

# Assessment of Clinical Drug-Drug Interactions of Elagolix, a Gonadotropin-Releasing Hormone Receptor Antagonist

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## Abstract

Elagolix is an oral gonadotropin-releasing hormone receptor antagonist indicated for the management of endometriosis-associated pain and in combination with estradiol/norethindrone acetate indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. Elagolix coadministered with estradiol/norethindrone acetate is in late-stage development for the management of heavy menstrual bleeding associated with uterine fibroids. Based on the in vitro profile of elagolix metabolism and disposition, 9 drug-drug interaction (DDI) studies evaluating the victim and perpetrator characteristics of elagolix were conducted in 144 healthy volunteers. As a victim of cytochrome P450 (CYPs) and transporter-mediated DDIs, elagolix area under the curve (AUC) increased by ~2-fold following coadministration with ketoconazole and by ~5- and ~2-fold with single and multiple doses of rifampin, respectively. As a perpetrator, elagolix decreased midazolam AUC (90% confidence interval) by 54% (50%-59%) and increased digoxin AUC by 32% (23%-41%). Elagolix decreased rosuvastatin AUC by 40% (29%-50%). No clinically significant changes in exposure on coadministration with sertraline or fluconazole occurred. A elagolix 150-mg once-daily regimen should be limited to 6 months with strong CYP3A inhibitors and rifampin because of the potential increase in bone mineral density loss, as described in the drug label. A 200-mg twice-daily regimen is recommended for no more than 1 month with strong CYP3A inhibitors and not recommended with rifampin. Elagolix is contraindicated with strong organic anion transporter polypeptide B1 inhibitors (eg, cyclosporine and gemfibrozil). Consider increasing the doses of midazolam and rosuvastatin when coadministered with elagolix, and individualize therapy based on patient response. Clinical monitoring is recommended for P-glycoprotein substrates with a narrow therapeutic window (eg, digoxin). Dose adjustments are not required for sertraline, fluconazole, bupropion (or any CYP2B6 substrate), or elagolix when coadministered.

## Keywords

CYP3A, drug-drug interaction, elagolix, endometriosis, GnRH antagonist, uterine fibroids

Endometriosis and uterine fibroids are estrogen-dependent conditions affecting up to 10% and 50%, respectively, of women of reproductive age.<sup>1,2</sup> In the past 20 years, there have not been any major advancements in medical therapy for these gynecological conditions.<sup>1</sup> Elagolix was approved by the United States Food and Drug Administration (FDA) for the management of moderate to severe pain associated with endometriosis (Orilissa) and in combination with estradiol/norethindrone acetate indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) (Oriahnn) in premenopausal women.<sup>3,4,5</sup> Elagolix, an oral, nonpeptide gonadotropin releasing hormone (GnRH) receptor antagonist, offers patients a novel oral medical treatment option. Elagolix coadministered with estradiol/norethindrone acetate has demonstrated robust efficacy for the treatment of heavy menstrual bleeding associated with uterine fibroids (UFs) in

pivotal phase 3 clinical trials (ELARIS UF-1 and ELARIS UF-2).<sup>2,4,5</sup> Common adverse reactions associated with elagolix have been hot flush, headache, and nausea.<sup>3,6</sup> Hypoestrogenic adverse effects such as

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**Table 1.** Medications Evaluated in Drug-Drug Interaction Studies With Elagolix

Mechanism-Based Drug Interactions				
Drug Class	Coadministered Drug (Dose)	Mechanism	Elagolix Dose	Enrolled (Completed <sup>d</sup> ), n
Drug interactions of elagolix as victim drug				
Antifungals	Ketoconazole (400 mg once daily)	CYP3A and P-gp inhibition	150 mg single dose	12 (11)
Antimycobacterials	Rifampin (600 mg once daily)	OATP1B1/IB3 inhibition, CYP3A/P-gp induction	150 mg single dose	12 (12)
Drug interactions of elagolix as perpetrator drug				
Antiarrhythmics	Digoxin (0.5 mg once daily)	P-gp inhibition	200 mg twice daily	12 (11)
Antianxiety	Midazolam (2 mg once daily)	CYP3A induction	300 mg twice daily	20 (20)
Antianxiety	Midazolam <sup>b</sup> (2 mg once daily)	CYP3A induction	150 mg once daily	12 (11)
Antidepressant	Bupropion (150 mg once daily)	CYP2B6 induction	300 mg twice daily	24 (24)
Proton pump inhibitors	Omeprazole <sup>c</sup> (40 mg once daily)	CYP2C19 inhibition, CYP3A induction	300 mg twice daily	20 (20)
Statins	Rosuvastatin (20 mg once daily)	OATP1B1/IB3 and BCRP inhibition	300 mg twice daily	12 (10)
Drug Interactions With Commonly Coprescribed Medications				
Drug Class	Coadministered Drug (Dose)	Study Aim (Metabolic Pathway)	Elagolix Dose	Enrolled (Completed <sup>d</sup> ), n
Antidepressant	Sertraline (25 mg once daily)	Effect of steady-state elagolix on steady-state sertraline and vice versa	300 mg twice daily	20 (20)
Antifungal	Fluconazole (200 mg once daily)	Effect of steady-state elagolix on single dose of fluconazole (CYP2C9 and CYP3A4 inhibitor)	300 mg twice daily	20 (19)

CYP, cytochrome P450; P-gp, P-glycoprotein; OATP, organic anion-transporting polypeptide.

<sup>a</sup>Number of participants evaluated for pharmacokinetics. For ketoconazole study, 1 participant discontinued because of inability to eat provided meals. For male midazolam study, 1 participant discontinued for nonmedical personal reasons. For digoxin, participant failed urine test for drug and alcohol. For rosuvastatin, dermatitis occurred at ~1.5 hours for 1 participant after taking the first 20-mg dose of rosuvastatin and another participant discontinued because of pregnancy. For fluconazole, participant data were removed from analysis because of identity issues.

<sup>b</sup>Study participants were male. All other studies reported here were female participants.

<sup>c</sup>Results for drug interaction studies with omeprazole are reported elsewhere; see references 3 and 37.

hot flush and bone mineral density (BMD) decrease are dose dependent, and both may be mitigated with coadministration of hormonal add-back therapy.<sup>5,7</sup>

Elagolix is rapidly absorbed from the gastrointestinal tract with time to mean maximum observed plasma concentration ( $T_{max}$ ) values of approximately 1 hour and an apparent terminal-phase elimination half-life ( $t_{1/2}$ ) of 4 to 6 hours.<sup>8</sup> Exposure of elagolix is approximately dose proportional from 100 to 400 mg twice daily, and the endometriosis-indicated dose regimens of 150 mg once daily and 200 mg twice daily are also dose proportional.<sup>8</sup> Elagolix is primarily excreted in feces, and less than 3% is excreted unchanged in urine.<sup>9</sup> However, plasma exposure of elagolix metabolites is low (<3%) relative to the parent compound with no clinically relevant effects of the metabolites.<sup>9</sup> In vitro, elagolix is metabolized primarily by the cytochrome P450 (CYP) enzyme CYP3A4.<sup>10</sup> In vitro experiments also demonstrated that elagolix is a substrate of organic anion transporter polypeptide (OATP) 1B1 and efflux P-glycoprotein (P-gp) transporters. It is also an inhibitor of P-gp, OATP1B1, breast cancer resistance protein (BCRP), and CYP2C19 and is an inducer of CYP3A4.<sup>3,11</sup>

Based on in vitro results, clinical drug interaction studies in healthy volunteers were conducted to assess the potential for interactions between elagolix and specific enzymes or transporters with standard probe substrates, inhibitors, or inducers. Elagolix clinical pharmacology studies were conducted in healthy men and women (premenopausal). A summary of these studies including the drug-drug interaction (DDI) studies with commonly coprescribed drugs is provided in Table 1. The coadministered probes were chosen based on the literature and regulatory guidance from the FDA and the European Medicines Agency (EMA).<sup>12,13</sup> This article provides an in-depth discussion of these studies including study design details and mechanistic reasoning behind outcomes.

## Methods

### Participants and Study Designs

Several open-label, multiple-dose phase 1 clinical studies in healthy volunteers (Table 1) were conducted in accordance with their respective protocols, International Council for Harmonization Good Clinical Practice guidelines,<sup>14</sup> applicable regulations, and guidelines governing clinical study conduct and ethical principles

that have their origin in the Declaration of Helsinki. The study protocols were approved by the institutional review boards for each study site (see Supplementary Table S1). All participants gave written informed consent before participation in the study. All the studies were conducted in healthy premenopausal women except for the midazolam DDI study with 150 mg of once-daily elagolix, which was conducted in healthy men. Enrolled participants were between the ages of 18 and 49 years with a body mass index (BMI)  $\geq 18.0$  to  $\leq 30$  kg/m<sup>2</sup>. Female participants were eligible if they had a history of regular menstrual cycles for at least 3 months before study drug administration; agreed to use 2 forms of nonhormonal birth control; were at least 6 months postpartum, postabortion, or postlactation at the start of study drug dosing; and had not received a GnRH agonist or antagonist in the previous 6 months. Participants were not to have used CYP3A and/or OATP1B1/3 inhibitors or inducers within 1 month before the study; consumed alcohol, grapefruit, star fruit, or Seville oranges within 3-7 days or nicotine-containing products within 3-6 months before study drug administration. Participants were excluded if they had positive test results for hepatitis A, B, or C or human immunodeficiency virus infection.

DDIs were assessed for elagolix covering specific mechanistic interactions or commonly used medications within the intended population for elagolix (Table 1). Key components of all 9 studies are summarized in Figure 1. The selection of doses and duration of dosing were chosen based on the potential effect (inhibition or induction) on the metabolic enzymes/transporters. Drug interaction studies of elagolix as the perpetrator drug (eg, digoxin, midazolam, bupropion, and rosuvastatin) used relatively high doses (200 or 300 mg twice daily) to maximize the induction or inhibitory potential of elagolix on the pathway. The midazolam DDI study in healthy male volunteers was performed during the early development of elagolix at the 150-mg once-daily dose and then repeated at a higher dose (300 mg twice daily) at a later stage of the development. The dose and duration of the coadministered drugs as victims were chosen based on their pharmacokinetic properties, available literature, and regulatory guidance documents from the FDA and the EMA.<sup>12,13</sup> Drug interaction studies of elagolix as the victim drug used the low-dose regimen (150 mg, single dose), which is more sensitive to the impact of the perpetrator drug on elagolix exposure. Perpetrator drugs (eg, ketoconazole and rifampin) were administered at their highest prescribed dose and duration to maximize their inhibitory/induction potential. Commonly coprescribed drugs were administered at their commonly prescribed doses.

Participants were confined to the study site and supervised for the duration of each study period. Participants had the option to be discharged between periods in all studies except the midazolam, sertraline, and bupropion studies. All study drugs were administered under fasting conditions (no food consumption for >10 hours) except for fluconazole and sertraline, consistent with the drug administration recommendations on their labels. For fluconazole and sertraline, no food was consumed for 2 hours before dosing continuing through 1 hour after study drug administration in each period. For rosuvastatin, study drugs were administered 1 hour before breakfast, and the evening dose was administered 2.5 hours after dinner. Morning and evening doses were separated by at least 12 hours for the twice-daily administration. Participants received a standardized diet providing approximately 30% to 40% of the daily 1900 to 2420 calories from fat for all meals during confinement. The meal content was identical on the intensive pharmacokinetic sampling days.

#### Safety and Tolerability Assessments

Safety and tolerability were evaluated during the studies through adverse event monitoring, vital sign measurements, physical examinations, 12-lead electrocardiogram (ECG) recordings, and laboratory tests. Any subject who received at least 1 dose of study drug was included in the safety analyses.

#### Pharmacokinetic Sampling and Bioanalytical Methods

Serial blood samples were collected by venipuncture for determination of elagolix and the coadministered drugs and their relevant metabolites before dosing and at multiple times throughout the dosing periods. Plasma concentrations of elagolix<sup>15</sup> and coadministered drugs (see Table S2) were determined using validated liquid chromatography with tandem mass spectrometric methods. The lower limit of quantitation (LLOQ) for elagolix ranged from 0.126 to 1.59 ng/mL across all studies. The LLOQ for the coadministered drugs were 0.100  $\mu$ g/mL for ketoconazole, 50 ng/mL for rifampin, 10.0 pg/mL for digoxin, 0.1 ng/mL for rosuvastatin, 0.100 ng/mL for midazolam and 1-OH-midazolam (male study), 0.0474 ng/mL for midazolam and 1-OH-midazolam (female study), 0.5 ng/mL for bupropion, 5.00 ng/mL for OH-bupropion, 20.0 ng/mL for fluconazole, and 0.2 ng/mL for sertraline. Samples for all analytes quantified below the lowest standard were reported as zero.

#### Pharmacokinetic Analyses

Values for the pharmacokinetic parameters were estimated by noncompartmental methods using Phoenix WinNonlin, version 6.1 (Pharsight Corporation, Mountain View, California) or SAS version 8.2 or

**Mechanism-based drug interactions**

Period 1		Period 2			
Day 1*	≥5 Days	Days 6-8	Day 9*	Days 10-11	
elagolix	washout	ketoconazole	elagolix+ ketoconazole	ketoconazole	
Day 1*	≥5 Days	Day 6*	Day 7-14	Day 15*	
elagolix	washout	elagolix+ rifampin	rifampin	elagolix+ rifampin	
Day 1*	14 Days	Day 15*	Day 16-23	Day 24*	
digoxin	washout	elagolix+ digoxin	elagolix	elagolix+ digoxin	
Day 1*	3 Days	Day 4*	Days 5-12	Day 13*	Day 14
midazolam (f)	washout	elagolix+ midazolam	elagolix	elagolix+ midazolam	elagolix
Day 1*	Days 2-3	Day 4*	Days 5-13	Day 14*	
midazolam (m)	elagolix	elagolix+ midazolam	elagolix	elagolix+ midazolam	
Day 1*	5 Days	Days 6-15	Day 16*	Days 17-19	
bupropion	washout	elagolix	elagolix+ bupropion	elagolix	
Day 1*	≥5 Days	Days 6-11, 12*		Days 13*, 14-18, 19*	
elagolix	washout	rosuvastatin		elagolix+ rosuvastatin	

**Drug interactions with commonly coprescribed medications**

Period 1		Period 2		
Day 1*	2 Days	Days 3-11, 12*		Days 13* <sup>SD</sup> , 14-22, 23*
elagolix	washout	sertraline		elagolix+ sertraline
Day 1*	4 Days	Days 5-12, 13*	Day 14*	Days 15-16
fluconazole	washout	elagolix	elagolix+ fluconazole	elagolix

**Figure 1.** Study designs used for assessing drug-drug interactions with elagolix. All drugs on day 1 were administered as a single dose (SD). Washout intervals are noted by the number of days separating the SD on day 1 in period 1 with the first dose in period 2. Days in period 2 are counted from the minimum number of days in the washout interval. Male (m) and female (f) midazolam studies are noted. Elagolix and sertraline were administered as a SD on the morning of day 13. \*Intensive PK sampling days.



higher (SAS Institute, Inc., Cary, North Carolina). Pharmacokinetic parameters included the maximum observed plasma concentration ( $C_{\max}$ ), area under the plasma concentration-time curve (AUC) during a dosing interval (AUC<sub>24</sub> for once-daily administration, AUC<sub>12</sub> for twice-daily administration, AUC<sub>t</sub> for time zero to the time of the last measurable concentration, or AUC<sub>∞</sub> for time zero to infinity, as appropriate), and  $T_{\max}$ . Additional pharmacokinetic parameters included  $t_{1/2}$  and trough concentration ( $C_{\text{trough}}$ ).

### Statistical Analyses

To assess the effect of elagolix on the coadministered drug and vice versa, repeated-measures analyses were performed using the natural logarithms of  $C_{\max}$  and AUC using data for the coadministered medication alone or elagolix alone and the coadministered drug in combination with elagolix. The models included a fixed effect for the study day. Within-subject variability was accounted for by using the repeated statement for the effect of day. Similar analyses were performed for elagolix using the natural logarithms of  $C_{\max}$  and AUC to assess the effect of the coadministered drug on elagolix. Central value ratios (antilogarithm of the least-squares means for logarithms) and 90% confidence intervals (CIs) for  $C_{\max}$  and AUC were calculated to quantify the magnitude of the drug interactions.

## Results

### Participant Demographics and Disposition

A total of 132 premenopausal women were enrolled in 8 studies, and 12 men were enrolled in 1 study. Pharmacokinetic data sets from 138 participants were used for the analyses reported here. Data for 1 participant were removed because of identity issues. Five participants discontinued study participation for reasons not related to elagolix, which included (1) inability to eat provided meals (ketoconazole study), (2) failed drug and alcohol test via urine analysis (digoxin study), (3) nonmedical personal reasons (midazolam male study), (4) appearance of dermatitis ~1.5 hours after taking the first 20-mg dose of rosuvastatin (dermatitis resolved after 4 days; rosuvastatin study), and (5) pregnancy occurring during study (rosuvastatin study). Across all studies, 38% of participants were white, 49% were black, and 14% were other races. Demographics of all participants were similar across all studies: mean age from all 8 studies ranged from 27 to 37 years (min, max, 19, 48 years), mean weight ranged from 66 to 73 kg (min, max, 45, 89 kg), and mean BMI ranged from 25 to 26 kg/m<sup>2</sup> (min, max, 19, 30 kg/m<sup>2</sup>).

### Pharmacokinetics

The impact on  $C_{\max}$  and AUC of elagolix or the coadministered drugs is presented in Figure 2 as central

value ratios and their 90%CIs. As a victim, the largest change in elagolix exposure (AUC) was observed with a single dose of rifampin (5.6-fold increase with CI of 4.9-6.4); as a perpetrator, a large change in rosuvastatin exposure (40% decrease with CI of 29%-50%) was observed. These changes are shown graphically by the mean plasma concentration-time profiles for elagolix and rosuvastatin in Figure 3A,B, respectively.

### Assessment of Drug Interactions

*Effect of CYP3A and P-gp Inhibition on Elagolix (by Ketoconazole).* Following multiple doses of ketoconazole, single-dose  $C_{\max}$  and AUC of elagolix (coadministered with ketoconazole) increased by 1.8- and 2.2-fold, respectively, compared with elagolix alone.<sup>16</sup> Elagolix half-life was similar with or without ketoconazole coadministration.

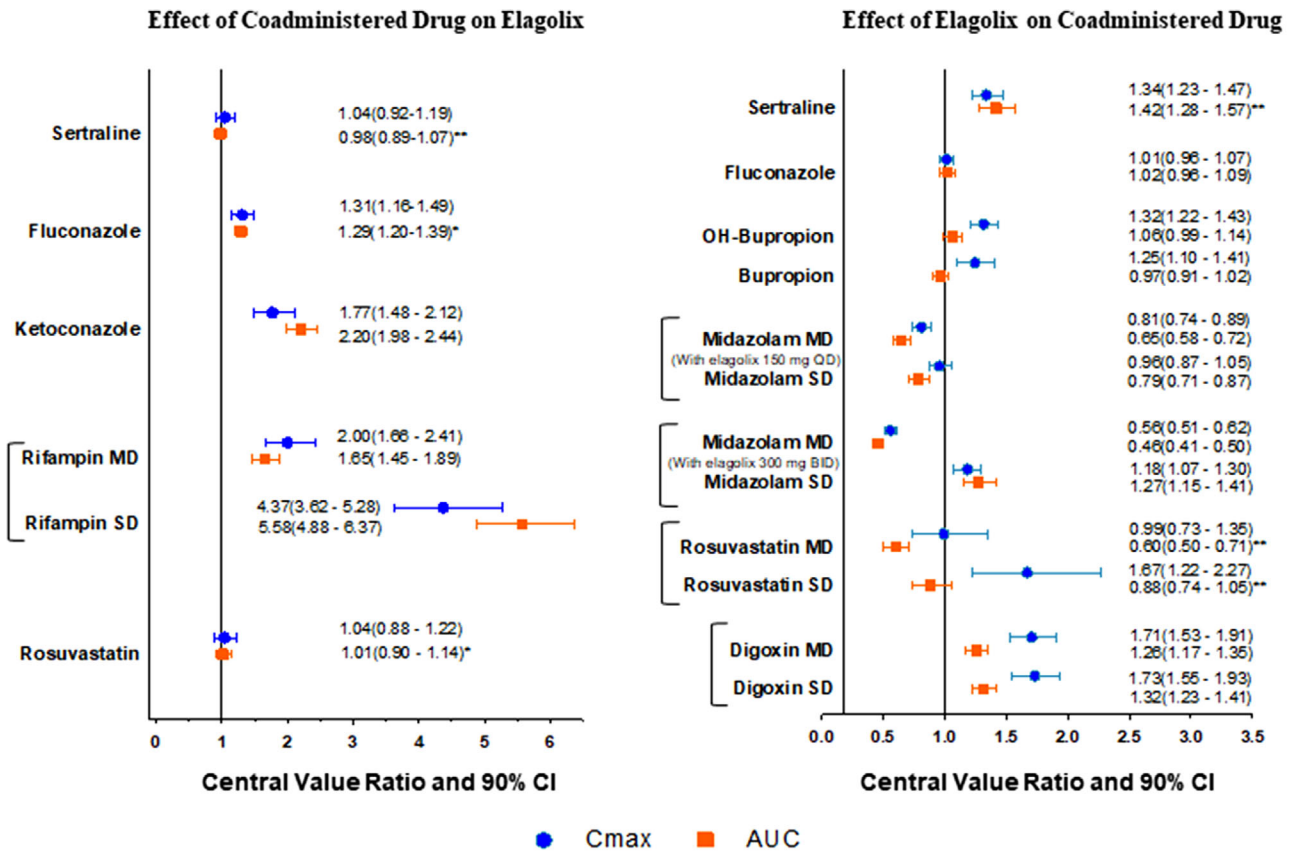
*Effect of OATP1B1 Inhibition and CYP3A and P-gp Induction on Elagolix (by Rifampin).* Following elagolix coadministration with a single dose of rifampin, elagolix  $C_{\max}$  and AUC increased 4.4- and 5.6-fold, respectively, compared with elagolix alone. Multiple doses of rifampin (dosing for 10 days) increased elagolix  $C_{\max}$  and AUC by 2.0- and 1.7 fold, respectively.<sup>17</sup> The plasma concentration-time profiles for elagolix administered alone or with single or multiple doses of rifampin are presented in Figure 3A.

*Effect of Elagolix on P-gp-Mediated Transport (Digoxin as Probe Substrate).* Coadministration of either a single dose (on the first day) or multiple doses (10 days of dosing) of elagolix 200 mg twice daily with digoxin increased digoxin  $C_{\max}$  and AUC by approximately 70% and 30%, respectively.<sup>18</sup>

*Effect of Elagolix on CYP3A-Mediated Metabolism (Midazolam as Probe Substrate).* Following single and multiple doses of 150 mg elagolix once daily in male participants, midazolam AUC decreased by approximately 21% and 35%, respectively. However, 1-OH-midazolam exposures slightly increased (up to 11%) with 150 mg elagolix once daily.

Following coadministration of midazolam with the first dose of elagolix 300 mg twice daily in female participants, midazolam  $C_{\max}$  and AUC increased by approximately 18% and 27%, respectively, and metabolite exposures increased by up to 39%; however, multiple doses of elagolix 300 mg twice daily (11 days of dosing) decreased midazolam  $C_{\max}$  and AUC by approximately 44% and 54%, respectively, and metabolite exposures decreased by 19%.

*Potential of Elagolix to Induce CYP2B6-Mediated Metabolism (Bupropion as Probe Substrate).* The



**Figure 2.** Effect of coadministered drug on elagolix (left) and elagolix on the coadministered drug (right). Closed circles represent central value ratios of C<sub>max</sub>, and closed squares represent central value ratios of AUC. Note: all AUC values are AUC<sub>∞</sub> except where noted as AUC<sub>12</sub>\* or AUC<sub>24</sub>\*\*<sub>SD</sub>, single-dose conditions; MD, multiple-dose conditions (adapted with permission from reference 9).

coadministration of a single dose of bupropion following 10 days of elagolix (300 mg twice-daily) dosing resulted in no/minimal changes ( $\leq 9\%$ ) in AUC values and 25% and 32% increases in the C<sub>max</sub> of bupropion and OH-bupropion, respectively.

**Effect of Elagolix on OATP1B1/B3 and BCRP-Mediated Drug Transportation and Vice Versa (Rosuvastatin).** Rosuvastatin C<sub>max</sub> increased by 67% after coadministration of the first dose of elagolix (300 mg twice daily), but there was no significant change in AUC (Figure 2). By contrast, after coadministration of multiple doses of elagolix 300 mg twice daily, the C<sub>max</sub> of rosuvastatin (steady state) was not significantly changed, but the AUC decreased by 40% compared with when rosuvastatin was administered alone. Rosuvastatin had no effect on elagolix exposure. The mean plasma concentration-time profiles for rosuvastatin administered alone and with either a single dose or multiple doses of elagolix are presented in Figure 3B.

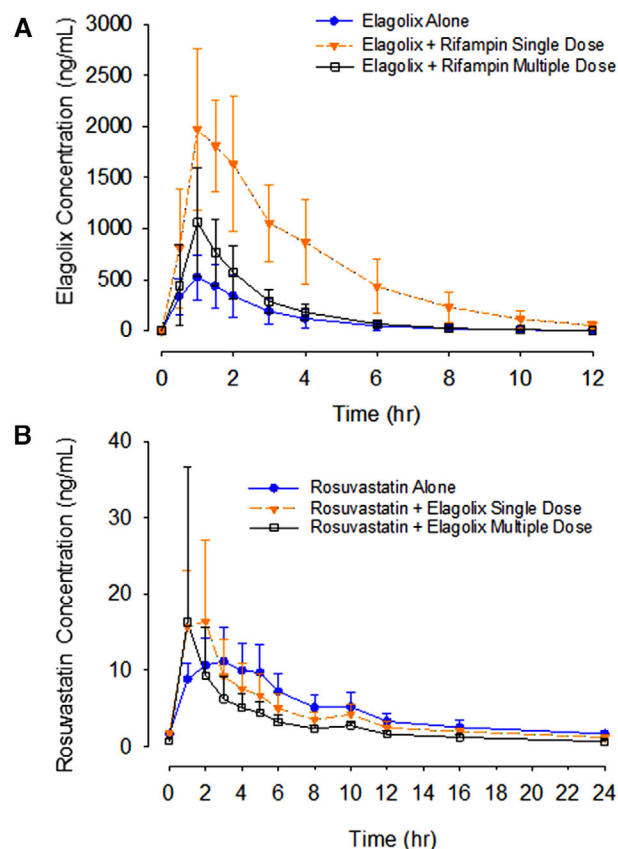
**Commonly Coprescribed Antifungal With Elagolix (Fluconazole).** The elagolix steady-state C<sub>max</sub> and AUC<sub>12</sub> after 10 days of elagolix 300 mg twice daily were increased

by approximately 30% following the coadministration with a single dose of fluconazole 200 mg. However, fluconazole exposures (C<sub>max</sub> and AUC) were not affected on coadministration with elagolix (Figure 2).

**Commonly Coprescribed Antidepressant With Elagolix (Sertraline).** Single-dose 300-mg elagolix plasma exposures (C<sub>max</sub> and AUC) were not affected by multiple doses of sertraline (25 mg once daily for 10 days). However, multiple doses of elagolix 300 mg twice daily increased sertraline steady-state C<sub>max</sub> and AUC<sub>24</sub> by 34% and 42%, respectively (Figure 2).

**Safety and Tolerability**

Elagolix and the coadministered drugs across the regimens tested were generally well tolerated by the 144 female and male participants in the 9 phase 1 studies. The highest incidence of treatment-emergent adverse event (TEAEs) was reported in the ketoconazole study, with 82% of participants reporting 1 or more TEAE during the ketoconazole-alone portion of the test regimen, compared with zero participants during the elagolix-alone portion of the test regimen. Across all studies, the most common adverse events assessed by the



**Figure 3.** Mean plasma concentration-time profiles for (A) elagolix administered alone (closed circle), with a single dose of 600 mg rifampin (closed triangle), and after multiple doses of rifampin (open square), and for (B) rosuvastatin (20 mg once daily) administered alone (closed circle), with a single dose of 300 mg elagolix (closed triangle), and following multiple doses of 300 mg elagolix (open square). Error bars represent standard deviation. See Figure 1 for study design details.

investigators as mild and reasonably related to elagolix included hot flush, headache, nausea, and amenorrhea. Across all studies, adverse events that were assessed by the investigator as moderate and not related included vomiting and headache (rifampin once daily alone), abdominal pain (elagolix alone in rifampin study), headache (elagolix with rifampin once daily), and vomiting (elagolix with sertraline). Across all studies, 3 severe adverse events occurred, and all were assessed by the investigator as not related to elagolix. These adverse events were not related, did not lead to study discontinuation, and included (1) induced abortion that occurred 35 days after the last dose of both rifampin and elagolix, (2) headache after a single dose of digoxin alone, and (3) migraine (resolved spontaneously after 1 day) after a single dose of rifampin alone. Across all studies, there were no clinically significant changes observed in vital sign values, ECG parameters, physical examination findings, or laboratory measurements.

## Discussion

Women who have endometriosis or uterine fibroids may often have other comorbidities, such as depression, anxiety, or gynecological comorbidities. As such, medical therapy for these other conditions may be needed long term, increasing the likelihood for coadministration of medications and thus potential drug interactions. Findings from *in vitro* studies guided the evaluation of potential mechanistic drug interactions of elagolix in phase 1 healthy volunteer studies. In this article, 6 mechanism-based clinical DDI evaluations assessing elagolix as a substrate of CYP3A, OATP1B1, and P-gp, an inhibitor of P-gp, BCRP, and OATP1B1, and an inducer of CYP3A and CYP2B6 are reported. Sertraline and fluconazole, 2 commonly coprescribed medications, were also evaluated. Dosing recommendations for these medications when prescribed with elagolix are discussed in the following sections and are summarized in Table 2.

Potential effects of inhibition of CYP3A/P-gp and OATP1B1 and induction of CYP3A/P-gp on the pharmacokinetics (PK) of elagolix (as a victim) were assessed by coadministration with ketoconazole and rifampin in phase 1 healthy volunteer studies. At the time of conducting the ketoconazole study, the gold standard used to determine the impact of the maximal effect of CYP3A inhibition on the clearance of CYP3A substrates *in vivo* was the ketoconazole 400-mg once-daily regimen.<sup>12,19,20</sup> Because of the risk of hepatotoxicity and adrenal insufficiency associated with ketoconazole, other strong CYP3A inhibitors (ie, itraconazole) have replaced its use in clinical DDI studies.<sup>12,21,22</sup> Based on results from the ketoconazole study, elagolix is not considered a sensitive CYP3A substrate, as the increase in overall exposures ( $\leq 2.2$ -fold) was much lower than the criteria ( $\geq 5$ -fold increase) per the FDA guidance on drug interaction studies.<sup>12</sup> The  $t_{1/2}$  of elagolix was similar with or without ketoconazole coadministration, thus indicating that the observed increase in elagolix exposure may occur during first-pass intestinal and hepatic metabolism. Inhibition of intestinal P-gp may also have contributed to the increase in elagolix exposure observed with ketoconazole coadministration; this is supported by the similar increase in elagolix  $C_{max}$  and AUC (1.8 and 2.2, respectively). Based on these DDI results and the potential BMD loss that may be associated with increased elagolix exposure, the elagolix 150-mg once-daily regimen should be limited to 6 months and the elagolix 200-mg twice-daily regimen is not recommended for more than 1 month when coadministered with strong CYP3A inhibitors.<sup>3</sup>

Rifampin is a potent inducer of CYP3A and P-gp<sup>23</sup> and also inhibits P-gp and OATP1B1/1B3.<sup>24</sup> Rifampin is used in clinical drug interaction studies

**Table 2.** Dosing Recommendations Based on Drug Interaction Trials<sup>a</sup>

Mechanism Evaluated	Probe Substrate, Inhibitor, or Inducer	Effect on Overall Exposure (AUC) of Elagolix or Coadministered Drug <sup>b</sup>	Clinical Recommendations
Drug interactions of elagolix as victim drug			
CYP3A and P-gp inhibition	Ketoconazole	2.2-fold ↑ in elagolix (SD)	No dose adjustment.
OATP1B1/1B3 inhibition and CYP3A4/P-gp induction	Rifampin	5.6-fold ↑ in elagolix (SD)	Concomitant use of elagolix 200 mg twice daily and rifampin is not recommended. Limit concomitant use of elagolix 150 mg once daily and rifampin to 6 months.
Drug interactions of elagolix as perpetrator drug			
P-gp inhibition	Digoxin	Up to 32% ↑ in digoxin (SD)	Clinical monitoring is recommended for digoxin when coadministered with elagolix.
CYP3A4 induction	Midazolam	54% ↓ in midazolam (MD)	Consider increasing the dose of midazolam and individualize therapy based on the patients' response.
CYP2B6 induction	Bupropion	↔ in AUCs of bupropion and OH-bupropion; 25% ↑ in C <sub>max</sub> of bupropion, 32% ↑ C <sub>max</sub> of OH-bupropion	No dose adjustment.
OATP1B1/1B3 and BCRP inhibition	Rosuvastatin	40% ↓ in rosuvastatin (MD)	Consider increasing the dose of rosuvastatin, no dose adjustment for elagolix.
Drug interactions with commonly coprescribed medications			
CYP2C9 and CYP3A inhibitor	Fluconazole	29% ↑ in elagolix (SD), ↔ fluconazole	No dose adjustment.
NA	Sertraline	42% ↑ in sertraline (SD), ↔ elagolix	No dose adjustment.

AUC, area under the plasma concentration-time curve; CYP, cytochrome P450; P-gp, p-glycoprotein; OATP, organic anion-transporting polypeptide; BCRP, breast cancer resistance protein; NA, not applicable; ↓, decrease; ↑, increase; ↔, no change; SD, single dose; MD, multiple dose.

<sup>a</sup>See reference 3.

<sup>b</sup>Exposure changes are reported for dosing conditions that resulted in the greatest effect on area under the plasma concentration-time curve (AUC) denoted by single dose (SD) or multiple dose (MD) wherever applicable. See Figure 2 for all data.

to evaluate acute PK interaction effects through inhibition of OATP1B1 after a single dose and chronic PK interaction effects through induction of CYP3A and P-gp after multiple once-daily doses.<sup>12,25</sup> Based on the elagolix disposition profile, the increase in exposure of elagolix when coadministered with rifampin can be attributed to (1) inhibition of hepatic uptake transporter OATP1B1 by rifampin and (2) inhibition of enterocyte P-gp, thereby preventing elagolix efflux into the intestinal lumen and increasing the overall bioavailability. These explanations are further reinforced by the rifampin plasma concentrations (18 μmol/L; data on file with AbbVie) being higher than the reported maximal inhibitory concentration (IC<sub>50</sub>) values (1-10 μmol/L) for inhibiting hepatic OATP1B1,<sup>5-8</sup> and the expected intestinal concentrations with a 600-mg dose of rifampin are higher than the reported IC<sub>50</sub> values (70-220 μmol/L) for inhibiting P-gp.<sup>26-29</sup> The smaller increase in exposures (C<sub>max</sub> and AUC) of elagolix (≤2-fold) following multiple days of rifampin dosing compared with a single dose of rifampin (<6-fold) may be attributed to rifampin inductive effects on CYP3A and P-gp. Thus, the relatively small increase can be attributed to the net effect of OATP1B1 inhibition and CYP3A and P-gp induction. Based on these DDI results and accounting for the potential BMD loss with

elagolix, concomitant use of rifampin with the elagolix 150-mg once-daily regimen is limited to 6 months, and the 200-mg twice-daily regimen with rifampin is not recommended. Because most other strong inhibitors of OATP1B1 (ie, cyclosporine) do not pose induction potential for CYP3A/P-gp and the potential magnitude of increase in elagolix exposures (C<sub>max</sub> and AUC) with such inhibitors may be similar to that caused by single-dose rifampin (>4.4-fold), concomitant use of strong OATP1B1 inhibitors that are devoid of CYP3A induction is contraindicated with elagolix.<sup>3</sup>

Several phase 1 DDI studies were conducted to evaluate the effects of elagolix as a perpetrator on the PK of CYP3A, CYP2B6, P-gp, OATP1B1/1B3, and BCRP substrates (midazolam, bupropion, digoxin, and rosuvastatin). Oral midazolam is a sensitive substrate of gut and hepatic CYP3A and is one of the recommended probe substrates<sup>12,30</sup> for evaluating CYP3A-mediated drug interactions. Multiple doses of elagolix 150 mg once daily and 300 mg twice daily resulted in 35% and 54% decreases, respectively, in the overall exposure (AUC) of midazolam. Therefore, elagolix is considered a weak or moderate inducer of CYP3A depending on the dose administered. Based on these findings, clinicians should consider increasing the midazolam dose when coadministered with elagolix.



Bupropion is considered a clinical CYP2B6 probe substrate for clinical DDI evaluations, although it is not a sensitive CYP2B6 substrate (with fraction metabolized about 0.5).<sup>31</sup> No other CYP2B6-sensitive substrates (with fraction metabolized > 0.9) have been identified to date; therefore, bupropion was used to evaluate the CYP2B6 induction potential of elagolix based on in vitro observations. In the DDI evaluation with elagolix 300 mg twice daily, bupropion PK was not affected ( $\leq 25\%$  increase); however, its metabolite  $C_{\max}$  increased to a minimal extent (32%). These results are not considered clinically significant, and thus, no dose adjustment is recommended for bupropion (or any CYP2B6 substrate) when coadministered with elagolix.

The  $C_{\max}$  and AUC of digoxin, a known sensitive P-gp substrate, were increased slightly following a single dose or with daily 200-mg twice-daily dosing of elagolix (Figure 2). The modest increase in digoxin  $C_{\max}$  (~70%) and AUC (~30%) in the presence of elagolix may be attributed to inhibition of intestinal P-gp. The clinical relevance of this increase may be limited to P-gp substrates that have a narrow therapeutic index such as digoxin. In addition, the similarity of increase in exposure after single and multiple doses suggests that elagolix does not induce P-gp after multiple doses. Elagolix did not affect the renal clearance of digoxin as indicated by the similar  $t_{1/2}$  of digoxin alone and in the presence of elagolix. As with other drugs that increase the exposure of digoxin, clinical monitoring for digoxin is recommended when coadministered with elagolix.

Rosuvastatin, unlike other statin drugs, does not undergo extensive CYP-mediated metabolism and primarily follows hepatic transporter-mediated elimination mechanisms.<sup>32-34</sup> Coadministration of rosuvastatin with a single dose of elagolix 300 mg increased rosuvastatin  $C_{\max}$  by approximately 67% relative to that observed for rosuvastatin alone, suggesting elagolix may have an effect on the rate of absorption of rosuvastatin. This may be explained by an initial inhibition of OATP1B1 and/or BCRP transporters by elagolix. Following coadministration of multiple doses of elagolix 300 mg twice daily with rosuvastatin, the rosuvastatin AUC was decreased by approximately 40% with no change in  $C_{\max}$  relative to administration of rosuvastatin alone. In addition, the  $T_{\max}$  of rosuvastatin was decreased following both a dose (1.6 hours) and multiple doses (1.2 hours) of elagolix relative to when rosuvastatin was administered alone (2.8 hours). By contrast, the apparent  $t_{1/2}$  of rosuvastatin unchanged when rosuvastatin was administered alone (8.8 hours) or in combination with single or multiple doses of elagolix (9.5 and 8.2 hours, respectively). The mechanism(s) for a decrease in rosuvastatin AUC when coadministered with multiple doses of elagolix are

unknown. The decrease in rosuvastatin AUC could be explained if repeated administration of elagolix causes an induction in transporters and potentially modulating metabolism, which could then decrease the bioavailability or increase systemic clearance of rosuvastatin. However, no data are currently available to support this hypothesis. The reduction of rosuvastatin AUC may be considered clinically relevant, and an increase in rosuvastatin dose should be considered if clinically indicated in women taking elagolix and individualized therapy based on patient response.

Sertraline has been shown to increase the plasma concentrations of coadministered drugs that are metabolized by CYP2D6 and has not been shown to increase exposures of drugs that are metabolized by CYP3A.<sup>35</sup> Consistent with its lack of effect on CYP3A substrates, sertraline did not affect elagolix exposure, whereas elagolix increased the sertraline steady-state AUC and  $C_{\max}$  by approximately 42% and 34%, respectively. These increases in sertraline AUC and  $C_{\max}$  may partially be related to elagolix-mediated, time-dependent inhibition of CYP2C19.<sup>36</sup> The modest increase in sertraline exposure is not considered clinically relevant given the wide safety margin of sertraline.<sup>37</sup> Thus, no dose adjustment is required for elagolix or sertraline when coadministered.

Fluconazole is a potent CYP2C9 and CYP2C19 inhibitor and a moderate CYP3A inhibitor.<sup>38</sup> As observed with ketoconazole, a strong inhibitor of CYP3A, the minimal increase in elagolix exposures ( $C_{\max}$  and AUC) of approximately 30% can be attributed to the inhibition of CYP3A by fluconazole. Elagolix did not affect fluconazole exposures. Thus, no dose adjustment is required for elagolix or fluconazole when coadministered.

## Conclusions

The DDI profile of elagolix has been determined from clinical investigations in healthy volunteers. Mechanistic studies revealed that elagolix is not a sensitive substrate of CYP3A or P-gp, but it is an OATP1B1 substrate and a weak to moderate inducer of CYP3A, a weak inhibitor of CYP2C19<sup>3,36</sup> and a weak inhibitor of efflux transporter P-gp. Elagolix decreased rosuvastatin overall exposure by an unknown mechanism that does not appear to be related to modulation of OATP1B1.

In summary, no dose adjustments for elagolix are necessary for any of the drugs studied here, with the exception of the recommended limited duration of elagolix treatment when coadministered with rifampin or strong CYP3A inhibitors. Coadministration of rifampin with elagolix at low doses (150 mg once daily) should be limited to 6 months and is not recommended

for higher doses of elagolix (200 mg twice daily). The elagolix 150-mg once-daily regimen is also limited to 6 months with strong CYP3A inhibitors, whereas the elagolix 200-mg twice-daily regimen is not recommended for more than 1 month. Coadministration with strong OATP1B1 inhibitors is contraindicated. With regard to the effects of elagolix on the PK of other coadministered drugs, dose adjustments are not needed for bupropion or any other CYP2B6 substrate. Dose increases may be considered for midazolam and rosuvastatin when coadministered with elagolix, if clinically indicated. In the case of coadministration of drugs that are P-gp substrates, it is recommended to monitor exposure of the coprescribed drugs if the therapeutic index is narrow (eg, digoxin). No dose adjustments are needed for the commonly coprescribed drugs, sertraline and fluconazole, or elagolix when coadministered.

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## Conflicts of Interest

The authors declare that they have no conflicts of interest. The authors are employees of AbbVie Inc. and may hold AbbVie stock and/or stock options.

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## Data-Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical

trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and statistical analysis plan (SAP) and execution of a data-sharing agreement (DSA). Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

## References

1. As-Sanie S, Black R, Giudice LC, et al. Assessing research gaps and unmet needs in endometriosis. *Am J Obstet Gynecol*. 2019;221(2):86-94.
2. Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. *N Engl J Med*. 2020;382(4):328-340.
3. Orilissa™ (elagolix) [package insert]. North Chicago, IL: AbbVie Inc.; 2018.
4. Neri M, Melis GB, Giancane E, et al. Clinical utility of elagolix as an oral treatment for women with uterine fibroids: a short report on the emerging efficacy data. *Int J Womens Health*. 2019;11:535-546.
5. Oriahnn™ (co-package of elagolix, estradiol, and norethindrone acetate capsules and elagolix capsules) [package insert]. North Chicago, IL: AbbVie Inc.; 2020.
6. Archer DF, Ng J, Chwalisz K, et al. Elagolix suppresses ovulation in a dose-dependent manner: results from a 3-month, randomized study in ovulatory women. *J Clin Endocrinol Metab*. 2020;105(3):dgz086.
7. Archer DF, Stewart EA, Jain RI, et al. Elagolix for the management of heavy menstrual bleeding associated with uterine fibroids: results from a phase 2a proof-of-concept study. *Fertil Steril*. 2017;108(1):152-160 e154.
8. Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by elagolix in healthy premenopausal women. *J Clin Endocrinol Metab*. 2017;102(5):1683-1691.
9. Shebley M, Polepally AR, Nader A, et al. Clinical pharmacology of elagolix: an oral gonadotropin-releasing hormone receptor antagonist for endometriosis. *Clin Pharmacokinet*. 2020;59(3):297-309.
10. Chen C, Wu D, Guo Z, et al. Discovery of sodium R-(+)-4-{2-[5-(2-fluoro-3-methoxyphenyl)-3-(2-fluoro-6-(trifluoromethyl)benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenylethylamino} butyrate (elagolix), a potent and orally available nonpeptide antagonist of the human gonadotropin-releasing hormone receptor. *J Med Chem*. 2008;51(23):7478-7485.
11. Elagolix Multidiscipline Review, US FDA Center for Drug Evaluation and Research. 2018. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/210450Orig1s000MultiID.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210450Orig1s000MultiID.pdf). Accessed April 21, 2020.
12. United States Food and Drug Administration. Guidance for Industry: Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications. <https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf>. Published 2017. Accessed April 21, 2020.

13. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on the Investigation of Drug Interactions. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/07/WC500129606.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf). Published 2012. Accessed April 21, 2020.
14. International Council for Harmonisation. Good Clinical Practice (GCP) E6(R2). <https://www.ich.org/page/ich-guidelines>. Accessed April 21, 2020.
15. Ng J, Duan WR, Marbury T, Schmidt JM, Klein CE. Elagolix pharmacokinetic profiles in women with renal or hepatic impairment. *Clin Pharmacol Drug Dev*. 2019;8(8):1053-1061.
16. Ng J, Salem AH, Carter D, Williams LA, Klein CE. Effect of the Coadministration of Ketoconazole on the Pharmacokinetics and Safety of Elagolix in Healthy Premenopausal Females. Paper presented at: ASCPT Annual Meeting; March 8-12, 2016; San Diego, CA.
17. Ng J, Salem AH, Carter D, Williams LA, Klein CE. Effect of the Coadministration of Single and Multiple Doses of Rifampin on the Pharmacokinetics and Safety of Elagolix in Healthy Premenopausal Females. Paper presented at: ASCPT Annual Meeting; March 8-12, 2016; San Diego, CA.
18. Ng J, Salem AH, Carter DC, Klein CE. Effects of the Co-administration of Multiple Doses of Elagolix on the Pharmacokinetics and Safety of Digoxin in Healthy Women. Paper presented at: American College of Clinical Pharmacology; September 17-19, 2017; San Diego, CA.
19. Bjornsson TD, Callaghan JT, Einolf HJ, et al. The conduct of in vitro and in vivo drug-drug interaction studies: a Pharmaceutical Research and Manufacturers of America (PhRMA) perspective. *Drug Metab Dispos*. 2003;31(7):815-832.
20. Zhao P, Ragueneau-Majlessi I, Zhang L, et al. Quantitative evaluation of pharmacokinetic inhibition of CYP3A substrates by ketoconazole: a simulation study. *J Clin Pharmacol*. 2009;49(3):351-359.
21. Liu L, Bello A, Dresser MJ, et al. Best practices for the use of itraconazole as a replacement for ketoconazole in drug-drug interaction studies. *J Clin Pharmacol*. 2016;56(2):143-151.
22. Ke AB, Zamek-Gliszczynski MJ, Higgins JW, Hall SD. Itraconazole and clarithromycin as ketoconazole alternatives for clinical CYP3A inhibition studies. *Clin Pharmacol Ther*. 2014;95(5):473-476.
23. Lutz JD, Kirby BJ, Wang L, et al. Cytochrome P450 3A induction predicts P-glycoprotein induction; part 1: establishing induction relationships using ascending dose rifampin. *Clin Pharmacol Ther*. 2018;104(6):1182-1190.
24. Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol*. 2009;158(3):693-705.
25. Ho RH, Kim RB. Transporters and drug therapy: implications for drug disposition and disease. *Clin Pharmacol Ther*. 2005;78(3):260-277.
26. Zong J, Pollack GM. Modulation of P-glycoprotein transport activity in the mouse blood-brain barrier by rifampin. *J Pharmacol Exp Ther*. 2003;306(2):556-562.
27. Courtois A, Payen L, Vernhet L, de Vries EG, Guillouzo A, Fardel O. Inhibition of multidrug resistance-associated protein (MRP) activity by rifampicin in human multidrug-resistant lung tumor cells. *Cancer Lett*. 1999;139(1):97-104.
28. Furusawa S, Nakano S, Wu J, Sasaki K, Takayanagi M, Takayanagi Y. Potentiation of pirarubicin activity in multidrug resistant cells by rifampicin. *Biol Pharm Bull*. 1997;20(12):1303-1306.
29. Fardel O, Lecureur V, Loyer P, Guillouzo A. Rifampicin enhances anti-cancer drug accumulation and activity in multidrug-resistant cells. *Biochem Pharmacol*. 1995;49(9):1255-1260.
30. Hill A, van der Lugt J, Sawyer W, Boffito M. How much ritonavir is needed to boost protease inhibitors? Systematic review of 17 dose-ranging pharmacokinetic trials. *AIDS*. 2009;23(17):2237-2245.
31. Fahmi OA, Shebley M, Palamanda J, et al. Evaluation of CYP2B6 induction and prediction of clinical drug-drug interactions: considerations from the IQ consortium induction working group-an industry perspective. *Drug Metab Dispos*. 2016;44(10):1720-1730.
32. Olsson AG, McTaggart F, Raza A. Rosuvastatin: a highly effective new HMG-CoA reductase inhibitor. *Cardiovasc Drug Rev*. 2002;20(4):303-328.
33. Niemi M. Transporter pharmacogenetics and statin toxicity. *Clin Pharmacol Ther*. 2010;87(1):130-133.
34. Shitara Y. Clinical importance of OATP1B1 and OATP1B3 in drug-drug interactions. *Drug Metab Pharmacokinet*. 2011;26(3):220-227.
35. Lee MH, Yang HI, Lu SN, et al. Hepatitis C virus genotype 1b increases cumulative lifetime risk of hepatocellular carcinoma. *Int J Cancer*. 2014;135(5):1119-1126.
36. Nader A, Mostafa N, Ali F, Shebley M. Drug-drug interaction study to evaluate the effect of multiple doses of elagolix on the pharmacokinetics of omeprazole in healthy premenopausal females (PII-114). American Society for Clinical Pharmacology and Therapeutics. *Clin Pharmacol Ther*. 2020;107(suppl 1):S5-S121.
37. Cooper JM, Duffull SB, Saiao AS, Isbister GK. The pharmacokinetics of sertraline in overdose and the effect of charcoal. *Br J Clin Pharmacol*. 2015;79(2):307-315.
38. Diflucan (fluconazole) [package insert]. New York, NY: Pfizer, Inc.; 2017.

## Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.