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Pharmacokinetic Effects of Isavuconazole Coadministration With the Cytochrome P450 Enzyme Substrates Bupropion, Repaglinide, Caffeine, Dextromethorphan, and Methadone in Healthy Subjects

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Abstract

This report describes phase 1 clinical trials performed to assess interactions of oral isavuconazole at the clinically targeted dose (200 mg, administered as isavuconazonium sulfate 372 mg, 3 times a day for 2 days; 200 mg once daily [QD] thereafter) with single oral doses of the cytochrome P450 (CYP) substrates: bupropion hydrochloride (CYP2B6; 100 mg; n = 24), repaglinide (CYP2C8/CYP3A4; 0.5 mg; n = 24), caffeine (CYP1A2; 200 mg; n = 24), dextromethorphan hydrobromide (CYP2D6/CYP3A4; 30 mg; n = 24), and methadone (CYP2B6/CYP2C19/CYP3A4; 10 mg; n = 23). Compared with each drug alone, coadministration with isavuconazole changed the area under the concentration-time curves (AUC_∞) and maximum concentrations (C_{max}) as follows: bupropion, AUC_∞ reduced 42%, C_{max} reduced 31%; repaglinide, AUC_∞ reduced 8%, C_{max} reduced 14%; caffeine, AUC_∞ increased 4%, C_{max} reduced 1%; dextromethorphan, AUC_∞ increased 18%, C_{max} increased 17%; R-methadone, AUC_∞ reduced 10%, C_{max} increased 3%; S-methadone, AUC_∞ reduced 35%, C_{max} increased 1%. In all studies, there were no deaths, 1 serious adverse event (dextromethorphan study; perioral numbness, numbness of right arm and leg), and adverse events leading to study discontinuation were rare. Thus, isavuconazole is a mild inducer of CYP2B6 but does not appear to affect CYP1A2-, CYP2C8-, or CYP2D6-mediated metabolism.

Invasive fungal diseases are a growing healthcare burden and are associated with significant morbidity and mortality.[1,2] Patients with hematological malignancies, undergoing transplants, and receiving immunosuppressive therapy are particularly susceptible due to their immunocompromised state.[3] However, existing therapies are limited in their efficacy and safety, especially against rarer and resistant pathogens, and new antifungal agents are urgently needed.

Isavuconazonium sulfate is the water-soluble prodrug of the triazole antifungal agent isavuconazole and is available in cyclodextrin-free oral and intravenous formulations.[4,5] Isavuconazole disrupts biosynthesis of ergosterol, an essential component of fungal cell membranes.[6,7] On the basis of results in the SECURE trial[8] and the VITAL trial,[9,10] isavuconazonium sul-

fate has been approved by the US Food and Drug Administration (FDA) for the primary treatment of

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adult patients with invasive aspergillosis or invasive mucormycosis. It also has been approved by the European Medicines Agency for the primary treatment of adult patients with invasive aspergillosis and treatment of patients with mucormycosis for whom treatment with amphotericin B is inappropriate.

Establishing isavuconazole's drug-interaction profile is important because it may be prescribed for patients with coexisting illnesses who typically require a number of concomitant medications. Because plasma concentrations observed with clinically recommended dosing (200 mg 3 times daily [TID] for 2 days, then 200 mg daily) typically are <7 μg/mL (data on file), IC_{50} or K_i values of ≤ 16 μmol/L might be the most clinically relevant (isavuconazole molecular weight, 437.47 g/mol). Isavuconazole has demonstrated weak inhibition of the transporters P-glycoprotein (P-gp; in P-gp–transfected porcine kidney epithelial cell monolayers, inhibition constant [IC_{50}] with [^{3}H]digoxin substrate, 25.7 μmol/L), organic cation transporters 1 and 2 (OCT1 and OCT2; in stably transfected human embryonic kidney [HEK293] cells, IC_{50} for OCT1 with [^{14}C]tetraethylammonium bromide substrate, 3.74 μmol/L; IC_{50} for OCT2 with [^{14}C]metformin substrate, 1.97 μmol/L), and multidrug and toxin extrusion protein 1 (in stably transfected HEK293 cells, IC_{50} with ^{14}C-metformin substrate, 6.31 μmol/L; see also Yamazaki et al[11]), as well as weak inhibition of uridine diphosphateglucuronosyl transferase (in human liver microsomes, IC_{50} for 17β-estradiol 3-glucuronidation [UGT1A1], 9.0 μmol/L; propofol glucuronidation [UGT1A9], 19 μmol/L; morphine 3-glucuronidation [UGT2B7], 44 μmol/L; see also Groll et al[12]). It is also a sensitive substrate and moderate inhibitor of CYP3A4 (66.2% metabolized in CYP3A4-expressing pooled human liver microsomes; the K_i of isavuonazole for midazolam and testosterone, 0.62 μmol/L and 1.93 μmol/L, respectively; see also accompanying manuscripts[12,13]). However, interactions with other important CYP isoenzymes involved in drug metabolism are not documented.

In studies using human liver microsomes in vitro, isavuconazole has been identified as an inhibitor of CYP1A2 (IC_{50} 38.5 μmol/L), CYP2B6 (IC_{50} 15.1 μmol/L), CYP2C8 (IC_{50} 5.07 μmol/L), CYP2C9 (K_i 4.78 μmol/L), CYP2C19 (K_i 5.40 μmol/L), and CYP2D6 (K_i 4.82 μmol/L), but not CYP2A6 or CYP2E1 (IC_{50} >100 μmol/L; data on file). In experiments performed in cultured human hepatocytes, isavuconazole was also shown in vitro to be an inducer of CYP2B6 (increases up to 13.4-fold and 11.4-fold in bupropion hydroxylase activity and mRNA, respectively), and to a lesser extent CYP3A4 (increases up to 3.4-fold and 6.4-fold in testosterone hydroxylase activity and mRNA, respec-

tively), CYP2C8 (increases up to 2.6-fold and 4.3-fold in amodiaquine *N*-dealkylase activity and mRNA, respectively), CYP2C9 (increases up to 3.1-fold in diclofenac 4′-hydroxylase activity only), and CYP1A2 (increases up to 2.8-fold and 5.4-fold in phenacetin *O*-dealkylase activity and mRNA, respectively; data on file). In this article, we report the results of phase 1 trials using substrate probes to assess potential in vivo CYP-mediated interactions of isavuconazole with bupropion (CYP2B6[14]), repaglinide (CYP2C8; also a substrate for CYP3A4[15]), caffeine (CYP1A2[16]), dextromethorphan (CYP2D6; also a substrate for CYP3A4[17]), and methadone (CYP2B6, CYP2C19, and CYP3A4[18–26]), most of which are specified in regulatory guidance from the US FDA and European Medicines Agency.

Methods

Study Design

Study protocols were approved by the Institutional Review Board for each participating study site (bupropion study, Independent Investigational Review Board, Inc., Plantation, Florida; caffeine/repaglinide, dextromethorphan, and methadone studies, Aspire IRB, LLC, Santee, California). All studies were conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice, International Conference on Harmonisation guidelines, and local regulations. Participating subjects provided written, informed consent in advance of any study procedures.

These were phase 1, single-center, open-label, drug-interaction studies conducted to evaluate potential interactions between isavuconazole (administered as isavuconazonium sulfate; CRESEMBA® oral capsules; Astellas Pharma US, Inc., Northbrook, Illinois) and the CYP substrate probes. Study centers, trial registration numbers, and dates of the study for each drug were as follows: bupropion hydrochloride (WELLBUTRIN® oral tablets, GlaxoSmithKline, Research Triangle Park, North Carolina), Clinical Pharmacology of Miami (Miami, Florida), NCT01635972, May to July, 2012; repaglinide (PRANDIN® oral tablets, Novo Nordisk Inc., Princeton, New Jersey); and caffeine (VIVARIN® oral tablets, GlaxoSmithKline), PAREXEL Early Phase Clinical Unit (Baltimore, Maryland), NCT02128321, January to February, 2014; dextromethorphan hydrobromide (ROBITUSSIN® oral capsules, Pfizer Inc., New York, New York), PAREXEL Early Phase Clinical Unit (Baltimore, Maryland), NCT01651325, May to July, 2012; and methadone hydrochloride (DOLOPHINE® oral tablets, Roxane Laboratories, Inc., Columbus, Ohio), PAREXEL International (Glendale, California), NCT01582425, May to July, 2012.

Adult, medication-free, male and female subjects, aged 18 to 55 years, weighing ≥45 kg, with a body mass index (BMI) of 18 to 32 kg/m^2, and with no clinically significant coexisting disease history, were eligible to enroll in these studies.

Dosing and Sampling Schedules

In this report, dosing information is expressed as the isavuconazole equivalent of the prodrug: oral capsules each contained isavuconazonium sulfate 186 mg, equivalent to isavuconazole 100 mg. The clinically targeted dose of isavuconazole was 200 mg TID loading dose (administered as isavuconazonium sulfate 372 mg) for 2 days, followed by 200 mg QD.

Bupropion. Subjects were screened (from day –21 to day –2) and checked in at the study center (day –1), where they remained until day 21. A follow-up visit was conducted on day 27 (±2 days).

On day 1 of the study, subjects received a single oral dose of bupropion hydrochloride 100 mg, followed by a 7-day washout period (Figure 1A). On days 8 and 9, subjects received oral isavuconazole 200 mg TID (8 hours apart), then 200 mg QD on days 10 to 20. Subjects received a further single oral dose of bupropion hydrochloride 100 mg concurrently with isavuconazole on day 15. Subjects fasted for ≥10 hours prior to bupropion hydrochloride administration and continued to fast for 4 hours following administration. On day 15, isavuconazole was administered immediately before bupropion hydrochloride.

Blood samples were collected for pharmacokinetic (PK) analysis of bupropion and its metabolite, hydroxybupropion, at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 48, 72, and 96 hours postdose on days 1 and 15. Additional samples were also drawn at 120 and 144 hours postdose on day 15. Samples for PK analysis of isavuconazole were collected at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours postdose on days 14 and 15.

Repaglinide and Caffeine. Subjects were screened (day –28 to day –2) and checked in to the study center (day –1), where they remained until day 17. A follow-up telephone call was made on day 24 (±2 days).

Participating subjects received a single oral dose of repaglinide 0.5 mg on day 1 and a single oral dose of caffeine 200 mg on day 3 (Figure 1B). After a short washout period, subjects received oral isavuconazole 200 mg TID (8 hours apart) on days 5 and 6, then 200 mg QD on days 7 to 17. Subjects also received additional single oral doses of repaglinide 0.5 mg and caffeine 200 mg concurrent with isavuconazole on days 14 and 16, respectively. For doses on days 1, 3, 13, 14, and 16, subjects fasted for ≥10 hours prior to dosing and continued to fast for 4 hours after administration.

Blood samples were collected for PK analysis of repaglinide on days 1 and 14 at predose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose; and for PK analysis of caffeine/1,7-dimethylxanthine on days 3 and 16 at predose and at 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose. Samples for PK analysis of isavuconazole were collected at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose on days 13, and 14 as well as at predose and at 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose beginning on day 16.

Dextromethorphan. Subjects were screened (day –28 to –2), before check-in at the study center (day –1), where they remained until the end of study procedures (day 13). Subjects returned to the study center for a follow-up visit on day 21 (±2 days).

On day 1, subjects received a single dose of oral dextromethorphan hydrobromide 30 mg (Figure 1C). Following washout, subjects received oral isavuconazole 200 mg TID (8 hours apart) on days 6 and 7, then 200 mg QD on days 8 to 12. On day 10, subjects also received a single oral dose of dextromethorphan hydrobromide 30 mg concurrent with isavuconazole. Subjects fasted for ≥10 hours prior to dextromethorphan hydrobromide administration and continued to fast for 4 hours following administration. On day 10, isavuconazole was administered immediately before dextromethorphan hydrobromide.

Blood samples were collected for PK analysis of dextromethorphan and its metabolite, dextrorphan, at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 48, and 72 hours postdose on days 1 and 10. Samples were also collected for PK analysis of isavuconazole at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours postdose on days 9 and 10. In order to evaluate the impact of the effect of genetic polymorphism of the CYP2D6 enzyme on dextromethorphan metabolism, 1 sample was collected prior to dosing on day 1 for analysis of genotyping for CYP2D6 *2, *3, *4, *5, *6, *7, *9, *10, *14, *17, *29, *41, *45, *46, and gene diversity (GD) alleles using validated genotyping methods.[27–33] Subjects who carried 2 of the mutant alleles *3, *4, *5, *6, and *7 were considered poor metabolizers. Subjects who carried 1 mutant allele and 1 reduced-activity allele (*9, *10, *17, *29, *41, *45, or *46) or 1 mutant allele and 1 functional allele (wild-type [WT] or *2), or 2 reduced-activity alleles were considered intermediate metabolizers. Subjects with the following alleles were classified as extensive metabolizers: *10/WT, *17/GD, *17/WT, *2/*10, *2/*17, *2/*2, *2/*29, *2/*41, *2/*45, *2/*9, *2/WT, *29/WT, *4/GD, *41/WT, *46/GD, *5/GD, *6/GD, *9/WT or WT/WT. Subjects with at least 3 copies of a functional allele were ultrarapid metabolizers.
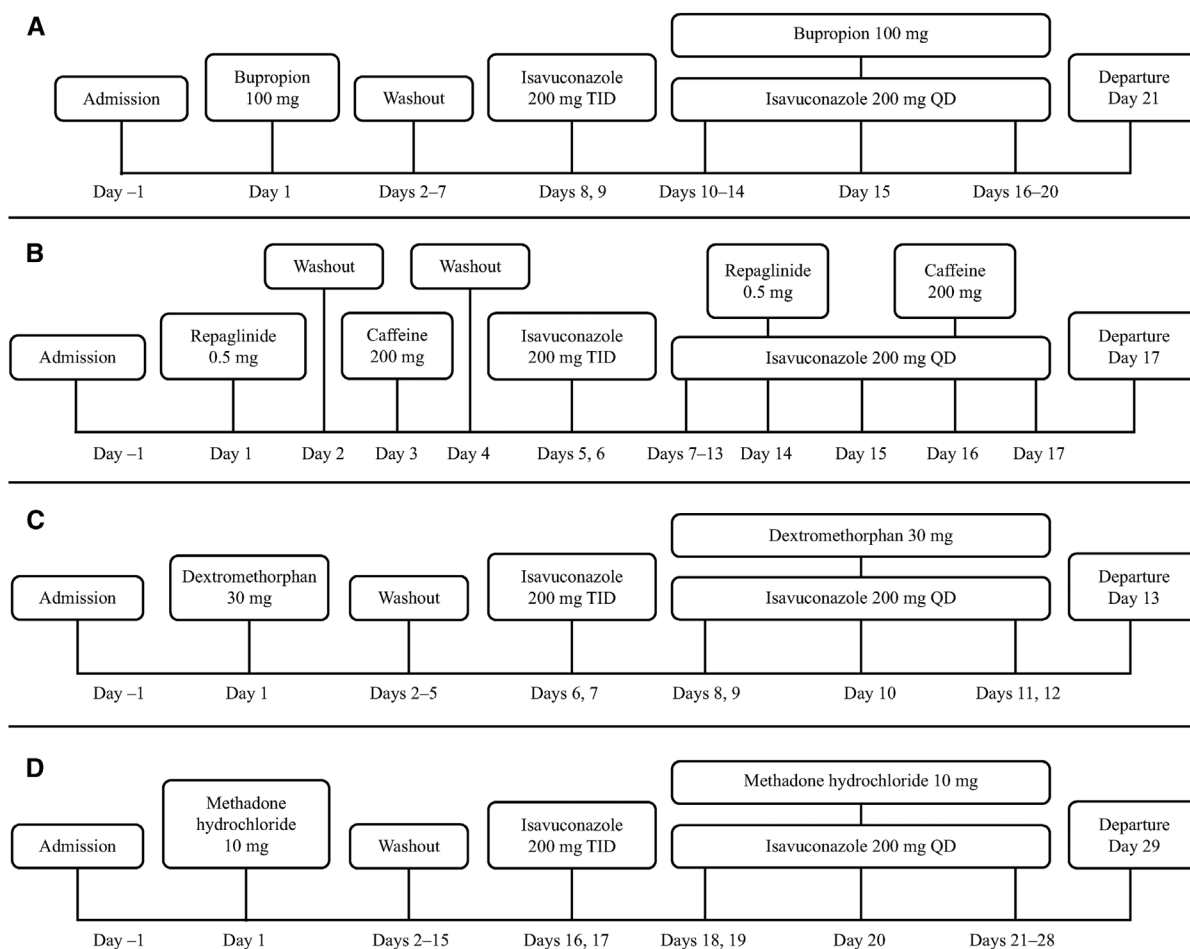
Figure 1. Clinical study designs. QD, once daily; TID, 3 times a day. Isavuconazole 200 mg was administered as isavuconazonium sulfate 372 mg.

Methadone. Following screening (day –28 to day –2), subjects checked in at the study center (day –1), where they remained intermittently until day 29. A follow-up visit was conducted at the study center on day 36 (±2 days).

Subjects received a single oral dose of methadone hydrochloride 10 mg on day 1, followed by a washout period (Figure 1D). On days 16 and 17, subjects received oral isavuconazole 200 mg TID (8 hours apart), then 200 mg QD on days 18 to 28. An additional single oral dose of methadone hydrochloride 10 mg was coadministered with isavuconazole on day 20. Subjects fasted for ≥10 hours prior to administration of methadone on days 1 and 20 and dosing of isavuconazole on day 19 and continued to fast for 4 hours after administration. On day 20, isavuconazole was administered immediately before methadone hydrochloride.

Blood samples were drawn for PK analysis of R- and S-methadone at predose on days 1 and 20 and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120, 144, 168, 192, and 216 hours postdose. Additional samples were taken for PK analysis of isavuconazole on days 19 and 20 at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours postdose.

Pharmacokinetic Assessments

Plasma concentrations of all analytes were measured using validated liquid chromatography–mass spectrometry/mass spectrometry methods. The method for bioanalysis of isavuconazole is described in an accompanying paper.[13] Details for bioanalysis of all other analytes are provided in the Methods section of Supplementary Materials. The primary parameters calculated for each of the substrate probes under investigation and their metabolites were area under the concentration-time curve (AUC) from time 0 to infinity (AUC_∞), AUC from time of dosing to time of last measurable concentration (AUC_{last}), and maximum drug concentration (C_{max}). Secondary variables included AUC for a dosing interval (AUC_τ; isavuconazole only), time to C_{max} (t_{max}), elimination half-life ($t_{1/2}$), volume of distribution (V_z/F), and clearance (CL/F).

The PK of both R- and S-enantiomers of methadone was assessed. Dextromethorphan and dextrorphan PK parameters were also calculated for the overall trial population and for groups subdivided according to their CYP2D6 metabolizer status (ie, intermediate or extensive).

Safety Assessments

Safety and tolerability were examined by monitoring treatment-emergent adverse events (TEAEs), vital-sign measurements, 12-lead electrocardiograms, clinical laboratory testing (hematology, chemistry, and urinalysis), and physical examinations.

Statistics

Baseline demographics, clinical characteristics, and TEAEs were summarized using descriptive statistics for all patients who received ≥ 1 dose of study drug. Pharmacokinetics were assessed in all subjects who received ≥ 1 dose of study drug and whose PK data were adequate for the calculation of ≥ 1 of the primary PK parameters. Levels of analyte below the level of quantification were entered as 0 for calculations.

Noncompartmental analyses were conducted with Phoenix® WinNonlin® version 5.2.1 or higher (Pharsight Corp, Mountain View, California). All data processing, summarization, and analyses were conducted using SAS® version 9.1 or higher (Statistical Analysis Software, Cary, North Carolina).

To assess the effect of isavuconazole on the PK of each substrate probe and metabolite, log-transformed AUC and C_{max} values were analyzed using a linear mixed-effects model, with treatment as a fixed effect and subject as a random effect. For dextromethorphan and dextrorphan, the model also included CYP2D6 predicted phenotype as a fixed effect. The 90% confidence intervals (CIs) were constructed around the geometric least-squares mean ratio of PK parameters measured during dosing with the substrate probe plus isavuconazole vs dosing with the substrate probe alone.

Results

Pharmacokinetics

Bupropion. In total, 24 subjects enrolled in and completed the bupropion study (Table S1). Coadministration with isavuconazole decreased mean plasma AUC_∞, AUC_{last}, and C_{max} of bupropion by 30% to 40% (Figure 2A, Tables 1 and 2) and resulted in a corresponding increase of these parameters for the hydroxybuproprion metabolite (Figure 2B, Tables S2, S3). The mean plasma AUC_τ, C_{max}, and median t_{max} of isavuconazole were similar in the presence and absence of bupropion compared with isavuconazole alone (Table 3).

Table I. Summary of Plasma Pharmacokinetic Parameters of CYP Substrate Probes in the Presence and Absence of Isavuconazole

Parameter[a]	Bupropion		Repaglinide		Caffeine		Dextromethorphan		R-methadone		S-methadone	
	Bupropion Alone (n = 24)	Bupropion + Isavuconazole (n = 24)	Repaglinide Alone (n = 24)	Repaglinide + Isavuconazole (n = 22)[b]	Caffeine Alone (n = 24)	Caffeine + Isavuconazole (n = 22)[b]	Dextromethorphan Alone (n = 24)	Dextromethorphan + Isavuconazole (n = 23)[c]	Methadone Alone (n = 23)	Methadone + Isavuconazole (n = 22)[d]	Methadone Alone (n = 23)	Methadone + Isavuconazole (n = 22)[d]
AUC_∞, ng·h/mL	715.7 (216.2)	425.9 (157.5)	11.4 (4.8)	10.5 (3.9)	44,896 (18,982)	47,724 (24,410)	45.7 (54.8)[e]	54.4 (64.5)[e]	557.1 (184.6)	500.5 (166.7)	739.2 (304.6)	500.2 (254.2)
AUC_{last}, ng·h/mL	684.9 (205.8)	406.2 (155.0)	10.8 (4.7)	9.9 (3.8)	43,367 (16,463)	45,581 (20,208)	40.3 (53.2)	48.6 (62.6)	519.9 (158.7)	476.9 (145.8)	714.9 (285.0)	491.9 (247.9)
C_{max}, ng/mL	148.6 (49.1)	102.5 (33.7)	8.7 (3.6)	7.6 (3.2)	4319 (745)	4256 (651)	3.9 (4.3)	4.6 (5.1)	12.7 (3.6)	13.1 (3.7)	22.0 (6.9)	22.1 (7.3)
t_{max}, hours	1.5 (1.0-2.0)	1.5 (1.0-2.0)	0.5 (0.5-1.0)	0.5 (0.5-1.5)	0.8 (0.5-2.0)	0.8 (0.5-3.0)	3.0 (1.5-5.0)	3.0 (1.5-5.0)	4.0 (2.0-6.0)	3.0 (2.0-8.0)	3.0 (1.5-4.0)	2.5 (1.0-6.0)
$t_{1/2}$, hours	25.0 (7.5)	19.2 (7.2)	1.1 (0.4)	1.0 (0.2)	6.9 (3.1)	7.4 (3.7)	8.2 (3.6)[f]	8.0 (2.8)[g]	53.0 (14.0)	42.1 (14.4)	39.2 (12.0)	23.6 (10.0)
CL/F, L/h	151.9 (44.2)	271.1 (107.3)	54.0 (27.6)	54.9 (23.0)	5.2 (2.3)	5.1 (2.1)	3952 (8034)[e]	2084 (2165)[e]	10.1 (3.8)	11.2 (4.2)	8.3 (4.6)	13.2 (7.5)

AUC, area under the concentration-time curve; CL/F, clearance; C_{max}, maximum concentration; ISAV, isavuconazole; ND, not done; t_{max}, time to maximum concentration; $t_{1/2}$, terminal half-life; TEAE, treatment-emergent adverse event.

[a]AUC_∞, AUC_{last}, CL/F, C_{max}, $t_{1/2}$, and V_z/F values are mean (standard deviation); t_{max} is median (range).

[b]Two subjects discontinued on day 13 due to TEAEs.

[c]One subject discontinued on day 8 due to TEAEs.

[d]One subject discontinued on day 5 due to a TEAE.

[e]Values for 2 subjects were excluded from calculation as unreliable because the percentage of area extrapolated in the calculation of AUC_∞ exceeded 20%.

[f]Values for 2 subjects were excluded from calculation because concentration was below the lower limit of quantification in the terminal phase, thereby precluding calculation of terminal half-life.

[g]Values for 1 subject was excluded from calculation because concentration was below the lower limit of quantification in the terminal phase, thereby precluding calculation of terminal half-life.
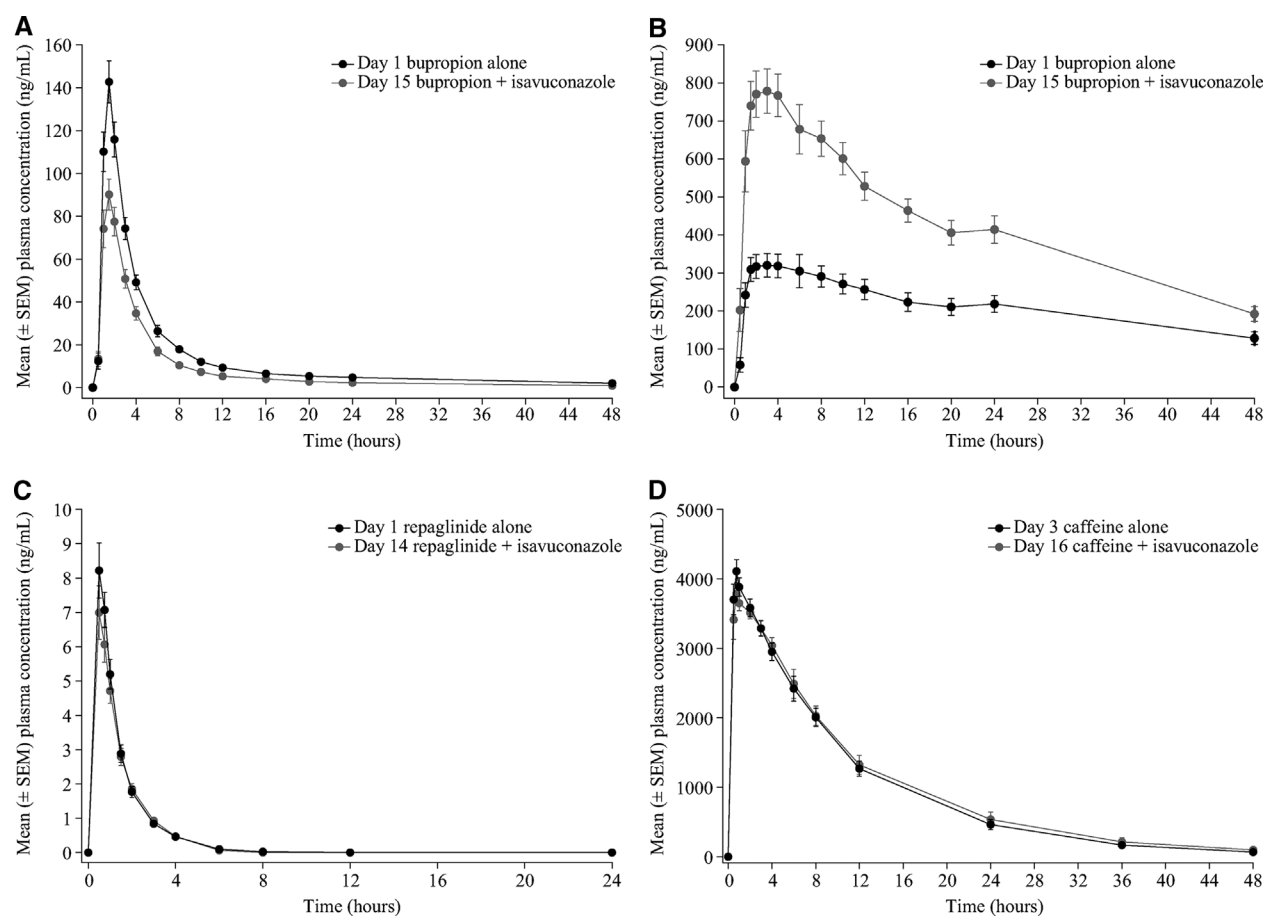
Figure 2. Mean plasma concentration-time profiles of bupropion (A), hydroxybupropion (B), repaglinide (C), and caffeine (D) in the presence and absence of isavuconazole. EM, extensive metabolizer; IM, intermediate metabolizer; SEM, standard error of the mean.

Table 2. Statistical Analysis of the Effect of Isavuconazole on the Plasma Pharmacokinetics of CYP Substrate Probes and Their Metabolites[a]

	Geometric Least-Squares Mean Ratio, % (90%CI)[b]					
Parameter	Bupropion	Repaglinide	Caffeine	Dextromethorphan	R-Methadone	S-Methadone
AUC_∞	58 (52, 64)	92 (86, 100)	104 (97, 112)	118 (102, 135)	90 (84, 96)	65 (59, 72)
AUC_{last}	57 (52, 64)	91 (85, 97)	104 (97, 111)	123 (106, 142)	92 (86, 97)	66 (59, 73)
C_{max}	69 (62, 77)	86 (79, 93)	99 (93, 107)	117 (102, 135)	104 (97, 111)	101 (95, 108)

AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum concentration.
[a]Results are based on a model of natural log–transformed parameters with treatment as a fixed effect (predicted phenotype also a fixed effect for dextromethorphan) and subject as a random effect.
[b](CYP substrate probe + isavuconazole)/CYP substrate probe alone.

Repaglinide and Caffeine. Twenty-four subjects enrolled in the repaglinide and caffeine study, and 22 subjects completed the study (Table S1). Repaglinide exposure (AUC_∞ and AUC_{last}) and C_{max} were slightly lower (~8% to 14%) in the presence vs absence of isavuconazole, whereas exposure and C_{max} for caffeine were comparable in the presence and absence of isavuconazole (Figure 2C, D; Tables 1 and 2). Coadministration

with either repaglinide or caffeine did not affect the AUC_τ, C_{max}, or t_{max} of isavuconazole (Table 3).

Dextromethorphan. A total of 24 subjects enrolled in this study, and 23 subjects completed the study (Table S1). Mean plasma AUC_∞, AUC_{last}, and C_{max} of dextromethorphan were increased by approximately 20% by coadministration of isavuconazole (Tables 1 and 2). Of those who completed, 12 subjects were

Table 3. Summary of Plasma Pharmacokinetic Parameters for Isavuconazole

Parameter[a]	Bupropion		Repaglinide/Caffeine			Dextromethorphan		Methadone	
	ISAV Alone (n = 24)	ISAV + Bupropion (n = 24)	ISAV Alone (n = 24)	ISAV + Repaglinide (n = 22)[b]	ISAV + Caffeine (n = 22)[b]	ISAV Alone (n = 24)	ISAV + Dextromethorphan (n = 23)[c]	ISAV Alone (n = 22)[d]	ISAV + Methadone (n = 22)[d]
AUC_τ, μg.h/mL	94.3 (13.1)	93.3 (14.8)	122.9 (29.6)	123.2 (26.6)	131.6 (28.9)	92.4 (36.1)	95.6 (38.0)	99.5 (44.1)	102.6 (46.3)
C_{max}, μg/mL	6.20 (1.00)	6.32 (1.18)	7.33 (1.51)	7.44 (1.59)	7.98 (1.72)	5.82 (1.8)	6.3 (1.9)	6.8 (3.0)	6.6 (2.7)
t_{max}, hours	3.0 (1.5-4.0)	3.0 (1.5-4.0)	3.0 (2.0-4.0)	3.0 (1.5-4.2)	3.0 (2.0-4.0)	3.0 (1.5-5.1)	2.0 (1.2-4.3)	3.0 (2.0-4.0)	3.0 (1.5-4.0)

AUC, area under the concentration-time curve; C_{max}, maximum concentration; ISAV, isavuconazole; TEAE, treatment-emergent adverse event; t_{max}, time to maximum concentration.
[a] AUC_τ and C_{max} values are mean (standard deviation); t_{max} is median (range).
[b] Two subjects discontinued on day 13 due to TEAEs.
[c] One subject discontinued on day 8 due to TEAEs.
[d] One subject discontinued on day 5 due to a TEAE.

classified as intermediate metabolizers, and 11 were classified as extensive metabolizers. The relative change in dextromethorphan exposure with coadministered isavuconazole was similar for both intermediate and extensive metabolizers (Figure 3A; data not shown). There were no clinically relevant changes to the PK of dextrorphan (Figure 3B, Tables S2 and S3; data not shown). The PK parameters of isavuconazole were unaffected by the presence of dextromethorphan and dextrorphan (Table 3) regardless of CYP2D6 genotype (data not shown).

Methadone. Twenty-three subjects enrolled, and 22 subjects completed the methadone study (Table S1). Mean plasma AUC_∞ and AUC_{last} of R-methadone were decreased approximately 10% in the presence vs absence of isavuconazole, whereas the C_{max} was slightly increased (Figure 3C; Tables 1 and 2). However, coadministration of isavuconazole resulted in a decrease in the exposure of S-methadone by approximately 35%, and the C_{max} was increased by 1% (Figure 3D; Tables 1 and 2). The PK parameters of isavuconazole were similar in the presence and absence of methadone (Table 3).

Safety

Among all studies, there were no deaths, 1 serious TEAE, and discontinuations due to TEAEs were rare (Table 4). In the bupropion study the incidence of TEAEs was low, and TEAEs experienced by ≥1 subject included rhinitis (n = 2) and headache (n = 2) (Table S4).

In the study of caffeine and repaglinide the most common TEAEs were dizziness (n = 2), headache (n = 2), and palpitations (n = 2) (Table S5). No other TEAEs were experienced by ≥1 subject. One subject experienced TEAEs of hypoesthesia, feeling drunk, memory impairment, dysgeusia, dizziness, and balance disorder, which were considered by the study investigator as probably related to isavuconazole administration. The other subject experienced TEAEs of insomnia, noncardiac chest pain, anxiety, and abnormal ECG T-wave, which were not considered related to isavuconazole administration. TEAEs in both subjects resolved fully following discontinuation of the study drug.

In the dextromethorphan study the most common TEAEs were somnolence (n = 4) and diarrhea (n = 4) (Table S6). One subject discontinued the study on day 8 during treatment with isavuconazole alone due to serious TEAEs of perioral numbness and numbness of the right arm and leg. Both events were considered by the study investigator as probably related to isavuconazole treatment and resolved fully by day 9.

In the methadone study the most common TEAEs were nausea (n = 10), vomiting (n = 8), and decreased appetite (n = 5) (Table S7). One subject
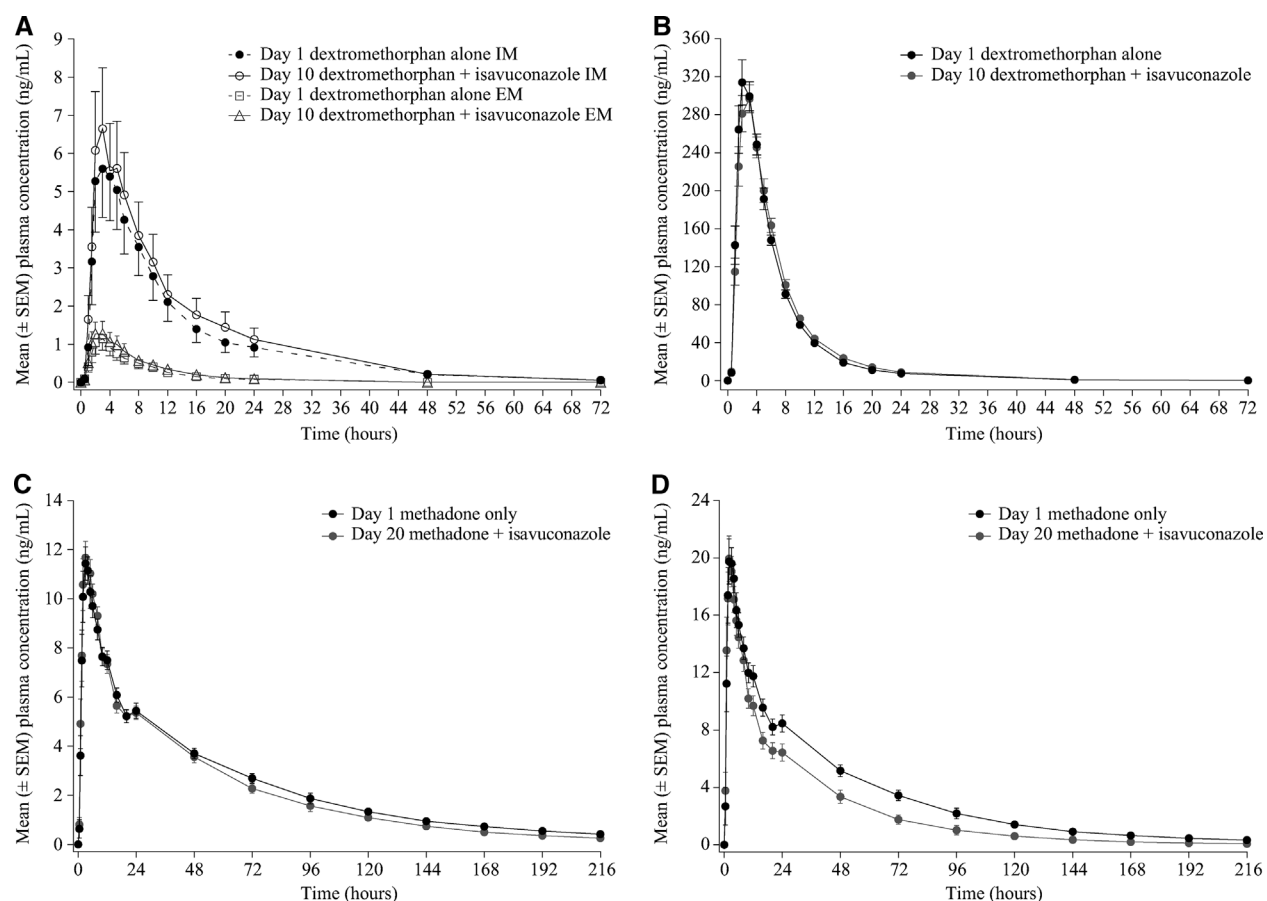
Figure 3. Mean plasma concentration-time profiles of dextromethorphan (A), dextrorphan (B), R-methadone (C), and S-methadone (D) in the presence and absence of isavuconazole. SEM, standard error of the mean.

discontinued the study during methadone administration on day 5 due to a moderate TEAE of toothache. This TEAE was not considered to be related to methadone and resolved fully following discontinuation from the study.

Discussion

This series of phase 1 studies was conducted to evaluate the PK effects of isavuconazole coadministration with the CYP substrate probes bupropion (CYP2B6), repaglinide (CYP2C8), caffeine (CYP1A2), dextromethorphan (CYP2D6 and CYP3A4), and methadone (CYP2B6, CYP2C19, and CYP3A4). Coadministration with isavuconazole was associated with an approximate 42% decrease in bupropion exposure, an 18% increase in dextromethorphan exposure, and a 35% decrease in S-methadone exposure. By contrast, isavuconazole coadministration had little effect on the exposure to caffeine, repaglinide, and R-methadone ($<15\%$ change in AUC or C_{max} for each). These findings indicate that isavuconazole is a mild inducer of CYP2B6 but does not affect the

metabolic activities of CYP1A2, CYP2C8, CYP2D6, or CYP2C19 (see also below).

Although isavuconazole decreased exposure to bupropion (a CYP2B6 substrate), the decrease in exposure to methadone, also a CYP2B6 substrate, was stereoselective. Multiple doses of isavuconazole decreased R-methadone exposure by 10% and S-methadone by 30%. Methadone is N-demethylated to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) by CYP2B6 and CYP3A4 in vitro but by CYP2B6 in vivo.[18] This evidence is consistent with the idea that CYP3A4 has little effect on the disposition, metabolism, and clearance of methadone in vivo[19–23] and the observation that CYP2B6 and CYP2C19 are known to have stereoselective effects on methadone metabolism, as CYP2B6 preferentially metabolizes S-methadone, whereas CYP2C19 preferentially metabolizes R-methadone.[24–26] Thus, our results are consistent with the idea that the effects of isavuconazole coadministration on methadone PK are attributable entirely to effects on these isoenzymes, including mild induction of CYP2B6 and little or no effect on CYP2C19. The lack of an effect of

Table 4. Treatment-Emergent Adverse Events

Safety, n (%)	Bupropion			Caffeine and Repaglinide				
	Bupropion Alone (n = 24)	ISAV Alone (n = 24)	Bupropion + ISAV (n = 24)	Repaglinide Alone (n = 24)	Caffeine Alone (n = 24)	ISAV Alone (n = 24)	Repaglinide + ISAV (n = 22)[a]	Caffeine + ISAV (n = 22)[a]
Any TEAE	I (4.2)	2 (8.3)	2 (8.3)	I (4.2)	0	5 (20.8)	2 (9.1)	3 (13.6)
Drug-related TEAE	0	2 (8.3)	2 (8.3)	I (4.2)	0	3 (12.5)	2 (9.1)	2 (9.1)
Serious TEAE	0	0	0	0	0	0	0	0
TEAE leading to discontinuation	0	0	0	0	0	2 (8.3)	0	0
Deaths	0	0	0	0	0	0	0	0

Safety, n (%)	Dextromethorphan			Methadone		
	Dextromethorphan Alone (n = 24)	ISAV Alone (n = 24)	Dextromethorphan + ISAV (n = 23)[b]	Methadone Alone (n = 23)	ISAV Alone (n = 22)[c]	Methadone + ISAV (n = 22)[c]
TEAE	I (4.2)	II (45.8)	9 (39.1)	16 (69.6)	7 (31.8)	12 (54.5)
Drug-related TEAE	I (4.2)	8 (33.3)	6 (26.1)	14 (60.9)	4 (18.2)	10 (45.5)
Serious TEAE	0	I (4.2)[d]	0	0	0	0
TEAE leading to discontinuation	0	I (4.2)	0	I (4.3)	0	0
Deaths	0	0	0	0	0	0

ISAV, isavuconazole; TEAE, treatment-emergent adverse event.
[a] Two subjects discontinued on day 13 due to TEAEs.
[b] One subject discontinued on day 8 due to TEAEs.
[c] One subject discontinued on day 5 due to a TEAE.
[d] Perioral numbness and numbness of the right arm and leg.

isavuconazole is also supported by observations of a lack of any significant effect on the PK of omeprazole as well (data on file).

The PK of repaglinide is determined by its interactions not only with CYP isoenzymes but also with the organic anion-transporting polypeptide 1B1 (OATP1B1).[34,35] However, isavuconazole does not affect OATP1B1 activity in vitro (data on file) or in vivo,[11] and so the lack of an effect of isavuconazole on repaglinide exposure can be interpreted to reflect the lack of an effect of isavuconazole on CYP2C8.

The slight increase in dextromethorphan exposure (<20%) with multiple doses of coadministered isavuconazole observed in the current study most likely resulted from inhibition of CYP3A4. Although dextromethorphan is also metabolized by CYP2D6, that isoenzyme is subject to highly variable levels of activity according to allelic variations[36]; whereas we found that changes in dextromethorphan exposure were comparable in both CYP2D6 intermediate and extensive metabolizers. Thus, isavuconazole is unlikely to have any clinically relevant interactions with CYP2D6.

Few clinical trials have examined interactions between other currently approved triazole antifungal agents and the substrate probes evaluated in our studies. In contrast to isavuconazole, voriconazole is associated with up to 2-fold increases in R-methadone exposure, which are attributed to CYP3A4 inhibition[37] (see also VFEND® package insert). Similar to isavuconazole, posaconazole does not inhibit CYP1A2, CYP2C8, or CYP2D6 activity.[38] In addition, coadministration with ketoconazole causes only minor increases (~15%) in repaglinide exposure.[39] No studies have evaluated interactions between bupropion and the triazole antifungal agents.

The effects of isavuconazole on these various CYP isoenzymes in vivo differ in some key respects from effects observed in vitro for some other triazole antifungal agents. For example, induction of CYP2B6 by isavuconazole in vivo contrasts with inhibition of this isoenzyme observed in vitro for itraconazole[40] and voriconazole.[41] The lack of any apparent effect of isavuconazole on CYP1A2 in vivo also contrasts with the moderate inhibition of that isoenzyme by

fluconazole observed in vitro.[42] These differences also further underscore the limitations of extrapolating in vitro data to clinical practice because the labels for those agents do not indicate any significant effects of those agents on these isoenzymes in vivo.

Taken together, these findings support that isavuconazole is a moderate inhibitor of CYP3A4 and indicate that isavuconazole is a mild inducer of CYP2B6. Thus, appropriate precautions should be observed when coadministering other substrates of these isoenzymes. There was no indication that isavuconazole had any substantial effect on CYP1A2, CYP2C8, CYP2D6, or CYP2C19. Therefore, it is unlikely that substrates of these isoenzymes would be affected by isavuconazole administration. Finally, given the lack of any effect of these agents on the PK of isavuconazole, it is unlikely that any dose adjustment of isavuconazole would be required during coadministration with substrates of these isoenzymes.

Acknowledgments

Declaration of Conflicting Interests

Isavuconazonium sulfate has been codeveloped by Astellas Pharma Global Development, Inc. and Basilea Pharmaceutica International Ltd. T.Y., A.D., C.H., S.A., D.K., C.L., H.P., and R.T. are employees of Astellas Pharma Global Development, Inc. R.G. and D.H. are employees of PAREXEL who were contracted to perform parts of the studies. D.R. is an in-house contractor employed by Astellas Pharma Global Development, Inc.

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Supporting Information

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