through day 42
		Voriconazole Loading dose: 6 mg/kg IV q12h on day 1; Maintenance dose: 4 mg/kg IV or 200 mg oral q12h	258/120	Male: 63.2% Female: 36.8% 51.2 (18-87)		
9766-CL-**0103** (WSA-CS-003)	Phase 3, open-label, uncontrolled, multicentre	Isavuconazole Loading dose: 200 mg, IV or oral q8h on days 1 and 2; Maintenance dose: 200 mg IV or oral q24h	146/72	Male: 68.5% Female: 31.5% 49.9 (18-92) (ITT)	As above in patients with CLCr <50 mL/min or proven/probable IFD due to moulds, yeasts or dimorphic fungi (other than *Aspergillus fumigatus* or *Candida* species) primary, refractory or intolerant to prior treatment	Outcome of treatment evaluated by the DRC at day 42

ITT: intent-to-treat, DRC: data review committee

Summary of main studies

Summary of efficacy for trial 9766-CL-0104 (Invasive Aspergillosis)

Title: A phase III, double-blind, randomized study to evaluate safety and efficacy of isavuconazole (BAL8557) versus voriconazole for primary treatment of invasive fungal disease caused by Aspergillus species or other filamentous fungi (the SECURE Study)		
Study identifier	9766-CL-0104 (WSA-CS-004)	
Design	randomized (1:1), multicenter, double-blind, noninferiority, comparative group study	
	Duration of main phase:	Total study: March 2007 to March 2013 Patients remained on therapy until they had reached a treatment endpoint or until they had received treatment for a maximum period of 84 days. Treatment was to continue for at least 7 days after resolution of all clinical symptoms and physical findings of infection. Mean duration of treatment for both treatment was 47 days.
	Duration of Run-in phase:	n/a
	Duration of Extension phase:	n/a
Hypothesis	Non-inferiority	
Treatments groups	Isavuconazole i.v. + oral	Loading dose: 200 mg administered q8h i.v. for 2 days Maintenance dose: 200 mg once per day i.v. **or** oral number randomized: 258 (ITT)
	Voriconazole i.v. + oral	Loading dose: 6 mg/kg administered q12h i.v. for 1 day Maintenance dose: 4 mg/kg q12h i.v. **or** 200 mg q12h oral number randomized: 258 (ITT)
Endpoints and definitions	Primary endpoint	Crude rate of all cause mortality through day 42 (ITT)
	Key Secondary endpoint	DRC assessed overall response at EOT (mITT)
	Secondary endpoint	DRC assessed overall response at days 42 and 84 (mITT)

	Secondary endpoint	DRC assessed Clinical, mycological and radiological response at EOT, and days 42 and 84 (mITT, myITT)	
	Secondary endpoint	All cause mortality through day 84 (ITT)	
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT: 516; mITT: 272; myITT: 231; (PPS-ITT: 347; PPS-mITT: 204, results not shown below)		
Descriptive statistics and estimate variability	Treatment group	Isavuconazole	Voriconazole
	Number of subject (ITT)	258	258
	Primary endpoint: (All cause mortality through day 42, ITT)	48/258 (18.6%)	52/258 (20.2%)
	% treatment difference; (95% CI)	-1.0 (-7.759, 5.683)	
	Key secondary endpoint: (DRC assessed overall response at EOT) (mITT)	50/143 (35.0%)	47/129 (36.4%)
	% treatment difference; (95% CI)	1.6 (-9.336, 12.572)	
	Secondary endpoint: (DRC assessed overall response at Day 42, mITT)	51/143 (35.7%)	46/129 (35.7%)
	% treatment difference; (95% CI)	-0.5 (-11.277, 10.329)	
	Secondary endpoint: (DRC assessed overall response at Day 84) (mITT)	36/143 (25,2%)	42/129 (32,6%%)
	% treatment difference; (95% CI)	8.2 (-1.993, 18.379)	
	Secondary endpoint: (DRC assessed overall response at EOT, myITT)	43/123 (35.0%)	42/108 (38.9%)
	% treatment difference; (95% CI)	4.0 (-7.973, 15.875)	
	Secondary endpoint: (All-cause mortality through day 42, mITT)	28/143 (19.6)	30/129 (23.3%)
	% treatment difference; (95% CI)	-2.6 (-12.184, 6.916)	
	Secondary endpoint: (All-cause mortality through day 84, mITT)	43/143 (30.1%)	48/129 (37.2%)
	% treatment difference; (95% CI)	-5.5 (-16.059, 5.148)	

Summary of efficacy for trial 9766-CL-0103 (Mucormycosis)

Title: Open-Label Study of Isavuconazole in the Treatment of Patients with Aspergillosis and Renal Impairment or of Patients with Invasive Fungal Disease Caused by Rare Moulds, Yeasts or Dimorphic Fungi (the VITAL study)		
Study identifier	Study report 9766-CL-01013/WSA-CS-003.	
Design	This was a phase 3, descriptive, open-label, multicenter study.	
	Duration of main phase:	Total study: April 2008 to January 2014 Patients were treated up to a maximum of 84 days. All patients enrolled under Amendments 3 and 5 and were eligible to receive

		treatment for a maximum of 180 days.	
	Duration of Run-in phase:	n/a	
	Duration of Extension phase:	Country-specific Amendment 4 allowed patients who were deriving clinical benefit to continue on treatment beyond 180 days.	
Hypothesis	Exploratory/descriptive		
Treatments groups	Isavuconazole i.v. + oral	Loading dose: 200 mg administered q8h i.v. **or** oral for 2 days. Maintenance dose: 200 mg once per day i.v. **or** oral. number enrolled: 146 (ITT)	
Endpoints and definitions	Primary endpoint	The primary objective of the study was to describe the efficacy of isavuconazole in the treatment of: invasive aspergillosis in patients with renal impairment **AND** In patients with IFD caused by rare moulds, yeasts or dimorphic fungi.	
	Secondary endpoint	The secondary objective of the study was to characterize the safety and tolerability while assessing additional efficacy of treatment with isavuconazole.	
	Exploratory endpoint	To summarize the concentration-time profiles of study drug and metabolite(s) if warranted in patients from the pharmacokinetic substudy.	
	Exploratory endpoint	To characterize pharmacokinetic trough values of study drug and metabolite(s) if warranted.	
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT (n=146) mITT-Aspergillus Population (n=24): RI (n-=20) + NRI (n=4) mITT-Mucorales Population (n=37): Primary (n=21) + Refractory (n=11) + Intolerant (n=5)		
Descriptive statistics	Treatment group: Isavuconazole		
Endpoints: ITT	All-cause Mortality through Day 42 and Day 84		
Endpoints: mITT-Aspergillus Population	All-cause Mortality through Day 42 and Day 84 DRC Assessed Overall Response at EOT by renal status DRC Assessed Overall Response at Day 42 and Day 84 DRC Assessed Clinical/Mycological/Radiological Response at EOT, Day 42 and Day 84		
Endpoints: mITT-Mucorales Population	All-cause Mortality through Day 42 and Day 84 DRC Assessed Overall Response at EOT DRC Assessed Overall Response at Day 42 and Day 84 DRC Assessed Clinical/Mycological/Radiological Response at EOT, Day 42 and Day 84		
Only results of the subgroup analyses considered most important are summarized below:			
mITT-Aspergillus Population (n=24), Endpoints:	**Total**	**RI**	**NRI**
All-cause Mortality through Day 42	12.5 (3/24)	15.0 (3/20)	0 (0/4)
All-cause Mortality through Day 84	25 (6/24)	25.0 (5/20)	25.0 (1/4)
DRC Assessed Overall Response at EOT	34.8 (8/23)	30.0 (6/20)	66.7 (2/3)

mITT-Mucorales Population (n=37), Endpoints:	**Total**	**Primary**	**Refractory**	**Intolerant**
All-cause Mortality through Day 42	37.8 (14/37)	33.3 (7/21)	45.5 (5/11)	40.0 (2/5)
All-cause Mortality through Day 84	43.2 (16/37)	42.9 (9/21)	45.5 (5/11)	40.0 (2/5)
DRC Assessed Overall Response at EOT	31.4 (11/35)	31.6 (6/19)	36.4 (4/11)	20.0 (1/5)

RI: Renally Impaired; NRI: Non Renally Impaired

Adverse events

Adverse events compared to voriconazole (phase 3 controlled population: Study 9766 CL 0104)

Overview of Treatment Emergent Adverse Events (TEAEs) and Deaths in the Phase 3 Controlled Population (study 9766-CL-0104)

	Isavuconazole (n = 257)	**Voriconazole (n = 259)**
Adverse events	247 (96.1%)	255 (98.5%)
Study drug-related adverse events	109 (42.4%)*	155 (59.8%)
Serious adverse events	134 (52.1%)	149 (57.5%)
Study drug-related serious adverse events	28 (10.9%)	29 (11.2%)
Adverse events leading to permanent discontinuation of study drug	37 (14.4%)*	59 (22.8%)
Study drug-related adverse events leading to permanent discontinuation of study drug	21 (8.2%)	35 (13.5%)
Adverse events leading to death	62 (24.1%)	72 (27.8%)
Study drug-related adverse events leading to death	7 (2.7%)	6 (2.3%)
Deaths through 28 days after the last dose of study drug	62 (24.1%)	70 (27.0%)
All deaths reported after the first dose of study drug†	81 (31.5%)	87 (33.6%)

*Statistical significance at ≤ 0.05 (Fisher's exact test). An AE with a missing seriousness is considered as serious.
†All reported deaths after first dose of study drug are summarized, regardless of the number of study days after the last dose of study drug.

Significant differences in TEAEs between the treatment groups observed for the following system organ classes (SOCs): skin disorders [isavuconazole: 86/257 (33.5%) vs voriconazole: 110/259 (42.5)%, P<0.05)], eye disorders [isavuconazole: 39/257 (15.2%) vs voriconazole: 69/259 (26.6%), P<0.05], hepatobiliary disorders [isavuconazole: 23/257 (8.9%) vs voriconazole: 42/259 (16.2%), (P<0.05) and numerically lower rates (by at least 5%) were reported for psychiatric and cardiac disorders.

The 5 most common TEAEs (occurring with an incidence ≥ 5%) in the isavuconazole or voriconazole treatment groups, respectively, were nausea (27.6% vs 30.1%), vomiting (24.9% vs 28.2%), diarrhea (23.7% vs 23.2%), pyrexia (22.2% vs 30.1%), and hypokalemia (17.5% vs 21.6%).

Drug-related TEAE's

Fewer isavuconazole-treated patients experienced study drug related TEAEs as determined by the investigators than voriconazole-treated patients (42.4% vs 59.8%, P<0.05) (see below table) and this overall lower rate with isavuconazole vs. voriconazole reflected the following SOCs: hepatobiliary disorders (1.9% vs. 10.0%), investigations (9.7% vs. 18.1%), eye disorders (3.1% vs. 10.8%) and psychiatric disorders (2.3% vs. 11.2%). These differences were primarily influenced by imbalances in rates for the following PTs:

- Hepatobiliary disorders SOC: hepatic function abnormal (2 (0.8%) vs. 9 (3.5%)), hyperbilirubinaemia (1 (0.4%) vs. 6 (2.3%)), cholestasis (0 vs. 3 (1.2%)), hepatic failure (0 vs. 3 (1.2%)) and jaundice (0 vs. 2 (0.8%))
- Investigations SOC: increased GGT (6 (2.3%) vs. 14 (5.4%)), ALP (5 (1.9%) vs. 11 (4.2%)), AST (5 (1.9%) vs. 11 (4.2%)) or ALT (4 (1.6%) vs. 11 (4.2%)) and QT prolonged (1 (0.4%) vs. 8 (3.1%))
- Eye disorders SOC: visual impairment (1 (0.4%) vs. 15 (5.8%)), visual acuity reduced (0 vs. 4 (1.5%))
- Psychiatric disorders SOC: hallucination (1 (0.4%) vs. 11 (4.2%)), visual hallucination (0 vs. 9 (3.5%))

The common study drug related TEAEs that occurred in ≥ 2% of patients in either the isavuconazole or voriconazole treatment groups are shown in the following table. The proportion of patients was generally similar between treatment groups. Study drug related TEAEs that occurred in ≥ 5% of patients in either the isavuconazole or voriconazole treatment groups, respectively, were nausea (7.4% vs 8.1%), vomiting (5.1% vs 8.5%), increased GGT (2.3% vs 5.4%) and visual impairment (0.4% vs 5.8%).

Study Drug Related Treatment Emergent Adverse Events in ≥ 2% of Patients in Either Treatment Group in the Phase 3 Controlled Population (study 9766-CL-0104)

MedDRA v12.1 Preferred Term	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**109 (42.4%)**	**155 (59.8%)**
Nausea	19 (7.4%)	21 (8.1%)
Vomiting	13 (5.1%)	22 (8.5%)
Dyspnoea	8 (3.1%)	2 (0.8%)
Hypokalaemia	7 (2.7%)	5 (1.9%)
Gamma-glutamyl transferase increased	6 (2.3%)	14 (5.4%)
Headache	6 (2.3%)	5 (1.9%)
Aspartate aminotransferase increased	5 (1.9%)	11 (4.2%)
Blood alkaline phosphatase increased	5 (1.9%)	11 (4.2%)
Rash	5 (1.9%)	7 (2.7%)
Alanine aminotransferase increased	4 (1.6%)	11 (4.2%)
Chills	4 (1.6%)	7 (2.7%)
Hepatic function abnormal	2 (0.8%)	9 (3.5%)
Electrocardiogram QT prolonged	1 (0.4%)	8 (3.1%)
Hallucination	1 (0.4%)	11 (4.2%)
Hyperbilirubinaemia	1 (0.4%)	6 (2.3%)
Visual impairment	1 (0.4%)	15 (5.8%)
Hallucination, visual	0	9 (3.5%)

Study drug-related adverse events include those reported as remotely, possibly or probably related to study drug by the investigator and those with a missing relationship.
Sorting order: descending percentage in isavuconazole group for all adverse events.

Overview of Treatment Emergent Adverse Events and Deaths in the Phase 3 Uncontrolled Population (study 9766-CL-0103)

	RI (n = 59)	NRI (n = 87)	Total (n = 146)
TEAEs	59 (100.0%)	80 (92.0%)	139 (95.2%)
Study Drug-Related TEAEs	26 (44.1%)	34 (39.1%)	60 (41.1%)
Serious TEAEs	43 (72.9%)	46 (52.9%)	89 (61.0%)
Study Drug-Related Serious TEAEs	4 (6.8%)	9 (10.3%)	13 (8.9%)
TEAEs Leading to Permanent Discontinuation of Study Drug	11 (18.6%)	8 (9.2%)	19 (13.0%)
Study Drug-Related TEAEs Leading to Permanent Discontinuation of Study Drug	5 (8.5%)	2 (2.3%)	7 (4.8%)
TEAEs Leading to Death	21 (35.6%)	23 (26.4%)	44 (30.1%)
Study Drug-Related TEAEs Leading to Death	1 (1.7%)	0	1 (0.7%)
Deaths†	24 (40.7%)	23 (26.4%)	47 (32.2%)
Deaths Through 28 Days after the Last Dose of Study Drug	20 (33.9%)	22 (25.3%)	42 (28.8%)

Moderate or severe TEAEs (determined by the investigators) were reported in the respective isavuconazole and voriconazole treatment groups in the following SOCs: hepatobiliary disorders (6.6% and 10.8%), skin disorders (11.3% and 15.8%) and cardiac disorders (8.6% and 14.3%).

RI patients mostly had higher rates of TEAEs vs. NRI patients. The most common were vomiting (24.7%) and nausea (23.3%) with diarrhoea in 18.5%. Overall, 49.3% experienced TEAEs of severe intensity and 28.8% had TEAEs with a maximum intensity of moderate. The most common drug-related TEAEs were nausea (7.5%) and vomiting (6.2%).

Other adverse effects of special interest are acute pancreatitis, psychiatric events, potential ocular toxicity, potential anaphylaxis and severe cutaneous adverse reactions (SCAR), injection site reactions, potential infusion-related reactions, Torsades de pointes, and Syncope and loss of consciousness.

3.3.7. Discussion on clinical efficacy and safety

As overall of efficacy and safety profile presented above (3.3.6) per EMA/CHMP assessment report, reviewed by PICOS model, the reviewer is certain of efficacy and safety to some extent, and agrees with risks listed in the RMP.

The Advisor Expert Committee has accessed to the information about breakthrough invasive fungal infections (IFIs), LOQ was listed. The applicant provided a justification. The expert and the reviewer agree. The point is solved.

3.3.8. Conclusions on clinical efficacy and safety

Based on a clinical perspective the indication for treatment of invasive aspergillosis is approvable.

The efficacy data for support the indication for "mucormycosis in patients for whom amphotericin B is inappropriate" is submitted with limitations of data.

The safety profile of isavuconazole, as observed when using the posology recommended in SmPC is considered reassuring.

3.3.9. Pharmacovigilance system and risk management plan

The Pharmacovigilance system and Risk Management Plan were provided in the eCTD 1.8 Information relating to Pharmacovigilance. The details were summarized as the following tables:

Important identified risks	Hepatic function abnormal or hepatitis Infusion-related reactions Severe cutaneous adverse reactions (SCARs) Arrhythmia due to QT shortening
Important potential risks	Teratogenicity Effect on children exposed to isavuconazole via breast milk Development of resistant strains Off-label use
Missing information	Use in patients < 18 years-old Use in patients with severe hepatic impairment Efficacy in invasive aspergillosis in Asian patients Clinical efficacy and safety of isavuconazole treatment in patients infected with Mucorales species

4. Benefit risk assessment

Benefit-risk balance

Based on the data from quality, non-clinic, and clinical aspects, the benefit-risk balance is positive for used in adults for the treatment of

- Invasive aspergillosis
- Mucomycosis in patients for whom amphotericin B is inappropriate.

5. Conditions for marketing authorisation and product information

5.1. Conditions for the marketing authorisation

Cresemba 100 mg hard capsules and Cresemba powder for concentrate for solution for infusion 200 mg/vial has the important conditions for the marketing authorisation:

1) Utilized under the only hospital, specified on the label.
2) Perform PIL user testing within 12 months after authorisation and report to Thai FDA.
3) Monitor the safety of medicine as the protocol in SMP (section 1.8.3).
4) Complied to the risk management plan as the information in section 1.8.2 Risk management system in eCTD.
5) Revise the product information including summary product characteristics (SmPC) and patient information leaflet (PIL) in the section related to efficacy and safety in accordance with technical knowledge which may be changed after authorisation.
6) Regardless to any cause of the incidents, applicant will send the details on re-call according to FDA request-form to authority within 30 days, after the protocol has been initiated.
7) Submit the carcinogenicity studies reports within 24 months after authorisation.

5.2. Summary of product characteristics (SmPC)

The SmPC of Cresemba 100 mg hard capsules and Cresemba powder for concentrate for solution for infusion 200 mg/vial was provided in appropriate contents and format that in accordance with the quality, non-clinical, and clinical data. The administrative contents were reflecting as the contents in eCTD and appropriate. The SmPC of Cresemba 100 mg hard capsules and Cresemba powder for concentrate for solution for infusion 200 mg/vial are available as the attachments in Appendix 6.2.

5.3. Labelling

The labelling meets the criteria for readability as set out in the standard of Thai FDA (2009) and Guideline for Leaflet Development and ASEAN Harmonization. The details of labelling are summarized as the following:

Cresemba 100 mg hard capsules

UNIT CARTON

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition	✓	✓
11	Name and address of Applicant	✓	✓
10	Country's Registration Number	✓	✓
12	Name and address of manufacturer	✓	✓
13	Special labelling	✓	✓
14	Recommended Daily Allowance (Vitamins and minerals)	n/a	n/a
15	Warning (as indicated by Ministerial Announcement)	n/a	n/a
16	Pack sizes	✓	✓

✓	Suitable data
X	Unavailable / Inappropriate
n/a	Not available or Not applicable

BLISTER

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Name of Active Ingredient(s)#	✓	✓
3	Strength of Active Ingredient(s)#	✓	✓
4	Batch Number	✓	✓
5	Expiration date	✓	✓
6	Name/Logo of Manufacturer or Applicant	✓	✓
7	Country's Registration Number	n/a	n/a

✓	Suitable data
X	Unavailable / Inappropriate
n/a	Not available or Not applicable
#	Exempted for product with more than 3 APIs

Cresemba powder for concentrate for solution for infusion 200 mg/vial

UNIT CARTON

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition	✓	✓
10	Country's Registration Number	✓	✓
11	Name and address of Applicant	✓	✓
12	Name and address of manufacturer	✓	✓
13	Special labelling	✓	✓
14	Recommended Daily Allowance (Vitamins and minerals)	n/a	n/a
15	Warning (as indicated by Ministerial Announcement)	n/a	n/a
16	Pack sizes	✓	✓

✓ Suitable data
X Unavailable / Inappropriate
n/a Not available or Not applicable

INNER LABEL

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Dosage form*	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date*	n/a	n/a
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition*	n/a	n/a
10	Country's Registration Number*	n/a	n/a
11	Name and address of Applicant*	n/a	n/a
12	Name and address of manufacturer*	n/a	n/a
13	Special labelling*	n/a	n/a
14	Recommended Daily Allowance (Vitamins and minerals)*	n/a	n/a
15	Warning (as indicated by Ministerial Announcement)*	n/a	n/a
16	Pack sizes	n/a**	n/a**

✓ Suitable data
X Unavailable / Inappropriate
n/a Not available or Not applicable
* Exempted for small ampoule and vial
** Cresemba powder for concentrate for solution for infusion 200 mg/vial has the pack size same as dosage strength due to single dose formula

5.4. Patient information leaflet (PIL)

The content and format of PIL complied with Thai FDA guideline for leaflet development (3 Jul 2013), as well as the Guideline for Leaflet Development (May 2019) implemented by Division of Health Product Entrepreneurship Promotion. However, the applicant has to commit for user testing to ensure that PIL is legible, clear, and easy to understand.