REVIEW ARTICLE

Clinical Pharmacology of Elagolix: An Oral Gonadotropin-Releasing Hormone Receptor Antagonist for Endometriosis

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Abstract

The clinical pharmacology of elagolix was extensively evaluated in clinical studies in healthy subjects and in women with endometriosis. Elagolix pharmacokinetics (PK) show significant population variability, however they are minimally affected by patients' baseline characteristics and demographics, except for clinically relevant extrinsic and intrinsic factors such as coadministered strong organic anion transporting polypeptide (OATP) 1B1 inhibitors and severe hepatic impairment, which are contraindications for the use of elagolix. These studies enabled a comprehensive understanding of elagolix mechanism of action and the downstream pharmacodynamic (PD) effects on gonadotropin and ovarian hormones, as well as full characterization of the PK/PD (PKPD) relationships of elagolix at various dosages, including the approved 150 mg once daily and 200 mg twice daily dosing regimens for the management of moderate to severe pain associated with endometriosis. Several model-based analyses have contributed to understanding of the benefit–risk profile of elagolix in patients with endometriosis, through characterization of the exposure relationship with responder rates, with changes in bone mineral density over time, as well as the interaction with coadministered drugs. Collectively, these studies and analyses served as supportive evidence for the effectiveness of the approved dosages and provided general dosing instructions of the first approved oral gonadotropin-releasing hormone receptor antagonist.

Key Points

Elagolix is the first approved oral gonadotropin-releasing hormone (GnRH) receptor antagonist for moderate to severe pain associated with endometriosis.

The clinical pharmacology profile of elagolix was fully characterized in several Phase 1 PKPD studies along with several model informed drug development approaches.

This comprehensive description of the clinical pharmacology attributes of elagolix provides a reference for prescribers and clinical pharmacologists who seek to use or understand the clinical PKPD properties of elagolix.

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1 Introduction

Elagolix (Orilissa™) is a novel, non-peptide oral, short-acting competitive gonadotropin-releasing hormone (GnRH) receptor antagonist approved by the US FDA for the management of moderate to severe pain associated with endometriosis [1], and is currently in development for the management of heavy menstrual bleeding associated with uterine fibroids [2, 3]. Both endometriosis and uterine fibroids are estrogen-dependent conditions [2, 4], and elagolix suppresses gonadotropin hormones and ovarian estrogen production in a dose-dependent manner, modulating circulating estrogen levels from partial suppression of estradiol (E2) at lower doses to nearly full suppression at higher doses [5, 6]. This is in contrast to GnRH receptor agonists, which, after an initial stimulatory phase (flare effect), desensitize the pituitary GnRH receptors and lead to profound suppression of ovarian sex steroid secretion similar to that of ovariectomized women [6].

The clinical development program for elagolix included several clinical pharmacology studies, which enabled full characterization of the pharmacokinetics (PK), pharmacodynamics (PD), effects of intrinsic and extrinsic factors, and population PK/PD, exposure–response (safety and efficacy)

analyses and physiologically based PK (PBPK) modeling and simulation. A summary of the extensive data, analyses, and conclusions generated from these studies is presented herein to offer a comprehensive overview of the clinical pharmacology attributes of elagolix.

2 Mechanism of Action of Elagolix

Elagolix is a highly potent ($K_D = 54$ pM) GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the anterior pituitary gland [7]. Elagolix mechanism of action (MoA) is different from long-acting GnRH receptor agonists, which induce 1–2 weeks of 'flare-up' by downregulating GnRH receptors [6]. The competitive nature of elagolix competitive antagonism of the GnRH receptors provides an advantage by allowing for rapid and reversible onset and offset, and hence more flexibility in modulating the hypothalamic–pituitary–gonadal axis. An illustration that describes elagolix MoA and downstream effects on gonadotropins and ovarian hormones is shown in Fig. 1.

3 Pharmacokinetics (PK) of Elagolix

3.1 Absorption

Elagolix sodium is a non-peptide, orally bioavailable small molecule, amorphous solid that is freely soluble in water. At either the 150 or 200 mg dose, elagolix is highly soluble per the Biopharmaceutics Classification System (BCS) throughout the physiological pH range, it exhibits high aqueous solubility (approximately 1 mg/mL), is a zwitterion with pK_a 4.0 (acid) and 7.9 (base), and has an apparent low to moderate permeability ($0.5–2.8 \times 10^{-6}$ cm/s) based on in vitro Caco-2 studies [7]. These data suggest that elagolix could be classified as a BCS class III drug. Elagolix contains one chiral center and is manufactured exclusively as the (R)-isomer. The structural formula of elagolix sodium is shown in Fig. 2.
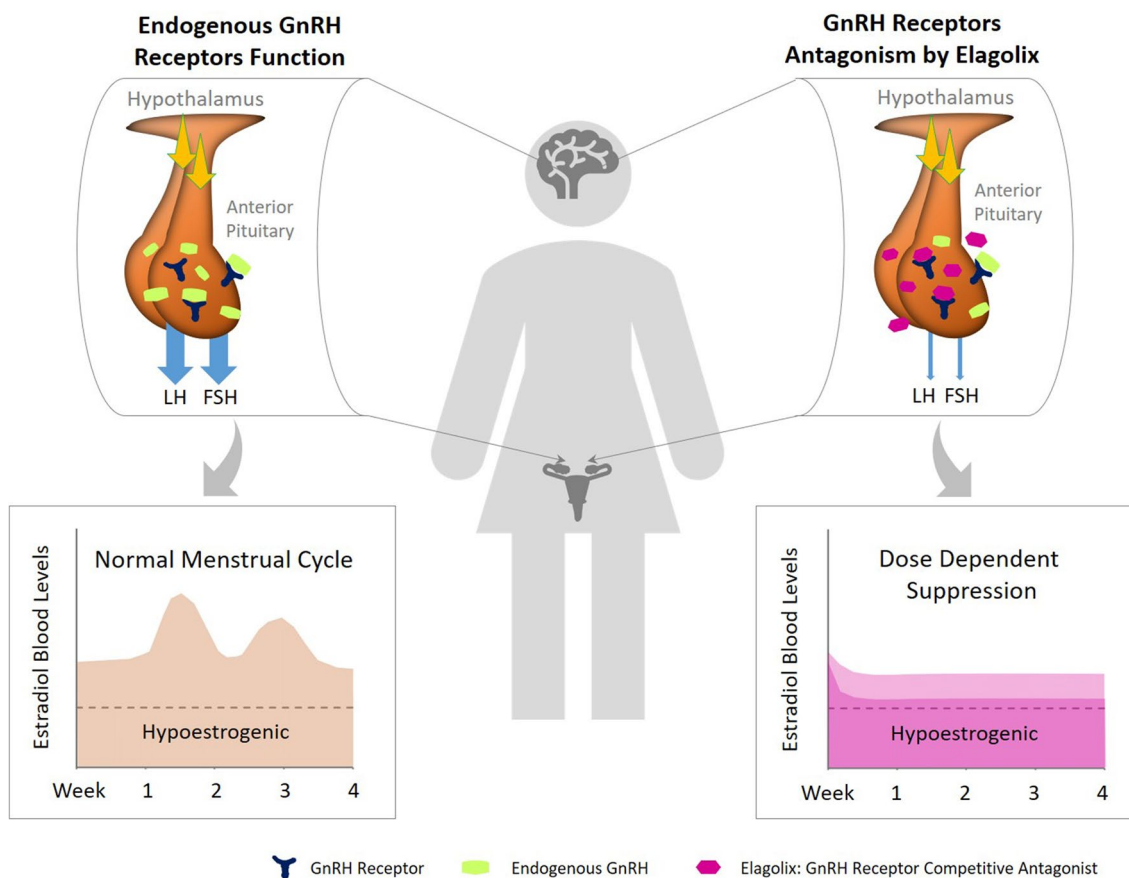

Fig. 1 Illustration of GnRH action and function during the normal female menstrual cycle, elagolix mechanism of GnRH receptors' competitive antagonism at the anterior pituitary gland, and its downstream dose-dependent effects on circulating estradiol levels in blood. *GnRH* gonadotropin-releasing hormone
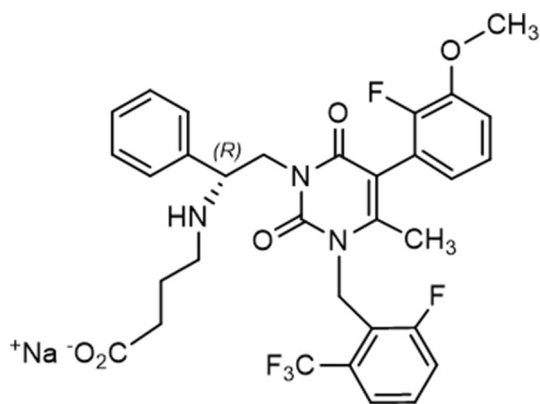
Fig. 2 Structure of elagolix sodium; molecular weight of 653.58. Elagolix free acid has a molecular weight of 631.60

In clinical PK studies in healthy subjects, elagolix absorption is rapid, with a time to maximum concentration (T_{max}) of approximately 1 h. Elagolix exposure (maximum concentration [C_{max}] and area under the curve [AUC]) is dose proportional from 100 to 400 mg twice daily [5], and more than dose proportional with single doses of 600–1200 mg. A regional absorption study was conducted in six healthy subjects to characterize the PK of elagolix 100 mg administered to the stomach via oral solution, and to the jejunum, ileum, and colon via a radiolabeled remote drug delivery capsule (InteliSite®). Based on the geometric mean AUC values, elagolix doses delivered as either a solution to the stomach or in an InteliSite® capsule to the jejunum and ileum resulted in comparable overall systemic exposure, with a geomean

AUC from time zero to infinity (AUC_∞) of 432.7, 411.8, and 443.9 ng•h/mL, respectively. However, the geomean AUC_∞ for the colon administration was only 35.22 ng•h/mL, representing < 10% that of the same dose deposited into the stomach/duodenum, jejunum, or ileum, and with a mean C_{max} for the colon administration at approximately 38 times lower than that following administration into the ileum (Electronic Supplementary Fig. 1).

Several elagolix formulations ranging from suspension to modified and immediate-release (IR) tablets were evaluated throughout the development program and across multiple phase I studies. While variability in the PK profiles of elagolix was observed across the tested formulations, the exposures did not vary significantly, consistent with a characteristic BCS III behavior. An IR tablet formulation was chosen for the endometriosis phase III studies, as well as for the commercial formulation. The final commercial tablet formulation of elagolix is bioequivalent to the phase III tablet formulation. Representative PK profiles of the phase III and commercial 200 mg IR tablet formulations is shown in Fig. 3. Elagolix 150 mg once-daily and 200 mg twice-daily PK parameters at steady state are summarized in Table 1. Dose proportional PK are demonstrated for both elagolix dosages based on the dose normalized C_{max} and AUC values; elagolix does not accumulate with repeated once daily or twice daily dosing.

3.2 Food Effect

The effect of food on elagolix plasma exposure was assessed following administration of a high-fat meal in a pivotal phase

Fig. 3 Elagolix plasma concentration–time profiles of the phase III and commercial formulations of Orilissa. Symbol represents the mean
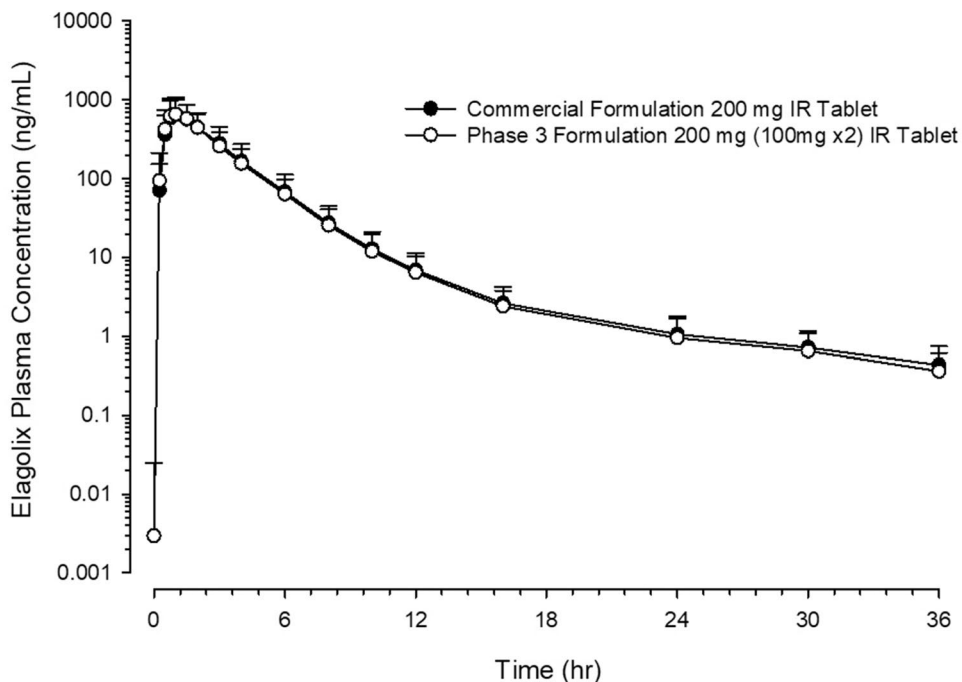
Table 1 Mean (percentage coefficient of variation) pharmacokinetic parameters at steady state of elagolix 150 mg qd or 200 mg bid

Pharmacokinetic parameters	150 mg qd	200 mg bid
T_{max} (h[a])	1.0 (0.5–1.0)	1.0 (0.5–1.5)
C_{max} (ng/mL)	574 (29)	774 (68)
AUC_τ (ng × h/mL)	1292 (31)	1725 (57)
$t_{1/2}$ (h[b])	6.42 ± 3.20	4.29 ± 0.47
CL/F (L/h)	123 (21)	144 (43)
V_{ss}/F (L)	1674 (94)	881 (38)
R_{ac}	0.98 (7)	0.89 (19)
C_{max}/dose	3.83 (29)	3.87 (68)
AUC_τ/dose	8.61 (31)	8.62 (57)

AUC_τ area under the concentration–time curve during the dosing interval (τ) of 24 h for once-daily administration and 12 h for twice-daily administration, *bid* twice daily, C_{max} maximum concentration, *CL/F* apparent clearance, *qd* once daily, R_{ac} accumulation ratio, T_{max} time to maximum concentration, $t_{1/2}$ terminal elimination half-life, V_{ss}/F apparent volume of distribution at steady state

[a]Data are reported as median (range)

[b]Data are reported as harmonic mean ± pseudo-standard deviation

I bioavailability study. With the high-fat meal condition, a slight reduction in elagolix plasma exposure relative to the fasted condition was observed, with a decrease of 24% and 36% in AUC_∞ and C_{max}, respectively (Fig. 4). In three of four endometriosis phase III pivotal trials, subjects were instructed to administer elagolix at least 1 h before or 2 h after a meal to avoid a potential lower exposure of elagolix. However, since administration of a high-fat meal demonstrated the worst-case

scenario for the effect of food on elagolix exposure, and due to the lack of clinical significance of the small reduction in elagolix exposure with meals, elagolix was administered without regard to meals in the fourth endometriosis phase III extension trial. Elagolix clinical efficacy results from all the phase III studies were similar, regardless of drug administration instructions with respect to meals; therefore, Orilissa is administered with or without food [1].
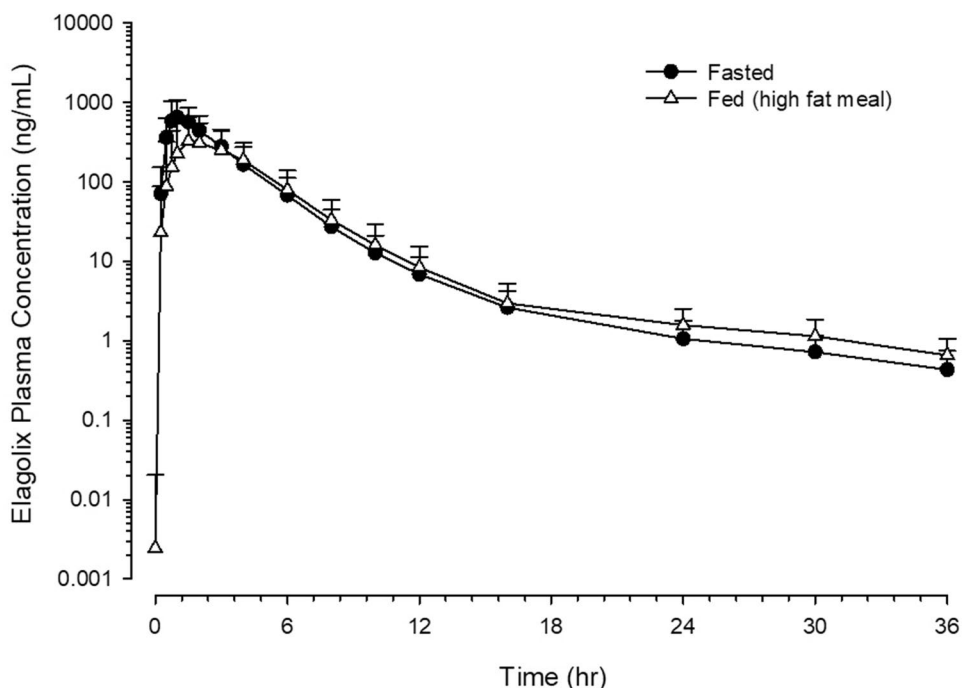
3.3 Distribution

Elagolix is moderately (80%) bound to human plasma proteins, and preferentially partitions into plasma rather than blood cellular components, with blood-to-plasma ratios of 0.6 [1]. Based on population PK analyses using data from five phase I healthy volunteers and four phase III endometriosis patient studies, the elagolix estimated apparent central volume of distribution (V_c/F) was 257 L [8]. Elagolix is a substrate of the hepatic uptake transporter organic anion transporting polypeptide (OATP) 1B1 based on in vitro studies [10], pharmacogenetics analysis of OATP1B1 variants [8], and clinical drug–drug interactions (DDIs) with single-dose rifampin [16]; however, population PK analysis did not identify the OATP1B1 genotype as a significant covariate on elagolix V_c/F [8].

3.4 Metabolism

Elagolix is metabolized by multiple cytochrome P450 (CYP) enzymes in vitro, with predominant contribution from

Fig. 4 Elagolix 200 mg commercial IR tablet formulation plasma concentration–time profiles under fasted and fed (high-fat meal) conditions in healthy subjects. Symbol represents the mean, error bars are the standard deviation. *IR* immediate-release

CYP3A4 (approximately 50%) [9], and minor contributions from other CYPs. In a mass balance study in humans, following administration of a single oral dose of 150 mg of [^{14}C]elagolix to six healthy subjects, elagolix was the predominant form of radioactivity in plasma. Mean AUC$_\infty$ values for the *O*-demethyl (M1) and *N*-dealkylated (M2) metabolites were approximately 2.4% and 3.3%, respectively, of the mean elagolix exposure (Fig. 5). Of the administered dose, 69% was recovered in feces and urine as metabolites, and a total of 11 minor metabolites were identified in plasma, each representing < 3% of total plasma radioactivity. None of the metabolites in human plasma were classified as major or disproportionate metabolites. In addition to CYP-mediated metabolites, a minor trace of an acyl-glucuronide metabolite in urine was detected, suggesting a minor contribution from uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes. Metabolite profiling of the feces (primary route of elimination, indicating biliary excretion) revealed that approximately 38% of the radioactive dose was eliminated as the M1 metabolite, 26% was unchanged elagolix, with the remainder being a combination of multiple minor metabolites. These data suggest that unchanged elagolix is the major drug-derived material in human plasma and elagolix is extensively metabolized.

3.5 Elimination

The elagolix concentration–time profile exhibits a biphasic characteristic after reaching C_{max}, with an apparent terminal elimination half-life ($t_{1/2}$) of approximately 4–6 h in healthy subjects [5, 10]. Thus, repeated dosing of elagolix once or twice daily does not result in significant drug accumulation in plasma.

In the mass balance single-dose study, 90.1% of total radioactivity was excreted in the feces, and urinary excretion accounted for only 2.9% of total radioactivity, with mean total recovery of 93% by approximately 9 days after dosing.

The minor urinary excretion of radioactivity was consistent with the population PK analysis, where renal function was not associated with elagolix PK parameters [8]. The OATP1B1 genotype was a statistically significant covariate on apparent clearance (CL/F), however the small change in CL/F (14%) was not considered clinically relevant when the poor and intermediate transporter genotypes were combined and compared with the extensive transporter genotype [8]. Figure 6 depicts the disposition and elimination mechanisms of elagolix in humans.

4 Pharmacodynamics of Elagolix

4.1 Effects on Hormones, Folliculogenesis, and Ovulation

Administration of elagolix results in dose-dependent suppression of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of the ovarian sex hormones E2 and progesterone (P). In a multiple-ascending dose study in premenopausal healthy female subjects, elagolix 150 mg

Fig. 5 Elagolix mean plasma concentration–time profiles and total plasma radioactivity (elagolix and metabolites M1 and M2)
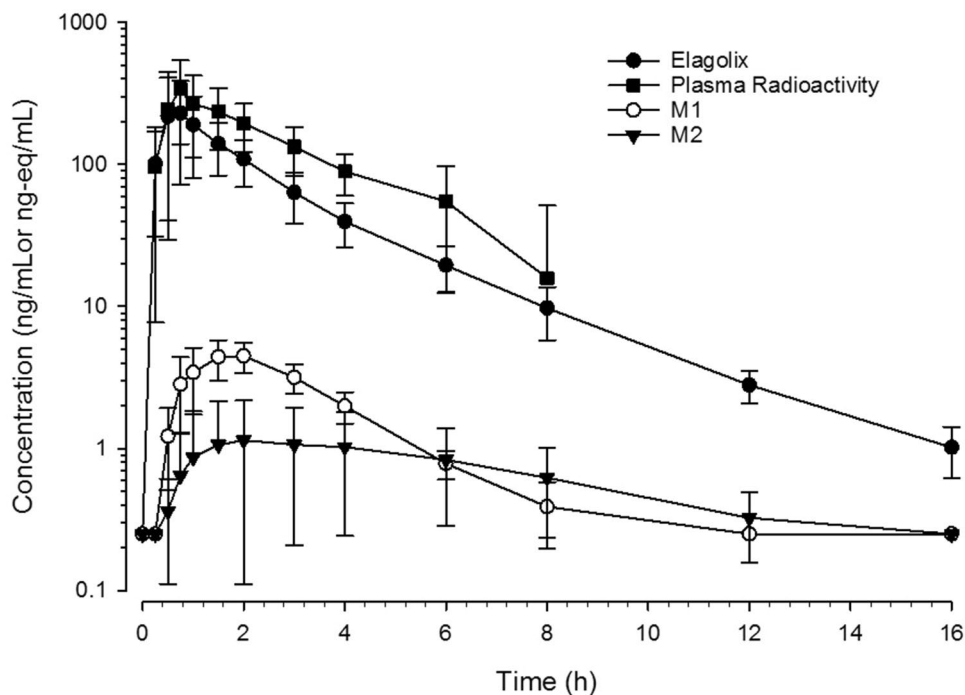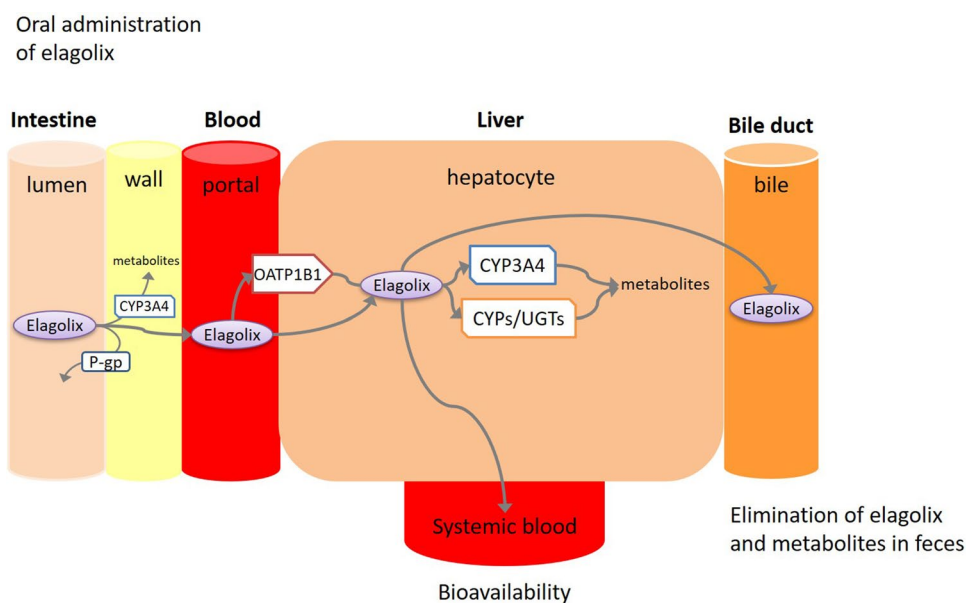
Fig. 6 Elagolix mechanisms of disposition via hepatic uptake transporter OATP1B1, metabolism by CYP3A and other CYP and UGT enzymes, and biliary elimination. *OATP* organic anion transporting polypeptide, *CYP* cytochrome P450, *UGT* uridine 5′-diphospho-glucuronosyltransferase

once daily, or 100, 200, 300, or 400 mg twice daily, or placebo, was administered for 21 days [5]. Dose-dependent suppression of sex hormones was achieved rapidly within hours after administration of the first dose on day 1 and continued through day 21, with maximum E2 suppression achieved with elagolix doses of 200 mg twice daily or higher. At elagolix doses ≥ 100 mg twice daily, P concentrations remained at anovulatory levels throughout 21 days of dosing. Dose-dependent suppression of FSH and LH was also observed, with maximal or near-maximal suppression achieved at elagolix doses of 300 mg twice daily and 200 mg twice daily, respectively. LH and FSH were suppressed compared with placebo, however LH suppression was more pronounced than that of FSH in all groups except the 150 mg once daily group. When elagolix administration was stopped, LH and FSH levels rose within 24 h after the last dose, and E2 levels began to rise 24 h after the last dose was administered [5]. The effects of different doses and dosing regimens of elagolix alone or with the hormonal add-back therapy standard dose Activella® (E2/norethindrone acetate, 1/0.5 mg) on ovulation, ovarian activity, and ovarian reserve were evaluated in an open-label study in healthy adult premenopausal females [11]. During the 3-month treatment phase, with three times weekly hormone sampling, suppression of gonadotropins and ovarian hormones were observed in a dose-dependent manner. Mean E2 levels observed at the 150 mg once-daily dose were approximately 40–50 pg/mL, consistent with partial E2 suppression. On the other hand, and consistent with the previous study, near maximal suppression was observed with the 200 and 300 mg twice-daily regimens, with mean E2 levels of approximately 20–40 pg/mL. When standard dose Activella was administered with the elagolix 300 mg twice-daily regimen, mean E2 levels

appeared to increase to slightly above the levels observed with the 150 mg once-daily regimen due to exogenous E2 administration. Comparing the E2 levels among the low dose Activella and other add-back therapies [28], the standard dose of Activella provided optimal levels of E2 when administered exogenously with elagolix. In the endometriosis pivotal phase III trials, the serum E2 profiles in endometriosis patients were similar to those in healthy subjects. The monthly average E2 concentrations in endometriosis patients demonstrated dose-dependent suppression with the 150 mg once-daily and 200 mg twice-daily regimens. The average E2 levels across placebo or elagolix treatments were maintained throughout the 6 months of the treatment period, with 150 mg once daily demonstrating partial suppression, and 200 mg twice daily demonstrating nearly full suppression, relative to placebo (Fig. 7).

Elagolix dose-dependently suppressed ovulation and ovarian activity and decreased endometrial thickness when compared with screening values. Across elagolix dosages ranging from 100 mg once daily to 300 mg twice daily, there was no trend of increasing endometrial thickness. Elagolix did not affect anti-mullerian hormone levels or ovarian reserve at any dose level. Although elagolix was able to suppresses gonadotrophic hormones and ovulation, it is not considered a contraceptive.

4.2 QT Interval

A placebo- and active-controlled (moxifloxacin 400 mg), randomized, single-dose (300 or 1200 mg), four-period, four-sequence crossover study was conducted to evaluate the potential for QTc interval prolongation by elagolix in healthy premenopausal adult females. From elagolix doses of

Fig. 7 Monthly average estradiol levels in endometriosis patients during the pivotal phase III trials
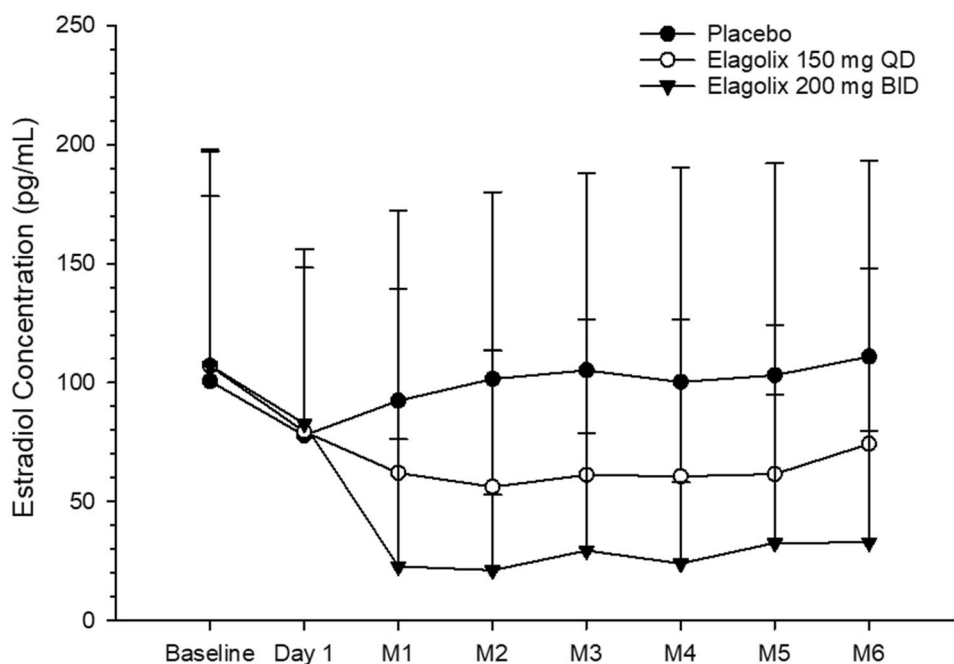
300–1200 mg, the C_{max} appeared to increase approximately 10-fold, and the AUC_t increased approximately 14-fold. Elagolix peak concentrations in subjects administered a single dose of 1200 mg was 17-fold higher than the concentration in subjects administered elagolix 200 mg twice daily. For both doses, the baseline-adjusted QT interval corrected for heart rate using Fridericia's correction formula (QTcF), compared with placebo ($\Delta\Delta$QTcF), was < 10 ms at all the time points evaluated. Elagolix does not cause clinically relevant prolongation of the QTc interval [12].

5 Intrinsic Factors

5.1 Race/Ethnicity

Elagolix PK and resulting hormone profiles were evaluated in Japanese and Han Chinese subjects after multiple doses of 150 mg once daily or 200 mg twice daily. Elagolix AUC from Japanese and Han Chinese subjects were comparable (approximately 7–20% higher) with exposures from Western subjects [13]. With no clinically meaningful PK or PD differences, elagolix dose adjustment is not warranted for Asian subjects.

5.2 Renal Function

The PK of elagolix in women with moderate to severe renal impairment (estimated glomerular filtration rate [eGFR] $\geq$ 15 and < 60 mL/min/1.73 m^2) and end-stage renal disease (ESRD, including women receiving dialysis)

[eGFR < 15 mL/min/1.73 m^2] were evaluated following a single dose of elagolix 200 mg. The mean elagolix C_{max} and AUC were comparable between women with normal renal function and those with ESRD. In women with moderate to severe renal impairment, the overall exposure was approximately 26% lower than that observed in women with normal renal function [14]. Elagolix T_{max} and $t_{1/2}$ were comparable among subjects with normal renal function and those with renal impairment. The unbound fractions of elagolix were also similar among subjects with normal renal function, moderate to severe renal impairment, and ESRD. Elagolix dose adjustment is not required in women with any degree of renal impairment or ESRD (including women receiving dialysis).

5.3 Hepatic Function

The PK of elagolix in women with mild (Child–Pugh A), moderate (Child–Pugh B), or severe (Child–Pugh C) hepatic impairment were evaluated following a single dose of elagolix 150 mg [14]. In women with mild hepatic impairment (Child–Pugh A), elagolix exposures are comparable (< 25% difference) with women with normal hepatic function; thus, dose adjustment is not required in women with mild hepatic impairment (Child–Pugh A). In women with moderate hepatic impairment (Child–Pugh B), elagolix C_{max} and AUC were increased by 160% and 170%, respectively. In these women, the 150 mg once-daily dose is recommended, with a maximum of 6 months' treatment duration, because elagolix exposure would be comparable with that of the 200 mg twice-daily dose in women with normal hepatic function.

The 200 mg twice-daily dosing regimen is not recommended in women with moderate hepatic impairment (Child–Pugh B) [1].

In women with severe hepatic impairment (Child–Pugh C), elagolix C_{max} and AUC were increased by 520% and 570%, respectively [14]. Hence, elagolix is contraindicated in women with severe hepatic impairment (Child–Pugh C) [1].

5.4 Pharmacogenetics

Pharmacogenetic analysis was conducted to assess the impact of variants in the OATP1B1/SLCO1B1 gene on subject's exposure to elagolix. The SLCO1B1 genetic variant 521T > C genotype was assayed to classify subjects into one of three OATP1B1 transporter genotype statuses, i.e. extensive transporter (ET, homozygous wild-type 521T > C), intermediate transporter (IT, heterozygous for 521T > C), and poor transporter (PT, homozygous variant 521T > C). A total of 1314 DNA samples from four phase III studies in subjects with moderate to severe endometriosis-associated pain, and a total of 462 samples from 19 phase I studies, were genotyped. The results suggest that 72% of subjects were ET, 25% were IT, and 2.5% were PT. The disposition of elagolix involves OATP1B1, and higher (less than twofold) plasma concentrations of elagolix were observed in groups of patients and healthy subjects who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO1B1 521T > C). The frequency of this SLCO1B1 521 C/C genotype is generally < 5% in most racial/ethnic groups [8]. The lack of clinical relevance of OATP1B1 genotypes on elagolix exposure is discussed in a later section on population PK analysis.

6 Extrinsic Factors

6.1 Mechanism-Based Drug–Drug Interactions (DDIs)

Mechanism-based DDI studies evaluated the effects of coadministration of CYP3A/P-glycoprotein (P-gp) and OATP1B1/P-gp inhibitors and CYP3A inducers on the PK of elagolix (victim), as well as the effects of elagolix (perpetrator) on the PK of CYP3A, P-gp, OATP1B1 and breast cancer-resistance protein (BCRP) substrates.

6.2 Elagolix as a Victim of Cytochrome P450 s (CYPs) and Transporter-Mediated DDIs

Following elagolix coadministration with ketoconazole, elagolix C_{max} and AUC increased 1.77- and 2.20-fold, respectively, compared with elagolix alone, indicating that

elagolix is not a sensitive substrate of CYP3A according to the FDA criteria [9, 15]. Despite these small changes in elagolix exposure, the duration of treatment is limited to 6 months with 150 mg once daily and 1 month with 200 mg twice daily, with concomitant administration of strong CYP3A inhibitors to avoid any potential BMD changes due to increased elagolix exposure.

Elagolix C_{max} and AUC increased 4.37- and 5.58-fold, respectively, when elagolix was coadministered with a single dose of rifampin (OATP1B1 and P-gp inhibitor), and 2.0- and 1.65-fold, respectively, after multiple doses of rifampin (CYP3A and P-gp inducer) compared with elagolix alone [16]. The increase in elagolix exposures with a single dose of rifampin may be attributed to OATP1B1 (and perhaps intestinal P-gp) inhibition. The increase in elagolix exposures with multiple doses of rifampin is likely due to the net effect resulting from acute OATP1B1 inhibition and CYP3A/P-gp induction. Because other strong inhibitors of OATP1B1 (i.e. cyclosporine) do not pose induction potential for CYP3A/P-gp, and the potential magnitude of increase in elagolix exposures with such inhibitors may be similar to that caused by single-dose rifampin, concomitant use of strong inhibitors of OATP1B1 is contraindicated with Orilissa. Figure 8 summarizes the clinically relevant DDI results of elagolix changes in exposure upon coadministration with CYP3A/P-gp modulators, which informed dosing instructions in the United States package insert (USPI) for Orilissa [1].

6.3 Elagolix as a Perpetrator of CYPs and Transporter-Mediated DDIs

In vitro data suggested that elagolix is a weak to moderate inducer of CYP3A [12]. The elagolix 150 mg once daily and 300 mg twice daily dosing regimens decreased midazolam (sensitive CYP3A substrate) AUC by 35% and 55%, respectively. Therefore, elagolix is clinically classified as a weak to moderate CYP3A inducer [17].

Elagolix is an inhibitor of the hepatic uptake transporter OATP1B1 and efflux transporters P-gp and BCRP, in vitro [12].

Following coadministration of elagolix as single (200 mg) or multiple (200 mg twice daily) doses with digoxin, the C_{max} and AUC of digoxin increased approximately 1.70- and 1.30-fold, respectively [18]. Due to the narrow therapeutic window of digoxin, clinical monitoring of digoxin is recommended when coadministered with elagolix.

Coadministration of rosuvastatin 20 mg once daily (steady-state) with the first 300 mg dose of elagolix increased rosuvastatin C_{max} by 1.67-fold, whereas rosuvastatin AUC from time zero to 24 h (AUC_{24}) was not altered. This may be explained by the inhibition of OATP1B1 and/or BCRP transporters by the single 300 mg dose of elagolix.
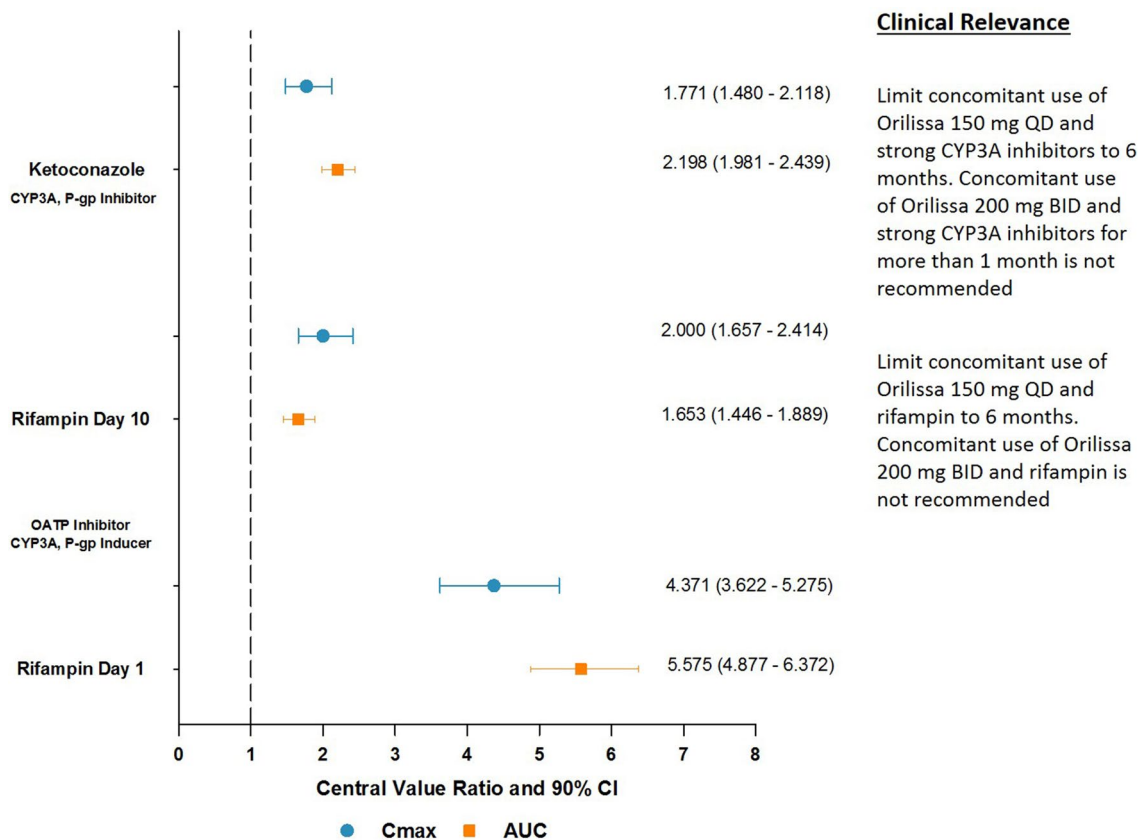
Fig. 8 Effect of coadministered drugs on elagolix exposures, and clinical implications for dosing

Coadministration of rosuvastatin 20 mg once daily (steady state) with elagolix 300 mg twice daily resulted in comparable rosuvastatin C_{max}, and decreased rosuvastatin AUC_{24} by 40%. The mechanism(s) for the decrease in rosuvastatin AUC when coadministered with multiple-dose elagolix is unknown [1, 12]. Rosuvastatin dose adjustment may be considered based on clinical objectives or observations. Figure 9 summarizes the clinically relevant DDI results of elagolix effects on exposure of coadministered drugs, which informed dosing instructions in the USPI for Orilissa [1].

6.4 DDIs with Oral Contraceptives

As elagolix is prescribed to women of reproductive age and is not a contraceptive, it was important to evaluate the coadministration of elagolix and oral contraceptives (OCs). In a DDI study of elagolix and progestin-only contraception of norethindrone 0.35 mg (i.e. mini-pill), the mean C_{max} and AUC_{24} values of norethindrone were comparable with and without coadministration of elagolix ($\leq 12\%$ change) [1], thus no dose adjustment was needed.

When elagolix 150 mg once daily was administered with a triphasic OC containing doses of ethinylestradiol and norgestimate equivalent to ethinylestradiol 0.035 mg and

triphasic norgestimate 0.18/0.215/0.25 mg, ethinylestradiol C_{max} and AUC_{24} increased to approximately 1.15- and 1.30-fold, respectively. There was a minimal decrease (up to 15%) in exposures for the norgestimate metabolites norelgestromin and norgestrel [1]. These results indicate minimal PK drug interaction between elagolix and ethinylestradiol containing OCs. In addition, the combination of elagolix and norethindrone or elagolix and triphasic OCs did not negatively impact the hormonal effects of either elagolix or the OC, therefore dose adjustment is not required. Based on the potential for E2-containing OCs to reduce the efficacy of elagolix, non-hormonal contraception is recommended.

6.5 DDIs with Commonly Coadministered Drugs

Two open-label DDI studies were conducted in healthy premenopausal females to evaluate the PK of elagolix alone and in combination with sertraline or fluconazole. Multiple-dose administration of sertraline (25 mg once daily) did not affect the 300 mg single-dose exposures (C_{max} and AUC) of elagolix. Although, elagolix 300 mg twice daily increased sertraline steady-state C_{max} and AUC_{24} to 1.34- and 1.42-fold, respectively [1], such increases in sertraline exposures
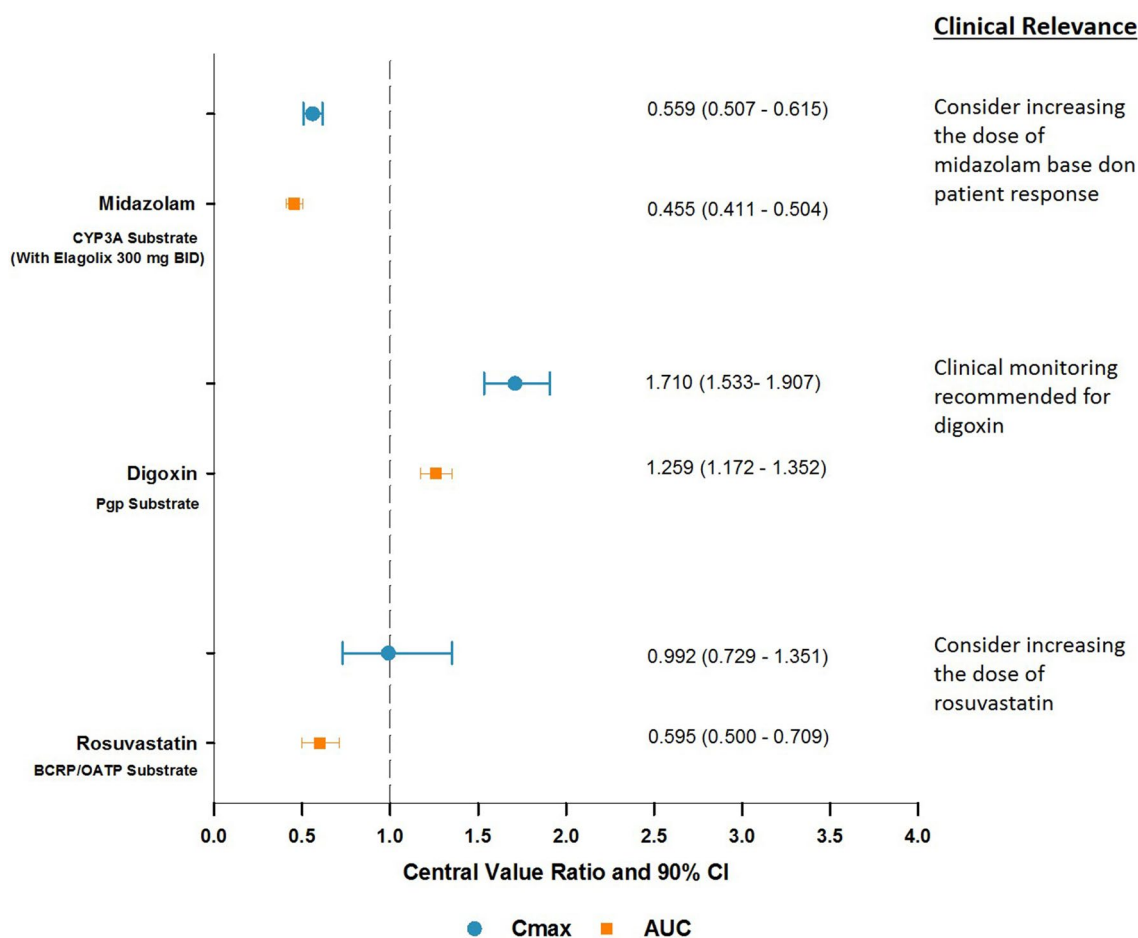
Fig. 9 Effect of elagolix on exposure of coadministered drugs, and clinical implications for dosing

are not considered clinically relevant given the wide safety margin of sertraline [19].

The steady-state exposures of elagolix 300 mg twice daily (C_{max} and AUC_{12} after 10 days) increased to 1.30-fold following coadministration with a single dose of fluconazole 200 mg, whereas the mean exposures of fluconazole were unaltered compared with and without coadministration of elagolix [1].

Based on these results, dose adjustments are not required when elagolix is coadministered with sertraline or fluconazole.

7 Population PK Analyses

Population PK analyses were conducted using data from five phase I and four phase III studies in a total of 1624 subjects [8]. Elagolix population PKs were best described by a two-compartment model with a lag-time in absorption. The population mean CL/F and V_c/F were 118 L/h and 257 L,

respectively. The interindividual variability on elagolix CL/F and V_c/F was 42.5% and 51%, respectively.

OATP1B1 genotype status was the only significant covariate on elagolix PK parameters (i.e. specifically for CL/F). When subjects with a transporter genotype status of PT/IT were compared with ET/not genotyped, CL/F was reduced by only 14% [8], and when stratified by subjects with a transporter genotype status of PT or IT, elagolix CL/F was 44% and 20% lower, respectively, compared with subjects with a transporter genotype status of ET/not genotyped. The predicted increase in elagolix average concentrations (C_{avg}) in subjects with OATP1B1 IT or PT relative to ET genotypes was 25% and 79%, respectively. Despite these predicted increases in elagolix exposures in IT and PT subjects, the exposures were significantly overlapping with ET subjects, suggesting that these changes were not clinically meaningful. Thus, dose adjustment is not required for elagolix based on OATP1B1 genotype status.

None of the other tested covariates (age, body weight, race/ethnicity, hepatic or renal function) were significantly associated with elagolix PK parameters. In addition, PK

exposures were similar between healthy women and women with endometriosis.

8 Physiologically Based PK Analyses

A PBPK model of elagolix was developed and verified using a combined bottom-up and top-down approach based on data from in vitro and several phase I single and multiple ascending dose, DDI, and special population studies [20]. The disposition pathways of elagolix, including metabolism by CYP3A and transport by P-gp, as well as hepatic uptake via OATP1B1, and their interplay, were quantified and verified using clinical DDI studies with prototypical inhibitors (rifampin and ketoconazole) and inducer (rifampin). A PBPK model of elagolix as a perpetrator was also verified using clinical DDI studies with a prototypical CYP3A substrate (midazolam) and a P-gp substrate (digoxin). The robust verification of this PBPK model provided confidence in predicting the DDI potential of elagolix as a perpetrator at the proposed clinical doses that were not evaluated in clinical DDI studies.

Based on the PBPK model prediction, elagolix could be classified as a moderate inducer of CYP3A at a 200 mg twice-daily dose (approximately 56% reduction in midazolam AUC). Elagolix 150 mg once daily is predicted to increase digoxin AUC by less than 1.25-fold (approximately 19% increase in digoxin AUC); however, since elagolix is predicted to increase the C_{max} of digoxin by 68% following a single 150 mg dose, the simulation results indicated that monitoring patients receiving digoxin along with elagolix (150 mg once daily or 200 mg twice daily) is recommended [1].

Overall, the PBPK model represents a novel approach, accounting for interplay between metabolism and transport. The model was applied to evaluate the potential DDI of elagolix under various dosages and clinical regimens as a victim with P-gp, OATP, and CYP3A4 modulators, and as a perpetrator for CYP3A and P-gp substrates.

9 Exposure–Response Relationship

9.1 Exposure–Efficacy Analysis for Dose Justification

Data from four phase III studies in premenopausal women with moderate to severe pain associated with endometriosis were included in a population PK analysis to describe the relationship between elagolix exposure and the clinical efficacy response variables of dysmenorrhea (DYS; pain with menstruation) and non-menstrual pelvic pain

(NMPP). A discrete-time, first-order Markov chain model adequately described the relationship between elagolix monthly C_{avg} values and transition probabilities between responder and non-responder states. Additionally, the model included transitions to account for the subject dropouts from responder state, non-responder state, and after month 6, and adequately predicted subject dropouts over time with placebo and elagolix treatments. The elagolix monthly C_{avg} values calculated over the preceding month were a better predictor of DYS and NMPP responses than trough concentration (C_{trough}) values [21].

Demographics (body size measurements, race, ethnicity, and geographic region), baseline hormone levels, disease severity measures (number of days and intensity of bleeding), time since endometriosis diagnosis, baseline analgesic use, alcohol or tobacco use, and prior GnRH therapies were not statistically significant covariates in the model, indicating that these covariates do not influence DYS and NMPP responder rates. On the other hand, baseline DYS and NMPP scores were significant covariates on respective placebo transition probabilities, with higher placebo response in subjects with higher baseline disease scores. The final model demonstrated strong exposure–efficacy relationships for both primary endpoints (DYS and NMPP), adequately described the phase III efficacy data for both elagolix dose regimens (150 mg once daily and 200 mg twice daily), and provided supportive evidence for the approval of Orilissa endometriosis doses [21].

9.2 Exposure–Safety Analysis to Support the Duration of Treatment

Exposure–bone mineral density (BMD) modeling using data from the four phase III studies noted above revealed an exposure–response relationship between elagolix C_{avg} and changes in BMD. An indirect response model was developed to describe the effect of elagolix C_{avg} on BMD and to evaluate the significance of clinically relevant covariates. The exposure–BMD model results showed that the estimated half maximal effective concentration (EC_{50}) of elagolix for reduction in BMD was 240 ng/mL, a concentration well above (more than fivefold) the plasma exposure associated with 150 mg once-daily dosing (C_{avg} concentrations of approximately 47 ng/mL). This result is consistent with the small BMD change with 150 mg once-daily dosing (approximately − 1% BMD change from baseline after 12 months) [21].

Final model results showed that African American race, higher baseline body mass index (BMI) and lower C-terminal telopeptide (CTX) levels (a bone resorption biomarker) were significant predictors of higher baseline BMD. African American race has been previously shown to be associated with higher BMD compared with other race groups in the

Table 2 Summary statistics of predicted percentage change from baseline in lumbar spine bone mineral density following treatment with elagolix 150 mg qd or 200 mg bid for 36 months

Month	Percentage change from baseline in lumbar spine BMD [mean (95% CI)]			
	150 mg qd		200 mg bid	
	Model	Observed[a]	Model	Observed[a]
6	− 0.6 (− 1.1 to − 0.2)	− 0.3, − 0.7	− 1.6 (− 2.0 to − 1.2)	− 2.6, − 2.5
12	− 1.1 (− 1.5 to − 0.5)	− 0.6, − 1.1	− 2.7 (− 3.3 to − 2.2)	− 3.6, − 3.9
24	− 1.6 (− 2.3 to − 0.9)	NA	− 4.3 (− 5.2 to − 3.7)	NA
36	− 1.9 (− 2.9 to − 1.2)	NA	− 5.2 (− 6.2 to − 4.3)	NA

bid twice daily, *BMD* bone mineral density, *CI* confidence interval, *NA* not available, *qd* once daily

[a]Mean from each phase III study [4, 27]

US [22, 23]. Similarly, BMI, body fat, and body weight have all been shown to be associated with higher BMD [24–26]. In addition to its effects on baseline BMD, BMI was also significantly associated with higher bone formation rates (K_{in}). After incorporating the above covariates, none of the tested covariates (including baseline BMD, expressed as a *Z* score) were significantly associated with BMD changes due to elagolix treatment [21].

The final exposure–BMD model was used to simulate a longer duration of treatment beyond the phase III, placebo-controlled, 6-month and extension studies (up to 12 months continuous treatment). The model predicted BMD changes at months 6 and 12 were consistent with the observed data in the pivotal and extension phase III trials (Table 2). Simulations of 36 months of continuous treatment of elagolix 150 mg once daily or 200 mg twice daily suggested that the mean percentage change from baseline in lumbar spine BMD is approximately − 2% and − 5% for each regimen, respectively (Table 1) [12]. These analyses supported approval of the indicated use of Orilissa 150 mg once daily or 200 mg twice daily for 24 months, or 6 months of continuous duration of treatment, respectively [1].

10 Conclusions

Elagolix clinical pharmacology characteristics, underlying sources of population variability, and the exposure–response (safety and efficacy) relationships were extensively characterized in clinical studies in healthy subjects and in women with endometriosis. Elagolix clinical pharmacology attributes consist of linear PK over the efficacious dose range (150 mg once daily to 200 mg twice daily), and rapid PD onset and offset, leading to dose-dependent partial suppression (150 mg once daily) and near full suppression (200 mg twice daily) of gonadotropin and ovarian hormones. Elagolix is eliminated primarily via hepatic metabolism by CYP3A, its bioavailability is not significantly impacted by food, has a manageable drug–drug interaction profile with most coadministered medications (only one contraindication

with strong OATP1B1 inhibitors), and is contraindicated in women with severe hepatic impairment (Child–Pugh C). Elagolix is a weak to moderate inducer of CYP3A and an inhibitor of P-gp, as demonstrated by the decreased exposure of midazolam (increasing the dose of midazolam may be considered) and increased exposure of digoxin (clinical monitoring is recommended) when coadministered with elagolix. Elagolix does not prolong the QTc interval at supratherapeutic doses and exposures. Elagolix exposures are not affected by any degree of renal impairment or mild hepatic (Child–Pugh A) impairment, while three- and sevenfold increases in elagolix exposure were observed in Child–Pugh B and C subjects, respectively. The phase III population PK analysis demonstrated a minimal impact of patients' characteristics and demographics on the PK of elagolix. It is worth highlighting that with elagolix 200 mg twice daily, E2 suppression is near maximal, and further increases in elagolix exposures due to intrinsic or extrinsic factors may not lead to further significant changes in E2 levels and the downstream hypoestrogenic effects. Elagolix demonstrated an exposure–response relationship with hormonal changes, as well as primary efficacy (DYS and NMPP) and safety (BMD changes) endpoints. Since the BMD changes observed with elagolix were time-dependent [4, 27], the exposure–BMD model enabled simulations of various durations of treatment that ultimately supported the 24 months' approved duration of use with 150 mg once daily with no coexisting conditions (dyspareunia or Child–Pugh B). Overall, the full characterization of the elagolix clinical pharmacology profile and the model-based analyses played a critical role in the approval of elagolix as the first oral GnRH receptor antagonist for the management of moderate to severe pain associated with endometriosis [1].

absorption, distribution, metabolism, and excretion studies, and the regional absorption studies.

Compliance with Ethical Standards

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