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ORIGINAL RESEARCH ARTICLE

Pharmacokinetic and Pharmacodynamic Profiles of Ethinylestradiol/Norgestimate Combination or Norethindrone upon Coadministration with Elagolix 150 mg Once Daily in Healthy Premenopausal Women

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Abstract

Background Two pharmacokinetic/pharmacodynamic studies were conducted to evaluate the potential drug–drug interaction between elagolix, an oral gonadotropin-releasing hormone receptor antagonist, and an oral contraceptive (ethinylestradiol [EE] 0.035 mg and norgestimate 0.18/0.215/0.25 mg) or progestin-only contraceptive (norethindrone 0.35 mg) in healthy premenopausal women.

Methods These phase I studies used a two-period, sequential design, where period 1 included treatment with oral contraceptives, followed by period 2 with contraceptives coadministered with elagolix 150 mg once daily.

Results In study 1, pharmacokinetic exposures for EE in period 2 increased by 30% and the norgestimate metabolites decreased by approximately 15% when coadministered with elagolix. Mean hormone exposure appeared lower for follicle-stimulating hormone (FSH; 31%), luteinizing hormone (LH; 38%), and estradiol (E2; 16%). The percentage of women with consecutive progesterone (P) concentrations above 5 nmol/L was similar in both periods. Norethindrone pharmacokinetic exposures were comparable in both periods. The hormone exposure for LH and FSH was similar, and mean E2 exposure was 32% lower in period 2. The percentage of subjects with consecutive ovulatory P concentrations was also similar in both periods (study 2). Safety and tolerability profiles were unremarkable in both studies.

Conclusions Coadministration of elagolix 150 mg once daily with oral contraceptives containing EE and norgestimate, or norethindrone, resulted in small pharmacokinetic changes in the oral contraceptive components. Similar or lower FSH, LH, and E2 exposures were observed during coadministration, with ovulatory P concentrations also comparable in both periods. The pharmacodynamic profiles of the oral contraceptives were maintained when coadministered with elagolix.

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1 Introduction

Elagolix, a novel, non-peptide, oral, short-acting competitive gonadotropin-releasing hormone receptor antagonist, was approved by the US FDA in 2018 for the management of moderate-to-severe pain associated with endometriosis [1]. Treatment with elagolix in women with endometriosis-associated pain has provided benefits with reductions in dysmenorrhea, non-menstrual pelvic pain, and dyspareunia [2], as well as improvements in workplace and household productivity [3, 4]. Elagolix pharmacokinetic (PK) and pharmacodynamic (PD) studies have shown dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), estradiol (E2), and progesterone (P), as well as suppression of ovulation [5–8].

Key Points

Small changes in the pharmacokinetics of oral contraceptives were observed when coadministered with elagolix 150 mg once daily.

Based on the assessments of luteinizing hormone, follicle-stimulating hormone, estradiol, and ovulatory progesterone concentrations, the coadministration of oral contraceptives with elagolix 150 mg once daily does not appear to lessen the hormone pharmacodynamics of the oral contraceptives.

Elagolix is not a contraceptive and effective methods of birth control should be used while taking elagolix. In addition, the elagolix product label states that its efficacy may be reduced in women taking estrogen-containing contraceptives [1]. As women are still looking for effective birth control options while receiving treatment for endometriosis, it is important to evaluate whether elagolix may be coadministered with hormonal contraceptives from a PK/PD and tolerability perspective.

Combination oral contraceptives (COCs) and progestin-only (mini-pill) contraceptives are two effective means of hormonal contraception and are options for women treated with elagolix. The main mechanism for these hormonal contraceptives is to inhibit ovulation through inhibiting the pituitary production and secretion of FSH and LH [9]. Two studies were conducted to evaluate the potential drug–drug interaction (DDI) between elagolix and COCs or the mini-pill and the impact of coadministration with elagolix on PK and PD, as well as the effects on safety and tolerability.

2 Methods

The studies were conducted in accordance with the protocol and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Institutional Review Board approval was obtained at each of the five sites (Schulman Associates IRB, Inc., Cincinnati, OH, USA). All women signed informed consent forms before participating.

2.1 Study Design

Two separate phase I, multiple-dose, open-label studies were conducted according to a two-period, sequential design with healthy premenopausal women (Fig. 1). In study 1, all women received COC pills with doses of ethinylestradiol (EE; 0.035 mg) and norgestimate (0.18/0.215/0.25 mg) for ≥ 3 months prior to study start (day 1). Period 1 consisted of 28 days of women continuing their existing regimen. During period 2 (days 29–84), women received a COC and elagolix 150 mg tablet once daily; this elagolix dose was one of the doses (150 mg once daily and 200 mg twice daily) evaluated in phase III trials. In study 2, women received a norethindrone 0.35 mg tablet once daily (a progestin-only contraceptive) for period 1; those who were naïve to the mini-pill had a 1-month lead-in. The same treatment pattern was followed as in study 1.

Women self-administered the study drug(s) throughout the treatment period. At each visit, women were counseled on medication adherence and appropriate and effective use of dual non-hormonal contraception. Women were followed until the resumption of menses or 60 days, whichever came first.

2.2 Inclusion/Exclusion Criteria

The following criteria apply to both studies. Subjects were required to be healthy premenopausal females aged between 18 and 49 years, inclusive; have a history of regular menstrual cycles prior to initial study drug administration; have a negative serum and urine pregnancy test; body mass index (BMI) 18–35 kg/m^2; and in general good health based on the results of a medical history, physical examination, vital signs, laboratory profile, and 12-lead electrocardiogram.

Subjects were excluded if they were < 6 months postpartum, post-abortion, post-pregnancy, or post-lactation; pregnant or breast feeding; were using hormonal medication other than the specified oral contraceptive; were using any known inhibitors or inducers of cytochrome P450 enzyme 3A (CYP3A), P-glycoprotein (P-gp) inhibitors within 1 month prior; and had a history of ovarian cysts, polycystic ovarian syndrome, oophorectomy, or hysterectomy. The hormonal therapies, known inducers/inhibitors of CYP3A, and inhibitors of P-gp were not to be taken during the screening, treatment, or follow-up periods of either study.

2.3 Pharmacokinetic/Pharmacodynamic Sampling

For intensive 24-h PK sampling for both studies, women remained at the study site during period 1 (oral contraceptives alone) and period 2 (oral contraceptives + elagolix). Blood samples for PK analysis {EE, metabolites of norgestimate (norelgestromin [NGMN], norgestrel [NG]), norethindrone, elagolix} were collected by venipuncture at the following time points: prior to dosing, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h after dosing (days indicated in Fig. 1). The steady-state PK sampling of norgestimate

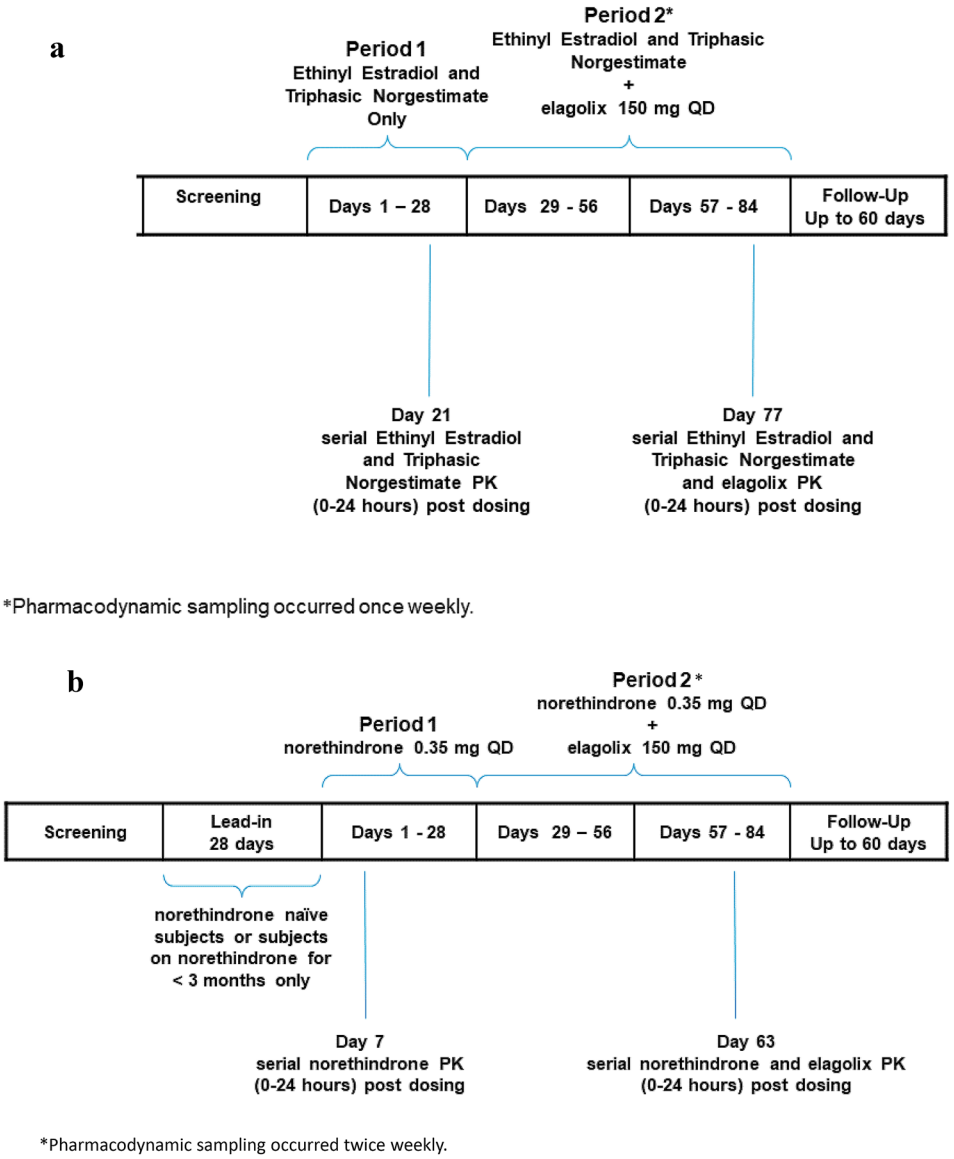

Fig. 1 Study design and procedure notes. **a** Study 1; **b** Study 2. *QD* once daily, *PK* pharmacokinetics

metabolites were taken when a norgestimate dose of 0.25 mg was administered in both periods.

Blood samples for PD analysis (FSH, LH, E2, and P) were collected by venipuncture once weekly for study 1 and twice weekly on non-consecutive days for study 2. During intensive PK days, PD samples were collected predose and 24 h after dosing.

Samples quantified below the lowest standard were reported as zero.

2.3.1 Pharmacokinetic Sample Analysis

EE, metabolites of norgestimate, norethindrone, and elagolix blood samples were collected in potassium (K2) ethylenediaminetetraacetic acid (EDTA)-containing collection tubes. The blood samples were centrifuged using a refrigerated centrifuge (1100–1300 g for approximately 10 min) within 60 min of collection to separate the plasma. The plasma samples were placed in the freezer within 2 h after collection and maintained at − 70 °C until shipped to AbbVie.

The elagolix, EE, NGMN, and NG plasma assays were performed by the Drug Analysis Department of AbbVie, North Chicago, IL, USA. Plasma concentrations of EE, NGMN, NG, norethindrone, and elagolix [5] were determined using a validated liquid chromatography method with tandem mass spectrometric detection (LC–MS/MS). The samples were analyzed by subject. The lower limits of quantitation (LLOQs) for EE, NGMN, and NG and norethindrone were established at 0.00247 ng/mL, 0.0198 ng/mL, and 0.0203 ng/mL and 0.0936 ng/mL, respectively. The LLOQ for elagolix was established at 0.126 ng/mL for

standard range A (0.126–196 ng/mL) and 1.57 ng/mL for standard range B (1.57–2460 ng/mL).

2.3.2 Pharmacodynamic Samples

Serum hormone concentrations (E2, P, LH, FSH) were measured using College of American Pathologist (CAP)/Clinical Laboratory Improvement Amendments (CLIA) assay methods at a central laboratory (Quest Diagnostics Nichols Institute, Valencia, CA, USA). LH and FSH were measured using the immunoassay methods, and E2 and P were measured using the LC–MS/MS methods. The LLOQ values were 0.5 IU/L for FSH, 0.2 IU/L for LH, 2 pg/mL for E2, and 0.32 nmol/L for P.

2.4 Statistical Analysis

2.4.1 Pharmacokinetics

The maximum observed plasma concentration (C_{max}) and time to C_{max} (peak time, T_{max}), as well as the terminal phase elimination half-life and area under the plasma concentration–time curve (AUC) over the 24-h dosing interval (AUC_{24}) were estimated for EE, NGMN, NG, norethindrone, and elagolix. Parameters were calculated using Phoenix™ WinNonlin® version 6.3 (Pharsight Corporation, Mountain View, CA, USA) for both studies. Each woman served as their own control. A repeated measures analysis of variance (ANOVA) was performed to compare the PK of coadministration and oral contraceptives administered alone. The model included a fixed effect for regimen (oral contraceptive alone and oral contraceptives coadministered with elagolix); subjects were viewed as a random effect. C_{max} and AUC were analyzed on the logarithmic scale. Within the framework of ANOVA, the relative bioavailability assessments with point estimate and 90% confidence interval (CI) were provided for the ratios of EE, NGMN, NG, and norethindrone C_{max} and AUC, to compare the coadministration of oral contraceptives with elagolix, versus alone.

2.4.2 Pharmacodynamics

Mean + standard deviation (SD) E2, P, LH, and FSH levels were descriptively summarized in graphical format. In order to compare the overall concentrations and exposures for FSH and LH and E2 in both periods, the AUC values over period 1 on days 1–28 ($AUC_{1–28\ days}$) and period 2 on days 57–84 ($AUC_{57–84\ days}$) were calculated using Phoenix™ WinNonlin® version 6.3 (Pharsight Corporation) for both studies. The mean hormone AUC values were calculated and compared between period 1 (days 1–28) and period 2 (days 57–84). Subjects who had the last PD samples collected before day 84 were excluded from E2, FSH, and LH AUC analysis. Additionally, the percentage of subjects with two consecutive P concentrations above 5 nmol/L were counted and assessed as markers for ovulation and compared between periods 1 and 2 [7].

2.4.3 Sample Size Calculations

For study 1, study size consideration was based on a comparison between day 21 (COC alone) and day 77 (COC in combination with elagolix) within the crossover ANOVA framework. Complete data from 26 subjects would provide approximately 80% power to detect the minimum detectable differences in AUC_{24}/C_{max} for NGMN, NG, and EE.

For study 2, study size consideration was based on a comparison between day 7 (norethindrone alone) and day 63 (norethindrone in combination with elagolix) within the crossover ANOVA framework. Complete data from 26 subjects would provide approximately 82% power to detect a 23% difference in the central value of norethindrone trough concentrations (C_{trough}) between day 63 and day 7. The power calculations were performed using logarithmic transformation. The calculation assumed the error term variance of 0.0967 for the natural logarithm of C_{trough}.

Both studies planned to enroll 30 subjects to provide allowance for premature discontinuations, assuming a drop-out rate of approximately 10%.

2.5 Safety and Tolerability

For both studies, adverse event (AE) monitoring and vital signs, physical examination, electrocardiogram, and laboratory test assessments were performed. Subjects who received at least one dose of study medication were included in the safety analyses. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0.

The number and percentage of women having treatment-emergent AEs (TEAEs) were tabulated by primary System Organ Class and MedDRA Preferred Term.

3 Results

3.1 Subject Dispositions

In study 1, 32 women were enrolled and 22 women completed the study. One woman was enrolled but was not dosed (positive drug screen). Nine women prematurely discontinued: exclusionary medication (1), abnormal pap test (1), positive pregnancy test (1), AE of headache (1), and withdrew consent (5). Of note, the woman with a positive urine pregnancy test only received one dose of COC on day 1 of period 1; screening serum and urine pregnancy tests were negative.

The analyses included 21 women for PK (one woman missed the intensive PK visit), 22 for PD, and 31 for safety.

In study 2, 34 women were enrolled and 26 women completed the study. Eight women prematurely discontinued for the following reasons: AEs of increased triglycerides (2, twin sisters) and hemoglobin decreased (1), positive drug screen (1), non-compliance (1), and withdrew consent (3). The analyses included 26 women for PK and PD, and 34 for safety.

Table 1 summarizes the demographic characteristics.

Table 1 Summary of demographic characteristics for studies 1 and 2

Characteristic	Study 1 ($n = 31$)	Study 2 ($n = 34$)
Age, years	31.0 ± 6.5 (20–43)	36.4 ± 8.5 (20–50)[a]
Weight, kg	66.5 ± 16.0 (44–106)	65.6 ± 12.8 (37–100)
Height, cm	161.4 ± 7.1 (150–175)	160.9 ± 6.1 (150–175)
Race [*n* (%)]	26 White (83.9) 5 Black (16.1)	28 White (82.4) 6 Black (17.6)

Data are expressed as mean ± standard deviation (minimum–maximum) unless otherwise specified

[a]Two subjects were 49 years of age at the time consent was signed. All subjects were female

4 Pharmacokinetics

In study 1, the PK parameters of EE, NGMN, and NG are presented in Table 2 and concentration–time profiles are presented in Fig. 2. The EE mean C_{max} and AUC_{24} values for period 2 were higher than those for period 1 ($p \leq 0.019$; ANOVA). The NGMN C_{max} and AUC_{24} were slightly lower in period 2 than those in period 1 ($p \leq 0.043$). For NG, no significant differences were observed between treatments ($p \geq 0.106$). Relative bioavailability assessments for EE, NGMN, and NG are presented in Table 3. Elagolix increased EE C_{max} and AUC by approximately 15% and 30%, respectively, reduced NGMN C_{max} and AUC by approximately

Table 2 Pharmacokinetic parameters of ethinylestradiol/NGMN/NG and elagolix in periods 1 and 2

Pharmacokinetic parameters (units)	Regimens	
	Period 1, day 21 (ethinylestradiol/norgestimate 0.035 mg/0.25 mg QD alone) [$n = 21$]	Period 2, day 77 (estradiol/norgestimate 0.035 mg/0.25 mg QD + elagolix 150 mg QD) [$n = 21$]
Ethinylestradiol		
C_{max} (ng/mL)	0.168 ± 0.061	0.195 ± 0.076[c]
T_{max} (h)	1.5 ± 0.5	1.9 ± 2.4
AUC_{24} (ng·h/mL)	1.27 ± 0.56	1.65 ± 0.72[c]
$t_{½}$[a,b] (h)	15.4 ± 5.7	14.2 ± 4.9
NGMN		
C_{max} (ng/mL)	2.29 ± 0.60	2.00 ± 0.51[c]
T_{max} (h)	1.4 ± 0.3	1.4 ± 0.3
AUC_{24} (ng·h/mL)	18.3 ± 4.8	15.5 ± 4.3[c]
$t_{½}$[a] (h)	22.8 ± 7.3	20.9 ± 6.8
NG		
C_{max} (ng/mL)	3.02 ± 1.91	2.72 ± 1.54
T_{max} (h)	2.7 ± 4.9	2.2 ± 2.5
AUC_{24} (ng·h/mL)	51.6 ± 32.9	49.0 ± 30.8
$t_{½}$[a,d] (h)	43.5 ± 24.6	43.5 ± 24.8
Elagolix		
C_{max} (ng/mL)	–	504.4 ± 179.3
T_{max} (h)	–	1.1 ± 0.4
AUC_{24} (ng·h/mL)	–	1100.9 ± 392.6
$t_{½}$[a,d] (h)	–	3.7 ± 1.7

C_{max}, maximum plasma concentration, T_{max} time to maximum plasma concentration, AUC_{24} area under the concentration–time curve from time zero to 24 h, $t_{½}$ terminal elimination half-life, *QD* once daily, *NGMN* norelgestromin, *NG* norgestrel, *ANOVA* analysis of variance

[a]Harmonic mean ± pseudo-standard deviation; evaluations of $t_{½}$ were based on statistical tests for β

[b]$N = 20$ for $t_{½}$ on day 77

[c]Statistically significantly different from triphasic OC alone (ANOVA, $p < 0.05$)

[d]$N = 19$

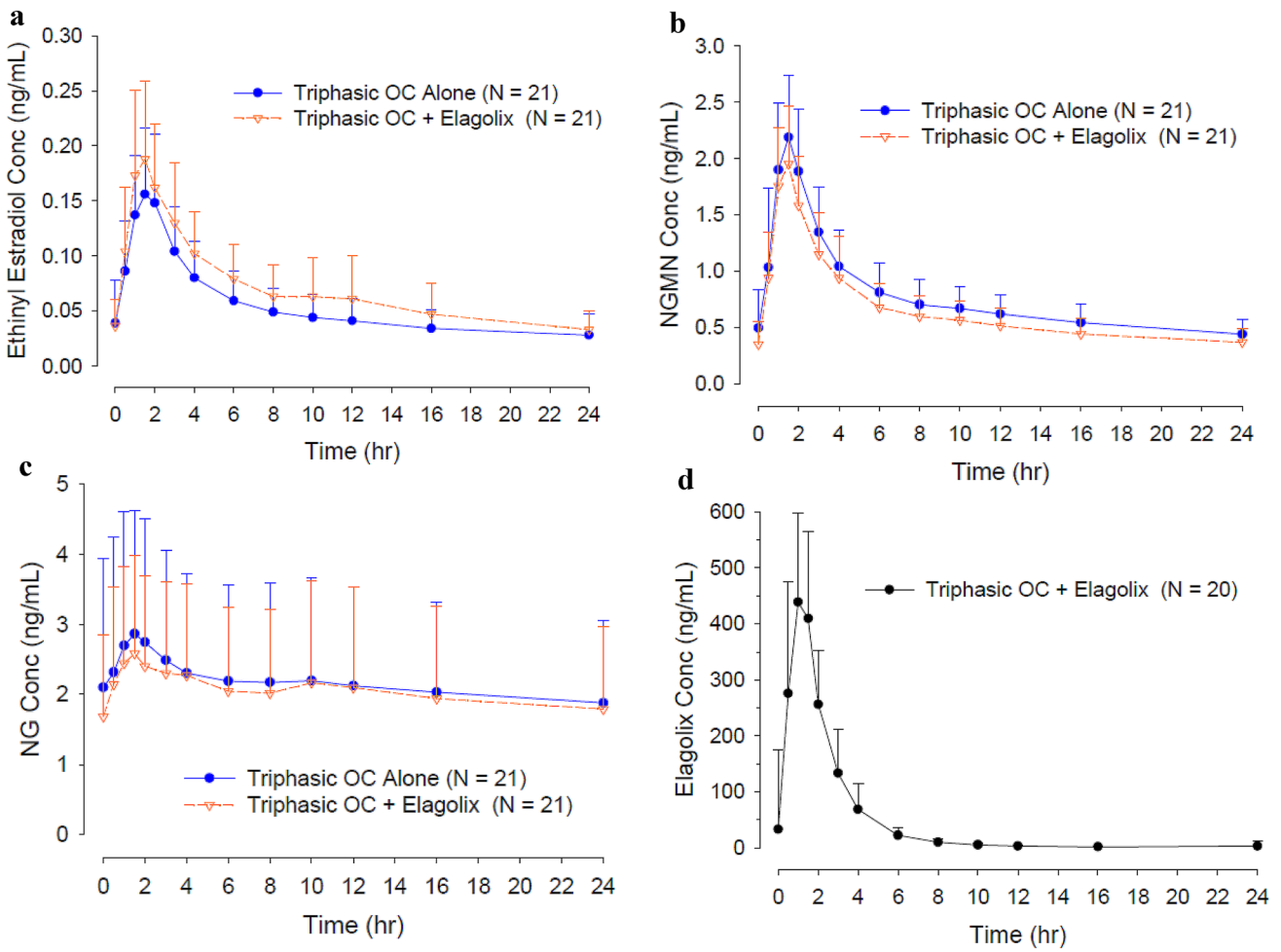

Fig. 2 Pharmacokinetic profiles mean + standard deviation of triphasic OC alone and triphasic OC with elagolix (linear scale, $n = 21$). **a** Ethinylestradiol; **b** NGMN; **c** NG; and **d** Elagolix ($n = 20$). *OC* oral contraceptive, *NGMN* norelgestromin, *NG* norgestrel

Table 3 Relative bioavailability and 90% CIs in study 1

Regimens (test vs. reference)	PK parameter	Central value[a]		Relative bioavailability	
		Test	Reference	Point estimate[b]	90% CI
Ethinylestradiol					
Ethinylestradiol/norgestimate + elagolix vs. ethinylestradiol/norgestimate alone	C_{max}	0.181	0.157	1.15	1.066–1.248
	AUC_{24}	1.50	1.16	1.30	1.186–1.416
NGMN					
Ethinylestradiol/norgestimate + elagolix vs. ethinylestradiol/norgestimate alone	C_{max}	1.93	2.21	0.872	0.781–0.973
	AUC_{24}	14.9	17.6	0.847	0.782–0.918
NG					
Ethinylestradiol/norgestimate + elagolix vs. ethinylestradiol/norgestimate alone	C_{max}	2.16	2.44	0.886	0.784–1.002
	AUC_{24}	36.1	39.1	0.923	0.840–1.013

Units for C_{max} and AUC_{24} central values are ng/mL and ng•h/mL, respectively

C_{max} maximum plasma concentration, AUC_{24} area under the concentration–time curve from time zero to 24 h, *NGMN* norelgestromin, *NG* norgestrel, *CI* confidence interval, *PK* pharmacokinetic

[a] Antilogarithm of the least squares means for logarithms

[b] Antilogarithm of the difference (test minus reference) of the least squares means for logarithms

13% and 15%, respectively, and reduced NG by 11% and 8%, respectively. The EE C_{max} and NG AUC_{24} 90% CIs were within the 'no-effect boundary' of 80–125% [10].

In study 2, the norethindrone PK parameters are shown in Table 4 and the concentration–time profiles are shown in Fig. 3. Other than an earlier mean T_{max} value ($p = 0.032$), no other norethindrone PK parameters were different between the two periods.

Relative bioavailability assessments for EE, NGMN, and NG are presented in Table 5. Elagolix decreased norethindrone C_{max} and AUC by approximately 5% and 12%, respectively. The 90% CI for norethindrone C_{max} was within the no-effect boundary, whereas the lower bound of the norethindrone AUC_{24} 90% CI extended slightly below 0.80 (0.788) [10].

Elagolix PK parameters for both studies (Tables 2, 3) are consistent with previously observed parameters [5, 8].

Table 4 Pharmacokinetic parameters of norethindrone

Pharmacokinetic parameters (units)	Regimens	
	Period 1 (norethindrone 0.35 mg QD alone) [$n = 26$]	Period 2 (norethindrone 0.35 mg QD + elagolix 150 mg QD) [$n = 26$]
Norethindrone		
C_{max} (ng/mL)	2.76 ± 0.88	2.59 ± 0.76
T_{max} (h)	1.67 ± 0.45	1.44 ± 0.32[b]
AUC_{24} (ng·h/mL)	14.16 ± 5.89	12.30 ± 4.02
$t_{½}$[a] (h)	7.85 ± 2.69	7.87 ± 3.51
Elagolix		
C_{max} (ng/mL)	–	555.4 ± 254.6
T_{max} (h)	–	1.2 ± 0.4
AUC_{24} (ng·h/mL)	–	1215.1 ± 540.6
$t_{½}$[a] (h)	–	3.8 ± 1.4

C_{max} maximum plasma concentration, *T_{max}* time to maximum plasma concentration, *AUC_{24}* area under the concentration–time curve from time zero to 24 h, *$t_{½}$* terminal elimination half-life, *QD* once daily, *ANOVA* analysis of variance

[a]Harmonic mean ± pseudo-standard deviation; evaluations of $t_{½}$ were based on statistical tests for β

[b]Statistically significantly different from norethindrone alone (ANOVA, $p < 0.05$)

4.1 Pharmacodynamic Changes

Figures 4 and 5 show the mean concentration–time profiles for FSH, LH, E2, and P in studies 1 and 2, respectively. In study 1, when elagolix was coadministered with COCs, the mean hormone exposure (assessed based on comparison of AUC values in periods 1 and 2; $n = 14$) for FSH, LH, and E2 appeared to be 31%, 38%, and 16% lower, respectively, compared with those observed with COCs alone. As an indirect marker of ovulation, 18% of women (4/22) had two consecutive ovulatory P concentrations > 5 nmol/L on days 1–28 in period 1, and 14% of women (3/22) on days 57–84 in period 2.

In study 2, when elagolix was coadministered with norethindrone, the hormone exposure for FSH, LH, and P, was similar to those observed with norethindrone alone. FSH and LH concentrations were 10% higher and 8% lower ($n = 19$), respectively, with coadministration when compared with norethindrone alone. E2 concentrations appeared to be 32% lower ($n = 19$) when elagolix was coadministered with norethindrone, compared with norethindrone alone. Sixty-one percent of women (16/26) had two consecutive ovulatory P concentrations on days 1–28 in period 1 and on days 57–84 in period 2.

For both studies, the observed interindividual variabilities in hormone exposure (AUC) are overall larger than reported for PK exposure, which may be explained by the sparse hormone sampling and large changes in hormone levels when ovulation occurred.

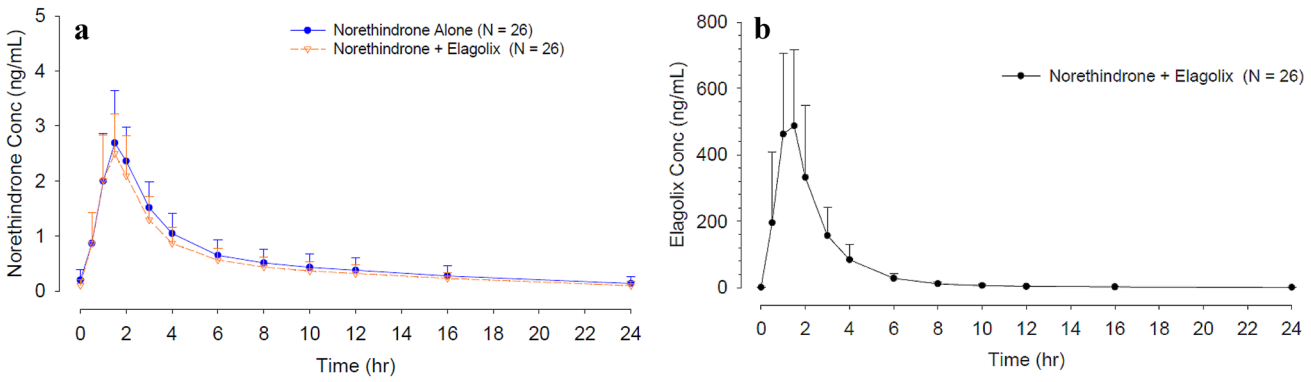

Fig. 3 Pharmacokinetic profiles mean + standard deviation of the mini-pill alone and mini-pill with elagolix (linear scale, $n = 26$). **a** Norethindrone; **b** Elagolix

Table 5 Relative bioavailability and 90% CIs in study 2

Regimens (test vs. reference)	PK parameter	Central value[a]		Relative bioavailability	
		Test	Reference	Point estimate[b]	90% CI
Norethindrone					
Norethindrone + elagolix vs. norethindrone alone	C_{max}	2.48	2.62	0.947	0.856–1.047
	AUC_{24}	11.6	13.2	0.882	0.788–0.987

Units for C_{max} and AUC_{24} central values are ng/mL and ng•h/mL, respectively

C_{max} maximum plasma concentration, AUC_{24} area under the concentration–time curve from time zero to 24 h, *CIs* confidence intervals, *PK* pharmacokinetic

[a]Antilogarithm of the least squares means for logarithms

[b]Antilogarithm of the difference (test minus reference) of the least squares means for logarithms

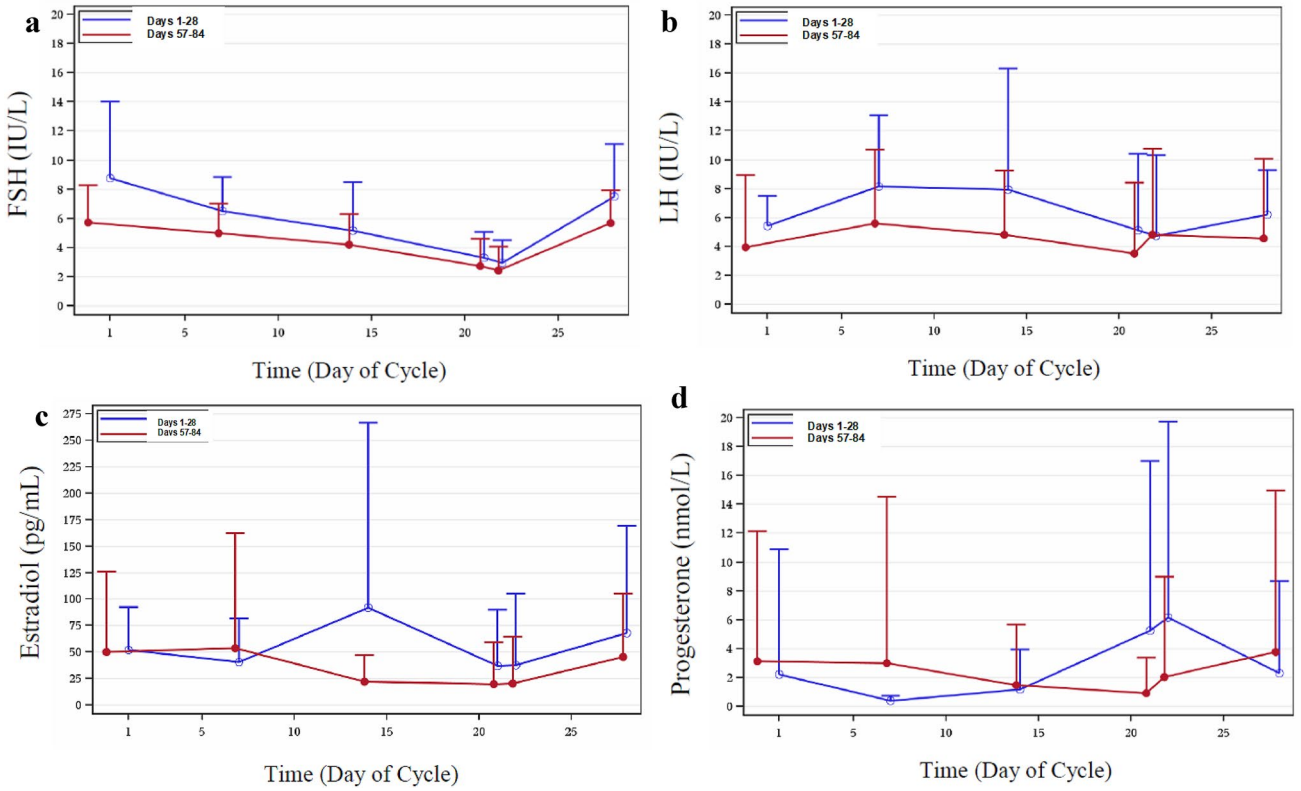

Fig. 4 Mean ± standard deviation concentration–time profiles after administration of triphasic OC alone and triphasic OC with elagolix in study 1 (linear scale, $n = 22$). Days 1–28, triphasic OC alone; days 57–84, triphasic OC with elagolix. **a** FSH; **b** LH; **c** estradiol; **d** progesterone. *FSH* follicle-stimulating hormone, *LH* luteinizing hormone

4.2 Safety and Tolerability

In study 1, 10/31 (32.3%) women experienced at least one TEAE during period 1 (COC) and 15/25 (60.0%) women during period 2 (COC + elagolix). The most common TEAEs reported for two or more women during period 1, in order of decreasing frequency, were headache and upper respiratory tract infection (URTI), and headache, nausea, URTI, and vomiting in period 2. The percentage of TEAEs assessed by the investigator as possibly or probably related to COC or elagolix were 6.5% (period 1, COC), 16.0% (period 2, COC), and 24.0% (period 2, elagolix). The AEs in periods 1 and 2 were assessed as mild or moderate by the investigator, except for one woman experiencing a single AE of tonsillitis streptococcal (period 1), which was assessed as severe.

In study 2, 17/31 (54.8%) women experienced at least one TEAE during period 2 (norethindrone + elagolix) compared with 12/34 (35.3%) women during period 1 (norethindrone). The most common TEAEs reported for two or more women in period 2, in order of decreasing frequency, were headache,

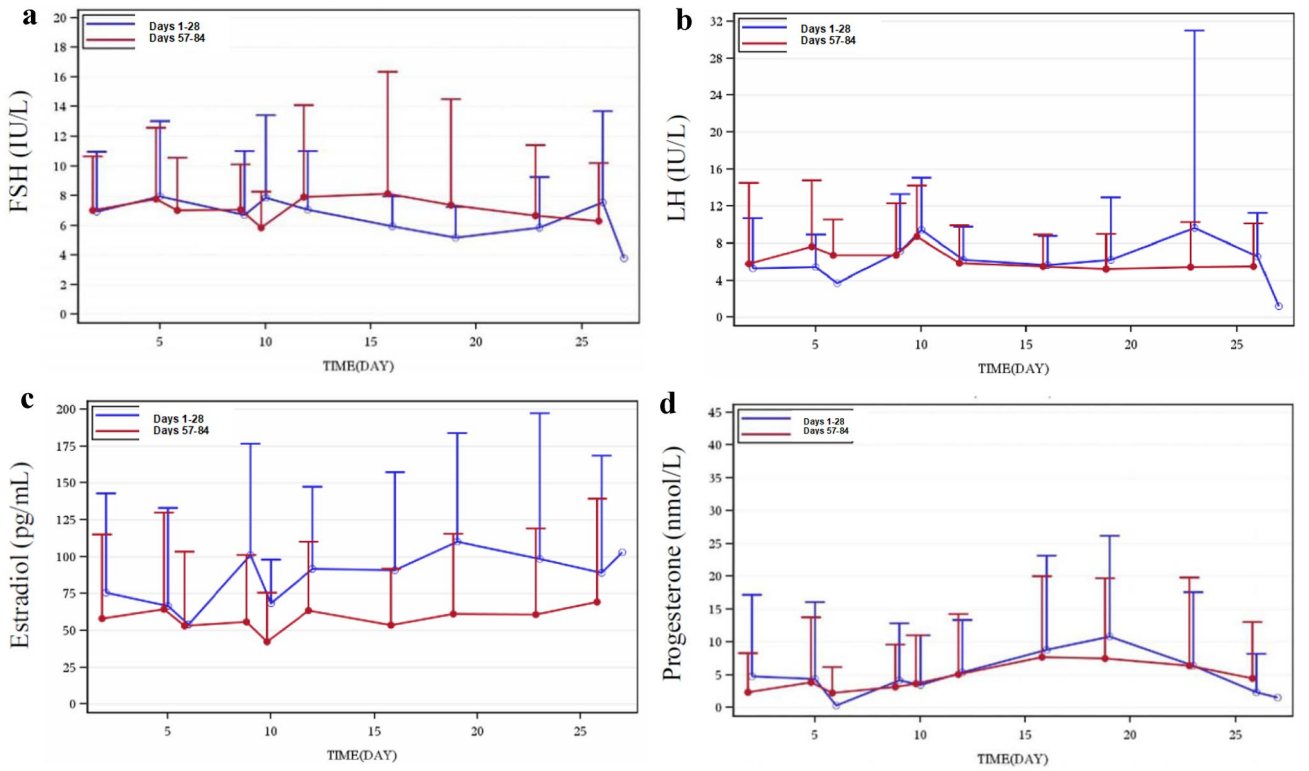

Fig. 5. Mean ± standard deviation concentration–time profiles after administration of norethindrone alone and norethindrone with elagolix in study 1 (linear scale, $n = 26$). Days 1–28, norethindrone alone; days 57–84, norethindrone with elagolix. **a** FSH; **b** LH; **c** estradiol; **d** progesterone. *FSH* follicle-stimulating hormone, *LH* luteinizing hormone

nausea, URTI, increase in blood triglycerides, influenza, and muscle spasms, and nausea, headache, breast tenderness, and uterine spasm in period 1. The percentage of TEAEs assessed by the investigator as possibly or probably related to norethindrone or elagolix were 26.5% (period 1, norethindrone), 19.4% (period 2, norethindrone), and 22.6% (period 2, elagolix). TEAEs were mostly assessed as mild to moderate for both drugs; one woman experienced a single AE (increase in blood triglycerides) assessed as severe during coadministration.

No deaths occurred during either study. No clinically significant vital signs, electrocardiogram, or changes in laboratory measurements were observed during study 1, and during study 2 all other changes were unremarkable. The regimens tested were generally well tolerated in both studies.

5 Discussion

Two DDI studies evaluated the effects of elagolix 150 mg once daily on COCs in study 1 or the progestin-only oral contraceptive in study 2. The PK results demonstrate that the administration of elagolix 150 mg once daily slightly reduced exposures of two progestins (norgestimate metabolites and norethindrone) by 8–15%. The small but not clinically relevant reduction in progestin concentrations is attributed to effects on the metabolic pathway of progestins [11–13]. Although the specific enzymes involved in progestin metabolism have not been well-defined, CYP3A4, CYP2B6, and uridine 5′-diphospho (UDP)-glucuronosyltransferases may play a role in the metabolism of norgestimate [14, 15], whereas CYP3A and CYP2C19 enzymes also contribute to the metabolism of norethindrone [16–18]. Consistent with previous findings where elagolix 150 mg once daily caused weak induction of CYP3A [8], this study demonstrated that elagolix 150 mg once daily causes a small or negligible induction of the metabolic pathways involved in progestin metabolism. The half-lives of the progestins were not altered by elagolix in this study, therefore the small impact by elagolix may be mostly at the level of the gastrointestinal tract.

Administration of elagolix 150 mg once daily resulted in a small increase in EE concentrations in study 1 (30%). CYP3A enzymes, sulfation (SULT1E1), and glucuronidation (UGT1A1) have been reported to be involved in the metabolism of EE [19–23]. Two previous studies support that elagolix is a weak to moderate CYP3A inducer [1], which indicates that elagolix coadministration may result

in slightly lower, not higher, EE concentrations [8, 24, 25]. Because elagolix is a P-gp inhibitor and caused increases in the exposure of the P-gp substrate digoxin [8], the small increase in EE exposures observed in this study may be attributed to inhibition of P-gp by elagolix and increase in the absorption of EE. This is also supported by in vitro evidence suggesting that EE is a P-gp substrate [26].

Elagolix exposure and variability was comparable with other phase I studies at the 150 mg once-daily dose [5, 8, 27]. Cross-study comparisons suggest that it does not appear that either contraceptive affected elagolix PK.

These studies also evaluated the impact of coadministration of elagolix 150 mg once daily on the PD of hormonal contraceptives. The studies demonstrate that coadministration of elagolix with hormonal oral contraceptives maintain the hormone suppressive profiles compared with oral contraceptives administered alone. Hormonal contraceptives inhibit ovulation by inhibiting LH and FSH [9], which then reduce E2 and P concentrations. Coadministration with elagolix resulted in similar or lower LH and FSH exposures, and ovulation rate (as assessed by P concentrations) did not appear to be impacted in both studies. Therefore, the coadministration of elagolix with hormonal contraceptives may offer similar contraceptive effects to hormonal contraceptives administered alone. This is based on (1) small PK changes in progestin (≤ 15%) and EE exposure (32%); (2) similar or lower FSH, LH, and P PD profiles (with elagolix); and (3) additional E2 suppression from elagolix in addition to E2 suppression by hormonal contraceptives.

The overall safety and efficacy of the combinations of elagolix and hormonal oral contraceptives needs to be further evaluated and confirmed in a larger study in women with endometriosis-associated pain. Future studies should determine if elagolix efficacy may be reduced when taking estrogen-containing contraceptives, and if the safety of coadministration is maintained given the small increase in EE concentrations that were observed in this study. The 30% increase in EE concentrations are considered small for oral contraceptives with low dose EE (< 25 µg); nevertheless, one may need to take into consideration oral contraceptives with a higher EE dose (> 25 µg).

The limitations of these studies include sparse hormone sampling, and elagolix was only tested at the 150 mg dose. Elagolix can be administered at the higher dose of 200 mg twice daily. A future study may evaluate the PK/PD at the higher elagolix dose.

6 Conclusion

Coadministration of elagolix with orally administered norethindrone or combination hormonal contraceptives containing EE and norgestimate resulted in small changes in the PK of oral hormonal contraceptive components; elagolix PK do not appear to be affected. The hormonal PD effects of oral contraceptives were not negatively impacted by coadministration with elagolix.

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Declarations

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Conflict of interest Juki Ng, Yi-Lin Chiu, and Cheri E. Klein are employees of AbbVie, Inc., and may own stocks or stock options. Robert A. Feldman is an employee of the Baptist Health Medical Group and was the principal investigator for these studies through Miami Research Associates, LLC, where he received payment for his role in leading the studies.

Ethics approval All studies were conducted in accordance with Good Clinical Practice guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The protocols and informed consent forms were approved by the Ethics Committee or Institutional Review Board at the site.

Consent to participate All participants provided written informed consent for participation in the studies.

Consent for publication Not applicable.

Data availability AbbVie is committed to responsible data sharing regarding the clinical trials they sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g. 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. This 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 the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html

Code availability Not applicable.

Author contributions All authors contributed to the study conception and design and approval of the final content in the manuscript. JN and CK contributed to material preparation, data collection and analysis. Y-LC conducted the study designs, developed statistical methodology, and oversaw the statistical analyses for both studies. RF was the principal investigator for both studies.

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