Elagolix suppresses ovulation in a dose-dependent manner: Results from a 3-month, randomized study in ovulatory women

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DISCLOSURE SUMMARY

J.N., K.C., Y.-L.C., and C.E.K. are employees of AbbVie and may hold AbbVie stock or stock options. D.F.A. has received research support from AbbVie, TherapeuticsMD, Bayer HealthCare, Endoceutics, Glenmark, Shionogi, and Radius Health and has served as a consultant for AbbVie, TherapeuticsMD, Endoceutics, Agile Therapeutics, Radius Health, InnovaGyn, Sermonix, and Exeltis. E.C.F. has served as a consultant for AbbVie. C.E.M. has served as a consultant, speaker, and has been involved in studies for AbbVie. R.A.F. has received payments from AbbVie to participate as Principal Investigator.

Abstract

Context: Elagolix is an oral gonadotropin-releasing hormone (GnRH) antagonist recently approved for the treatment of endometriosis-associated pain and being developed for heavy menstrual bleeding associated with uterine fibroids.

Objective: The objective was to evaluate the effects of elagolix on ovulation and ovarian sex hormones.

Design and setting: This was a randomized, open-label, multicenter study.

Participants: Participants were healthy ovulatory women aged 18 to 40 years.

Interventions: Elagolix was administered orally for 3, continuous 28-day dosing intervals at 100 to 200 mg once daily (QD), 100 to 300 mg twice daily (BID), and 300 mg BID plus estradiol/norethindrone acetate (E2/NETA) 1/0.5 mg QD.

Main outcome measures: The main outcomes measures were ovulation rates measured by transvaginal ultrasound, progesterone concentrations, and hormone suppression.

Results: Elagolix suppressed ovulation in a dose-dependent manner. The percentage of women who ovulated was highest at 100 mg QD (78%), intermediate at 150 and 200 mg QD and 100 mg BID (47%-57%), and lowest at 200 and 300 mg BID (32% and 27%, respectively). Addition of E2/NETA to elagolix 300 mg BID further suppressed the ovulation rate to 10%. Elagolix also suppressed luteinizing hormone (LH) and follicle stimulating hormone (FSH) in a dose-dependent manner, leading to dose-dependent suppression of estradiol and progesterone. Elagolix had no effect on serum biomarker of ovarian reserve, and reduced endometrial thickness compared to the screening cycle.

Conclusion: Women being treated with elagolix may ovulate and should use effective methods of contraception. The rate of ovulation was lowest with elagolix 300 mg BID plus E2/NETA 1/0.5 mg QD.

Keywords: Elagolix; Ovulation; Sex hormones; GnRH antagonist; Ovarian reserve; Endometrial thickness

Precis

We evaluated effects of elagolix on ovulation rates and hormone patterns in healthy, ovulatory women. Elagolix suppresses ovulation and hormones in a dose dependent manner, but it is not a contraceptive.

Introduction

Elagolix is an orally active, non-peptide GnRH antagonist. GnRH antagonists competitively inhibit GnRH receptors in the pituitary gland and lead to a rapid reduction in circulating gonadotropins and ovarian sex hormones (1). In contrast, GnRH agonists after an initial stimulatory phase desensitize GnRH receptors in the pituitary and subsequently cause cessation of pituitary gonadotropin production and provide profound estrogen suppression that is equivalent to that associated with bilateral oophorectomy (2).

Oral GnRH antagonists, such as elagolix, have the ability to suppress circulating estrogens in a dose-dependent manner, from partial suppression at lower doses to nearly full suppression at high doses, which creates an opportunity for dose titration in order to balance efficacy and safety. Elagolix (100 mg QD and 200 mg BID) has recently been approved by the United States Food and Drug Administration for the management of moderate to severe pain associated with endometriosis (3) based on the results of two randomized, placebo-controlled studies in women with surgical diagnosis of endometriosis (4). Elagolix is also under development for the management of heavy menstrual bleeding associated with uterine fibroids (5).

A previous study in healthy premenopausal women showed that elagolix was well tolerated and produced a dose-dependent suppression of gonadotropins and estradiol with rapid onset and rapid reversal of effects after discontinuation (6). These effects were later confirmed in a larger Phase 1 study in healthy premenopausal women during 21 days of continuous administration of increasing elagolix doses up to 400 mg BID (7). Continuous treatment with elagolix revealed a dose-dependent suppression of gonadotropins with a preferential effect on LH suppression. The estradiol suppression reached a maximum using elagolix at a dose of 200 mg BID. At elagolix doses $\geq$ 100 mg BID, anovulatory

progesterone concentrations were observed, which suggested a dose-dependent inhibition of ovulation. However, this study was too short to fully evaluate the effect of elagolix on ovulation.

The aim of the study reported herein was to rigorously evaluate the effects of various doses of elagolix on ovulation, gonadotropins, ovarian hormone production (estradiol, progesterone, and anti-Müllerian hormone [AMH], a serum biomarker of ovarian reserve), and endometrial thickness during 3, 28-day dosing intervals (84 continuous days) of elagolix administration.

Methods

Participants and Study Design

This was a Phase 1, randomized, open-label, multicenter, sequential dose-escalation study designed to evaluate the effects of different doses and dosing regimens of elagolix on ovulation, AMH a serum biomarker of ovarian reserve, and hormone patterns in healthy premenopausal women with normal ovulatory function in the United States and Puerto Rico (NCT01403038). The study was conducted at 20 sites in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. The study protocol was approved by the institutional review board at each site and written informed consent was obtained from each participant before any study-related procedures were performed. The general design of the study was similar to that used to evaluate new contraceptive regimens (8).

Women between the ages of 18 and 40 years, inclusive, who had a body mass index between 18 and 35 kg/m^2, inclusive, were in general good health, and had a history of regular menstrual cycles (24 to 32 days in duration; at least 3 and no more than 7 days of bleeding per month for the previous 6 months) with no evidence of significant gynecological disorders, such as ovarian cysts, polycystic ovary syndrome, endometriosis, or large uterine fibroids, were eligible to participate in the study. Women were also required to have an FSH concentration of 20 IU/L or less during menses at the first Week –4

visit. Women must have been at least 6 months postpartum, post any pregnancy event, or post lactation at the start of dosing, must have agreed to wash-out periods of hormonal therapies (e.g., GnRH agonists or antagonists, hormonal contraceptives, etc.), and must have agreed to use 2 forms of nonhormonal contraception with contraceptive counseling conducted throughout the study, including the screening and follow-up periods. Once eligibility was determined based on initial screening procedures, participants began a baseline assessment of ovulatory function at Week –4. Confirmation of ovulation by both ultrasound and hormonal parameters (protocol definition shown in **Table 1**) was required before participants were allowed to enter the treatment period, which was initiated on Day 1-3 of the subsequent menstrual cycle.

Women who met the eligibility criteria were assigned a randomization number. The randomization schedule was computer-generated at AbbVie before the start of each dosing regimen cohort. For cohorts that were conducted in parallel, efforts were made to randomize subjects to the dosing regimens to minimize treatment assignment biases. Women were assigned to 1 of 7 elagolix dose groups: 100 mg QD, 150 mg QD, 200 mg QD, 100 mg twice daily (BID), 200 mg BID, 300 mg BID, or 300 mg BID plus E2/NETA 1 mg/0.5 mg QD. Women self-administered elagolix with approximately 240 mL of water under fasted conditions in the morning for QD doses and in the morning and evening for BID doses. Women were instructed to avoid grapefruit, grapefruit products, star fruit, star fruit products, or Seville oranges during the treatment period.

The treatment period comprised up to 3, 28-day dosing intervals (84 consecutive days). After the end of the third dosing interval, women were followed until menses resumed or 60 days, whichever came first. Women returned to the study sites 3 times weekly (M, W, F or T, Th, S) for study procedures as described below.

Transvaginal Ultrasound Evaluation of Ovulation and Endometrial Thickness

Transvaginal ultrasounds (TVUS) were conducted once during the initial screening visit before Week -4 (safety TVUS to confirm eligibility) and serially 3 times weekly during the screening and treatment periods beginning on Day 1-3 of each woman's menstrual cycle. Serial TVUS were analyzed by a central reader facility (Perceptives Informatics, currently Parexel Informatics, Waltham, MA) and ovulation was assessed and classified based on measurements of the dominant follicle and its rupture/disappearance and luteal-phase progesterone concentrations (2 consecutive progesterone concentrations > 5 nmol/L within 10 days of dominant follicle measurement) (**Table 1**). Endometrial thickness (double layer) was also measured during each TVUS assessment. The Hoogland score was not used in this study because pilot studies with elagolix showed that this instrument was less suitable as an ovulation endpoint during elagolix treatment, particularly at lower doses that produce partial ovulation suppression and partial suppression in ovarian sex hormones (estradiol) and follicular activity (9).

The ovulation data were reviewed by an adjudication committee consisting of 3 expert reproductive endocrinologists who were blinded to study treatment and participant identifiers. The committee performed manual adjudication for all cases, including those that did not meet the protocol definition of ovulation (**Table 1**).

Sample Collection for Hormone Measurements and Elagolix Concentrations

Blood samples for assay of FSH, LH, estradiol and progesterone concentrations were obtained by venipuncture 3 times weekly in conjunction with TVUS during the 4-week screening period and through 3, 28-day intervals of elagolix dosing. Serum hormone concentrations were measured using College of American Pathologist (CAP)/Clinical Laboratory Improvement Amendments (CLIA) certified assay methods at the central laboratory (Quest Diagnostics Clinical Trials Laboratory, Valencia, CA). The lower limit of quantitation (LLOQ) values were 0.5 IU/L for FSH and LH, 2 pg/mL for estradiol, and 0.1 ng/mL for progesterone.

Blood samples for assay of AMH were obtained by venipuncture once per month at the end of each 28-day dosing interval. Serum AMH concentrations were analyzed using a CLIA-certified chemiluminescence assay at the central laboratory. The LLOQ for AMH was 0.2 ng/mL.

FSH, LH, estradiol, progesterone, and AMH concentrations were summarized using descriptive statistics. Baseline was defined as the time point prior to dosing. Hormone suppression was defined as a hormone concentration that was lower than the baseline value. Formal statistical comparisons among treatment groups were not performed for FSH, LH, estradiol, progesterone, or AMH concentrations.

Sparse blood samples for the assay of elagolix were collected every other week, for a total of 6 samples through the 3, 28-day intervals of elagolix dosing. Elagolix plasma concentrations were measured using a validated salt-assisted protein precipitation extraction, high performance liquid chromatography tandem mass spectrometric method (7). The elagolix plasma assays were performed by the Bioanalysis Department of AbbVie, North Chicago, IL. The LLOQ for elagolix was 0.126 ng/mL. The pharmacokinetic data were combined with the Phase 3 study results of elagolix and presented elsewhere (10).

Safety

The investigator monitored each participant for clinical and laboratory evidence of adverse events on a routine basis throughout the study. Blood samples for routine clinical laboratory tests were obtained during the initial screening period (prior to Week –4 and at Baseline), at Week 4 during dosing intervals 1 and 2, and at the final visit at the end of dosing interval 3. Adverse events in response to a query, observed by site personnel, or reported spontaneously by the participant were recorded. Serum and urine pregnancy testing was performed regularly and subjects were counseled at each visit on effective forms of dual, nonhormonal contraception and the need for consistent use to prevent pregnancy. If a pregnancy was confirmed, sites were instructed to obtain the following information on the outcome of

the pregnancy: fetal outcome (e.g., live infant or still birth), date of delivery, birth weight, birth length, gender, medically significant complications during pregnancy or labor or delivery, and birth defects.

Results

Participant demographics and disposition

A total of 205 women received study drug (**Table 2, Figure 1**). The mean age in each group ranged from 28 to 32 years and the majority of participants were white. The mean body mass index values ranged from 24.5 (minimum) to 27.6 kg/m^2 (maximum).

Twenty women (9.8%) prematurely discontinued from the study (**Table 2**). The available data from these women up to the time of discontinuation were included in the summaries of ovulation rates and hormone concentrations. Details of the 4 discontinuations that were due to adverse events are discussed under Safety.

Ovulation

Administration of elagolix suppressed ovulation in a dose-dependent manner (**Figure 2**). The percentage of women who ovulated at any time point during 3 intervals of dosing with elagolix was highest in the 100 mg QD group (78%), intermediate in the 150 mg QD, 200 mg QD, and 100 mg BID groups (47%-57%), and lower in the 200 and 300 mg BID groups (32% and 27%, respectively). Addition of E2/NETA to elagolix 300 mg BID further suppressed the percentage of women who ovulated to 10%. The percentage of women with ovulatory progesterone concentrations (2 consecutive measurements > 5 nmol/L, per the protocol definition described in Table 1) closely mirrored the percentage of women who ovulated based on TVUS measurements (**Table 3**). Attempts were made to compare ovulation rate between races (blacks vs white) by dose despite the small N; no differences were apparent.

Hormone Patterns

As shown in **Figure 3**, relative to screening, administration of elagolix resulted in dose-dependent suppression of LH, FSH and estradiol, in a manner that paralleled suppression of ovulation and luteal-phase progesterone concentrations. For LH and estradiol, suppression progressively increased with higher doses of elagolix, whereas, for FSH, suppression was observed for doses of 200 mg BID and higher. Addition of E2/NETA resulted in further suppression of FSH and LH, but not estradiol due to exogenous estradiol in E2/NETA. The cyclicity of FSH, the surge in LH, and cyclical peaks of estrogen and progesterone were overall diminished during dosing with elagolix. On a categorical basis, the percentage of women with mean estradiol concentrations less than 20 pg/mL was numerically highest in the 300 mg BID group (57-89% across dosing intervals) (**Table 4**).

Ovarian Reserve

Administration of elagolix had no effect on monthly AMH concentrations at any time point during the study (**Table 5**). Mean change of baseline in AMH concentrations at the end of each dosing interval were small (range across dose groups : –0.17 to 0.94 ng/mL for interval 1; –0.39 to 0.53 ng/ml for interval 2; –0.44 to 0.54 ng/mL for interval 3), indicating that the levels were similar to those measured at screening (range across dose groups: 2.26 to 2.92 ng/mL) and did not differ among elagolix dose groups.

Endometrial Thickness

Endometrial thickness was substantially lower during administration of elagolix than during the follicular and luteal phase of the screening period (**Figure 4**). During the screening period, a normal cycle of endometrial thickening was observed, in which mean endometrial thickness increased to approximately 9 to 12 mm at the midpoint of the menstrual cycle, was maintained at that thickness until near the end

of the luteal phase, and then decreased to baseline levels at the end of the menstrual cycle. In contrast, mean endometrial thickness remained relatively constant at around 5 to 7 mm through 84 days of dosing with elagolix, regardless of dose, and mean increases in mid-cycle were not observed.

Uterine Bleeding

The self-reported uterine bleeding observations were consistent with the ovulation data and the hormone data, in which ovulation was followed by bleeding (menses). Generally, there was a decrease in the number of light/moderate/heavy bleeding days at the higher elagolix doses (200 mg BID and above) compared to lower elagolix doses. In women who did not ovulate during elagolix dosing, amenorrhea (defined as neither bleeding nor spotting during last 28 days of elagolix dosing) was observed particularly in the higher doses (81%-96%, data not shown). When Std Activella was added to the 300 mg BID regimen, an initial increase in spotting and light bleeding days were observed, but decreased by Treatment Cycle 3 (from mean 3.4 days/subject at Screening to mean 6.1 days at Treatment Cycle 1 and mean 2.6 days at Treatment Cycle 3).

Return to Menses

The median number of days from the last dose of elagolix to the return of menses based on self-reported bleeding in a daily diary appeared to be dose dependent ranging from 11 days (range: 0-25 days) in the 100 mg QD group to 24 days (range: 0-32 days) in the 200 mg BID group (**Table 6**). The maximum number of days for menses to resume was 42 (in the 200 mg QD group).

Safety

Overall, 79% (162/205) of women experienced a treatment-emergent adverse event, the most frequently reported of which were headache (25%), hot flush (23%), and nausea (19%) (**Table 7**). All other events occurred in less than 10% of women. Aside from hot flush, which was reported by more

women in the 200 mg BID group (17/41, 42%), and the lowest rate in the 300 mg BID plus E2/NETA group (1/20, 5%), the rates of adverse events were similar across groups. The events of headache, hot flush, and nausea for most of the women were mild or moderate in severity and were considered to be related to elagolix by the investigator.

Five women became pregnant during the study: 1 in the 200 mg BID group with an estimated conception date during the treatment period (on Day 13) and 4 (1 each in the 100 mg QD, 150 mg QD, 300 mg BID, and 300 mg BID plus E2/NETA) with estimated conception dates after the last dose of study drug. The woman with 69 days of fetal drug exposure underwent an elective abortion. Of the four women with conception after the last dose of study drug, two women carried to term and had uncomplicated deliveries of healthy normal weight babies (conceived 69 and 55 days after the last dose of 100 mg QD and 300 mg BID plus E2/NETA, respectively), one woman underwent an elective abortion, and one woman underwent surgical treatment for an ectopic pregnancy.

Four women discontinued from the study due to adverse events: a staphylococcal infection at the site of a bug bite (one in the 200 mg BID group); an intervertebral disc protrusion (worsening of a herniated disc) (one in the 200 mg QD group); intermittent irritability and an increase in the severity of depression (one in the 300 mg BID group); and hot flush (one in the 300 mg BID group). Only the event of hot flush was considered by the investigator to be related to elagolix.

Results of other safety evaluations, including laboratory tests, electrocardiogram assessments, and vital signs values were generally unremarkable for each elagolix regimen. During dosing intervals 1 and 3, there was a dose-dependent trend for an increase from baseline in mean cholesterol and triglycerides; however, none of the women had a value that met the threshold of clinical concern of 2 times the upper limit of normal.

Discussion

The present study characterized the effects of elagolix on ovulation and the associated hormone patterns in 205 healthy women with normal ovulatory function. This study demonstrated that administration of elagolix 100 mg QD to 300 mg BID for 3, 28-day dosing intervals suppressed ovulation, gonadotropins, and ovarian sex hormones in a dose-dependent manner. At the highest dose (300 mg BID) tested, the ovulation rate was 27%, confirming that elagolix does not consistently inhibit ovulation and may not be a contraceptive. As expected, when E2/NETA 1/0.5 mg was added to the elagolix 300 mg BID regimen, the ovulation rate was reduced to 10% and gonadotropins were suppressed to the lowest levels. The low ovulation rate may be attributed to the dose of NETA used in this study (0.5 mg), which is higher than the dose used in progestin-only contraceptives (0.35 mg).

The study protocol used a strict definition of ovulation, i.e. follicular mean diameter of > 13 mm with rupture, with 2 consecutive progesterone concentrations > 5 nmol/L within 10 days of this follicle measurement. As the TVUS and hormone data were being evaluated during the course of the study, it became apparent that the 3-times weekly TVUS assessments may not have been sufficient to capture follicular rupture in some cases. Therefore, to be as comprehensive as possible, an adjudication committee was formed to review the data for each subject. The adjudication committee further expanded the protocol definition of ovulation to include ovulation based on consecutive progesterone concentrations >5 nmol/L with a follicle >13 mm, or evidence of rising estradiol concentrations and consecutive progesterone concentrations >5 nmol/L consistent with ovulation, with absence of TVUS observations on follicular rupture.

The ovulation rates observed in this study may be inflated due to unpredictable noncompliance with study drug dosing. The 3-month study with 1-month Screening and multiple procedures was considered a long duration and cumbersome for a healthy women multicenter study in an outpatient setting with

no treatment benefits of taking elagolix for 3 months. Multiple efforts were attempted to promote study drug compliance, including a paper diary and pill counts to confirm dosing. In addition, frequent three times weekly visits also encouraged compliance to study drug. While the paper diaries suggested good compliance to study medication, there were some instances in which plasma elagolix concentrations were below the limit of detection based on sparse measurements of every other week pharmacokinetic sampling (data not shown), which may suggest noncompliance. In some women with elagolix consistently below the limit of detection, hormone and follicle patterns were consistent with those observed in the screening cycle, also suggesting noncompliance. The number of pharmacokinetic samples with elagolix concentrations below the limit of detection were also significantly higher in the second dosing interval (n=19) than the first dosing interval (n=10), which may explain the higher ovulation rate observed in the second dosing interval. The pharmacokinetic samples below the limit of detection observed in the second dosing interval also happened to explain more than half of the ovulation cases observed in the second interval (data on file).

Elagolix administration may result in cycle lengthening beyond 28 days in some women, and as a result may have contributed to more ovulations in the second 28-day dosing interval than in the first or third dosing interval. In this current study, in women who did not ovulate, the suppressive effects of elagolix on gonadotropins and ovarian hormones were relatively constant across all 3 dosing intervals. Further analysis and reports of differences in hormone profiles between women who ovulated compared with those who did not ovulate will be forthcoming. Ovulations (as assessed by progesterone concentrations) were also observed in some women in the Phase 3 endometriosis studies (Elaris Endometriosis [EM]-I and Elaris EM-II; data on file). Despite the ovulations that were observed in these studies, elagolix demonstrated robust efficacy in reducing dysmenorrhea and non-menstrual pain associated with endometriosis (4). This efficacy was maintained through 6 and 12 months during the Phase 3 extension studies (Elaris EM-III and Elaris EM-IV) (11).

The dose-dependent reductions in ovulation rates observed in this study paralleled the dose-dependent suppression of hormone concentrations observed in this and previous studies (6,7). In the current study, partial suppression of LH was observed at the 150 mg QD dose, whereas partial suppression of FSH was not apparent until reaching the 200 mg BID dose. Hence, lower doses of elagolix suppressed LH to a greater extent than FSH, consistent with results observed in previous studies of elagolix (6,7), peptide GnRH antagonists (12,13), and other classes of compounds such as the NK3R antagonist, ESN364 (14,15). FSH suppression became more apparent at the 300 mg BID dose, with the largest suppression being observed in the group that received elagolix 300 mg BID plus E2/NETA.

The lack of maximal suppression of FSH at lower doses of elagolix may enable persistent, although reduced, secretion of estradiol from granulosa cells of growing follicles (14). Therefore, use of lower doses of elagolix that partially suppress estradiol (16-18) may help mitigate hypoestrogenic side effects, such as bone loss and severe hot flushes, that are commonly associated with the complete suppression of estradiol that is achieved with GnRH agonists (19-22) while maintaining efficacy.

When comparing the estradiol levels in this study to those in the previously published studies in healthy premenopausal women (7) and women with endometriosis (23), the results of the current study were overall consistent. In the previous study in healthy women, suppression of estradiol to levels near the limit of detection in that study (~10 pg/mL) was observed at doses of 200 mg BID and higher (7). Similarly, in the Phase 3 studies in women with endometriosis (23), the vast majority of women (approximately 60-80%) had estradiol concentrations that were less than 20 pg/mL at the 200 mg BID dose. In the current study, 54-73% of women had estradiol concentrations that were less than 20 pg/mL at the 200 mg BID dose.

The observation of a rapid return to menses suggests there is a return to normal ovarian hormonal activity shortly after elagolix is discontinued. In addition, elagolix had no effect on AMH, the serum

biomarker of ovarian reserve. AMH plasma concentrations reflect the continuous noncyclical growth of small follicles and mirror the size of the resting primordial ovarian follicle pool (24,25). AMH concentrations at the end of 84 days of dosing were similar to those measured during screening, suggesting that there was continued growth of small follicles during the treatment period. Given that endometriosis and uterine fibroids are common in women of reproductive age, the rapid return of ovulatory function may be desirable in this population.

Elagolix was generally well tolerated by the healthy women in this study. The most frequently reported adverse events were headache, hot flush, and nausea, which were mild or moderate in severity. The percentage of women who reported hot flush was lowest in the 300 mg BID plus E2/NETA group (5%), suggesting that hypoestrogenic side effects can be mitigated by the addition of low-dose hormonal replacement therapy. Although women were advised to use two forms of nonhormonal contraception in the study, one woman in the 200 mg BID group became pregnant during the treatment period. Thus, elagolix alone does not appear to be a contraceptive and women who take elagolix should consider effective methods of contraception during treatment to avoid pregnancy.

Consistent with the changes in ovarian hormones, mean endometrial thickness remained at early follicular phase levels (~5-7 mm) during the entire treatment period, and there was no trend of increasing thickness in any subject that are suggestive of endometrial changes for any dose group. This result has been confirmed in the Phase 3 studies in women with endometriosis-associated pain in which 6 months of treatment with elagolix reduced endometrial thickness and endometrial proliferation, and there were no adverse endometrial findings based on endometrial biopsy results (4).

Conclusion

Elagolix suppresses ovulation and pituitary and ovarian hormones in a dose-dependent manner, has no effect on AMH the serum biomarker of ovarian reserve, and decreases mean endometrial thickness at

doses being targeted for the treatment of endometriosis-associated pain and heavy menstrual bleeding associated with uterine fibroids.

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Author's Roles

D.F.A., J.N., K.C., Y.-L.C., and C.E.K. designed the study; D.F.A. and R.A.F. collected the data; J.N., K.C., Y.-L.C., and C.E.K. analyzed and interpreted the data; D.F.A., E.C.F., and C.E.M. adjudicated the classifications of ovulation; Y.-L.C. conducted the statistical analyses; all authors reviewed and approved the final manuscript.

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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 (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

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Figure Legends

Figure 1. Consort Diagram.

Figure 2. Ovulation rates across all elagolix dosing intervals (total) and during each individual dosing interval

Figure 3. Median hormone concentrations during screening and 3, 28-day intervals of dosing with elagolix.

Figure 4. Mean endometrial thickness profiles during screening and 3, 28-day intervals of dosing with elagolix.

Table 1. Protocol and adjudication definitions of ovulation

Rating	Definition
Ovulation (protocol definition)	Follicular mean diameter of > 13 mm, 2 consecutive progesterone concentrations > 5 nmol/L within 10 days of this follicle measurement, and rupture visible on ultrasound
Ovulation based on follicular activity and hormonal response without rupture	Follicular mean diameter of > 13 mm, 2 consecutive progesterone concentrations > 5 nmol/L within 10 days of this follicle measurement, but rupture not visualized on ultrasound
Ovulation based on hormonal response alone	Evidence of rising estradiol concentrations followed by a robust luteal phase (based on 2 consecutive progesterone concentrations > 5 nmol/L) but no evidence of follicular activity on ultrasound
No ovulation	No evidence of follicular activity on ultrasound or hormonal response
Insufficient information to draw a conclusion	Unable to determine due to missing data

Note: Ovulation during screening was determined based on the protocol definition (first row above) and was not subject to adjudication. The cutoff for the progesterone concentration was conservatively based on criteria described by Hoogland and Skouby (9).

Table 2. Participant demographic characteristics and disposition

	Elagolix Dose Group						
Characteristic	**100 mg QD N = 9**	**150 mg QD N = 40**	**200 mg QD N = 35**	**100 mg BID N = 38**	**200 mg BID N = 41**	**300 mg BID N = 22**	**300 mg BID + E2/NETA 1/0.5 mg QD N = 20**
Age, y, mean (SD)	32.1 (5.3)	28.8 (5.5)	30.1 (5.1)	30.4 (7.0)	30.5 (5.1)	31.8 (6.0)	29.6 (5.0)
BMI, kg/m^2, mean (SD)	27.6 (4.8)	26.1 (3.9)	26.3 (4.6)	26.9 (4.0)	26.9 (3.9)[a]	27.4 (3.9)[a]	24.5 (3.8)[a]
Race, n (%)							
White	9 (100)	31 (78)	27 (77)	26 (68)	29 (71)	17 (77)	16 (80)
Black	0	6 (15)	7 (20)	10 (26)	9 (22)	4 (18)	3 (15)
Asian	0	1 (3)	0	1 (3)	0	0	1 (5)
Other	0	2 (5)	1 (3)	1 (3)	3 (7)	1 (5)	0
Disposition							
Completers, n	7	38	32	32	38	18	20
Discontinued, n	2	2	3	6	3	4	0
Reason discontinued (n)	Withdrew consent (1), noncompliant (1)	Withdrew consent (1), lost to follow up (1)	AE (1), lost to follow up (1), moved out of state (1)	Withdrew consent (3), other reasons (3)[b]	AE (1), lost to follow up (1), pregnancy (1)	AE (2), lost to follow up (1), noncompliant (1)	--

QD, once daily; BID, twice daily; E2/NETA, estradiol/norethindrone acetate; BMI, body mass index

a. N = 40, 21, and 18 for the 200 mg BID, 300 mg BID, and 300 mg BID + E2/NETA groups, respectively.

b. Did not meet minimum progesterone concentration (1); failed to demonstrate follicle rupture on transvaginal ultrasound (1); transferred to another study (1)

Table 3. Number of women with 2 consecutive progesterone concentrations > 5 nmol/L

	Elagolix Dose Group						
Time period	100 mg QD N = 9	150 mg QD N = 40	200 mg QD N = 35	100 mg BID N = 38	200 mg BID N = 41	300 mg BID N = 22	300 mg BID + E2/NETA 1/0.5 mg N = 20
Interval 1, n	2	6	6	6	1	1	0
Interval 2, n	5	13	16	13	7	5	1
Interval 3, n	5	12	16	13	10	5	2
Overall[a], n (%)	6 (67)	21 (53)	20 (57)	17 (45)	13 (32)	6 (27)	2 (10)

QD, once daily; BID, twice daily, E2/NETA, estradiol/norethindrone acetate

a. Two consecutive progesterone concentrations > 5 nmol/L at any time during the treatment period

Table 4. Percent of women with mean estradiol concentrations in each concentration range

	Elagolix Dose Group						
Estradiol Concentration Range[a]	**100 mg QD N = 9**	**150 mg QD N = 40**	**200 mg QD N = 35**	**100 mg BID N = 38**	**200 mg BID N = 41**	**300 mg BID N = 22**	**300 mg BID + E2/NETA 1/0.5 mg QD N = 20**
Screening							
< 10 pg/mL	0%	0%	0%	0%	0%	0%	0%
< 20 pg/mL	0%	0%	0%	0%	0%	0%	0%
20 – 50 pg/mL	0%	3%	0%	3%	2%	0%	0%
> 50 pg/mL	100%	98%	100%	97%	98%	100%	100%
Interval 1							
< 10 pg/mL	0%	3%	0%	12%	43%	45%	0%
< 20 pg/mL	0%	26%	6%	44%	73%	85%	12%
20 – 50 pg/mL	38%	37%	61%	38%	20%	10%	35%
> 50 pg/mL	63%	37%	33%	18%	8%	5%	53%
Interval 2							
< 10 pg/mL	0%	3%	0%	14%	44%	41%	0%
< 20 pg/mL	0%	8%	6%	27%	59%	59%	5%
20 – 50 pg/mL	56%	50%	50%	30%	20%	18%	40%
> 50 pg/mL	44%	42%	44%	43%	22%	23%	55%
Interval 3							
< 10 pg/mL	0%	0%	0%	12%	29%	38%	0%
< 20 pg/mL	0%	8%	3%	18%	54%	57%	5%
20 – 50 pg/mL	11%	53%	42%	32%	15%	19%	20%
> 50 pg/mL	89%	40%	55%	50%	32%	24%	75%

QD, once daily; BID, twice daily, E2/NETA, estradiol/norethindrone acetate

a. Mean concentrations were estimated for each woman by averaging all values within each interval.

Table 5. Ovarian reserve as measured by anti-mullerian hormone (AMH) serum concentrations

	AMH (ng/mL)[a]						
	Elagolix Dose Group						
Time period	100 mg QD N = 9	150 mg QD N = 40	200 mg QD N = 35	100 mg BID N = 38	200 mg BID N = 41	300 mg BID N = 22	300 mg BID + E2/NETA 1/0.5 mg QD N = 20
Screening	2.73 ± 1.80	2.79 ± 2.72	2.32 ± 1.75	2.26 ± 1.32	2.44 ± 2.12	2.41 ± 1.33	2.92 ± 2.22
Interval 1 (Day 28)	0.31 ± 1.64	–0.17 ± 1.65	0.73 ± 1.89	0.06 ±1.09	0.89 ± 1.48	0.94 ± 1.16	0.51 ± 0.91
Interval 2 (Day 56)	–0.39 ± 1.14	0.22 ± 2.01	0.44 ± 1.22	0.53 ± 1.28	0.32 ± 1.61	0.38 ± 1.03	–0.07 ± 1.37
Interval 3 (Day 84)	–0.20 ± 1.38	0.24 ± 1.62	0.54 ± 1.47	0.18 ± 0.68	–0.09 ± 1.43	0.04 ± 0.99	–0.44 ± 1.29

QD, once daily; BID, twice daily; E2/NETA, estradiol/norethindrone acetate

a. Mean change from baseline ± SD , except for screening represents mean ± SD

Table 6. Time to return of menses after the last dose of elagolix

	Time to Return of Menses (days)						
	Elagolix Dose Group						
	100 mg QD N = 9	150 mg QD N = 40	200 mg QD N = 35	100 mg BID N = 38	200 mg BID N = 41	300 mg BID N = 22	300 mg BID + E2/NETA 1/0.5 mg QD N = 20
Median	11	15.5	17	16	21	21.5	24.0
Minimum - Maximum	0-25	0-38	0-42	0-29	3-38	3-27	0-32

QD, once daily; BID, twice daily, E2/NETA, estradiol/norethindrone acetate

Table 7. Treatment-emergent adverse events occurring in at least 5% of women across elagolix dose groups

	Elagolix Dose Group							
Adverse event term	**100 mg QD N = 9**	**150 mg QD N = 40**	**200 mg QD N = 35**	**100 mg BID N = 38**	**200 mg BID N = 41**	**300 mg BID N = 22**	**300 mg BID + E2/NETA 1/0.5 mg QD N = 20**	**Total N = 205**
Any Adverse Event, n (%)	7 (78)	29 (73)	32 (91)	27 (71)	34 (83)	16 (73)	17 (85)*	162 (79)
Headache	2 (22)	9 (23)	13 (37)	12 (32)	10 (24)	2 (9)	3 (15)	51 (25)
Hot flush	2 (22)	6 (15)	8 (23)	7 (18)	17 (42)	6 (27)	1 (5)	47 (23)
Nausea	1 (11)	5 (13)	8 (23)	5 (13)	9 (22)	5 (23)	5 (25)	38 (19)
Upper respiratory tract infection	1 (11)	3 (8)	3 (9)	2 (5)	5 (12)	1 (5)	0	15 (7)
Back pain	2 (22)	3 (8)	5 (14)	3 (8)	2 (5)	0	0	15 (7)
Dizziness	2 (22)	1 (3)	4 (11)	4 (11)	3 (7)	0	0	14 (7)
Acne	1 (11)	2 (5)	7 (20)	1 (3)	2 (5)	0	1 (5)	14 (7)
Diarrhea	1 (11)	1 (3)	2 (6)	1 (3)	6 (15)	0	1 (5)	12 (6)
Abdominal pain	0	4 (10)	2 (6)	1 (3)	3 (7)	1 (5)	0	11 (5)
Insomnia	1 (11)	3 (8)	2 (6)	3 (8)	1 (2)	1 (5)	0	11 (5)

QD, once daily; BID, twice daily; E2/NETA, estradiol/norethindrone acetate

*Participants could report more than one adverse event during the study. Using this the 300 mg BID dose with E2/NETA add back only lists n=11 events, not 17.

Figure 1

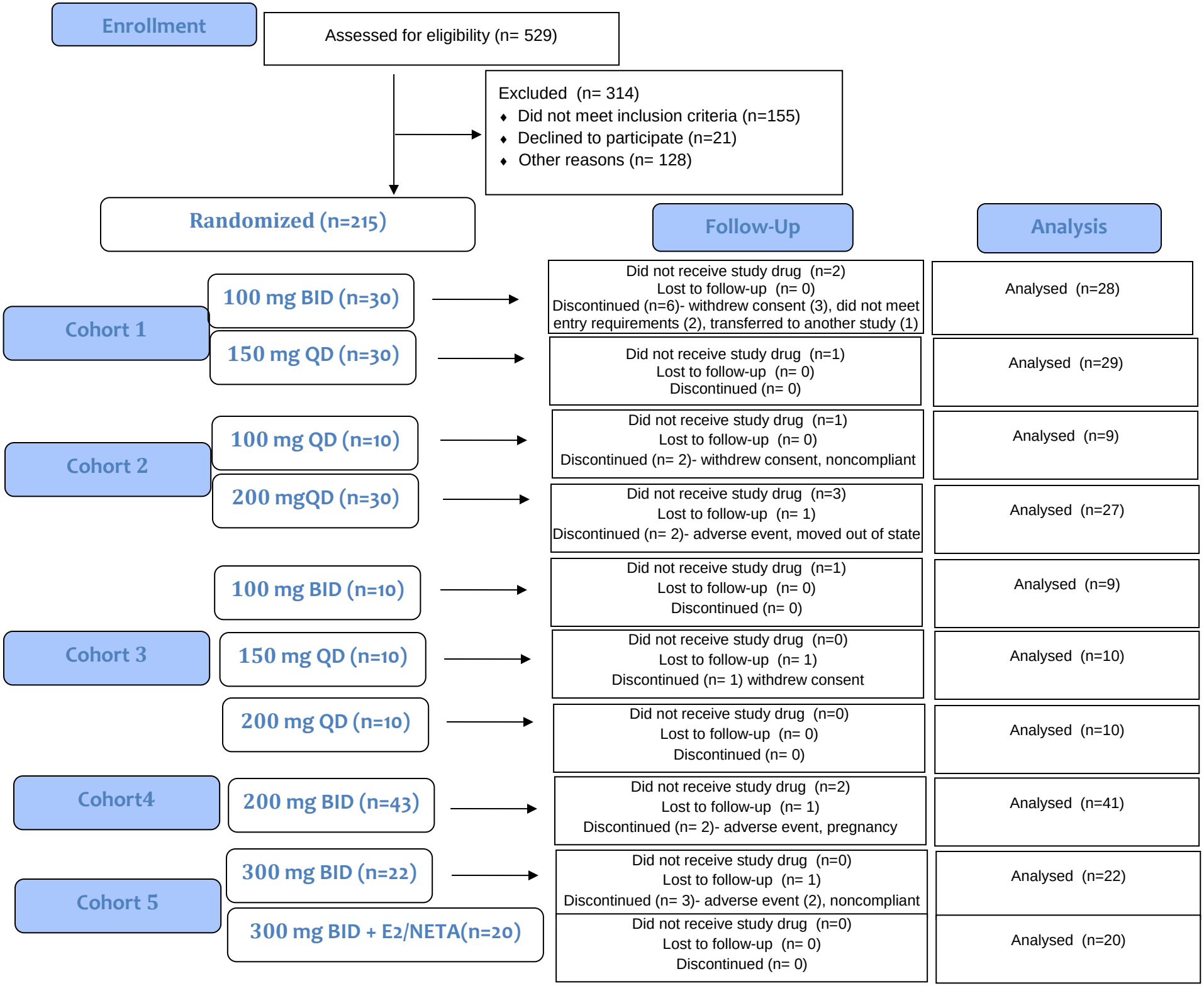

Figure 2

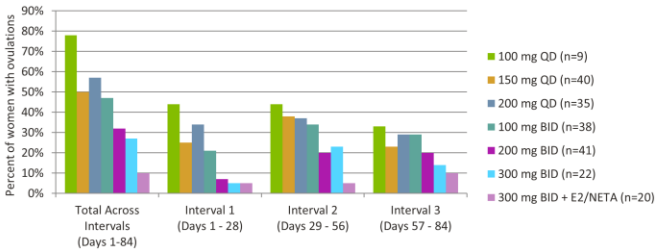

Figure 3

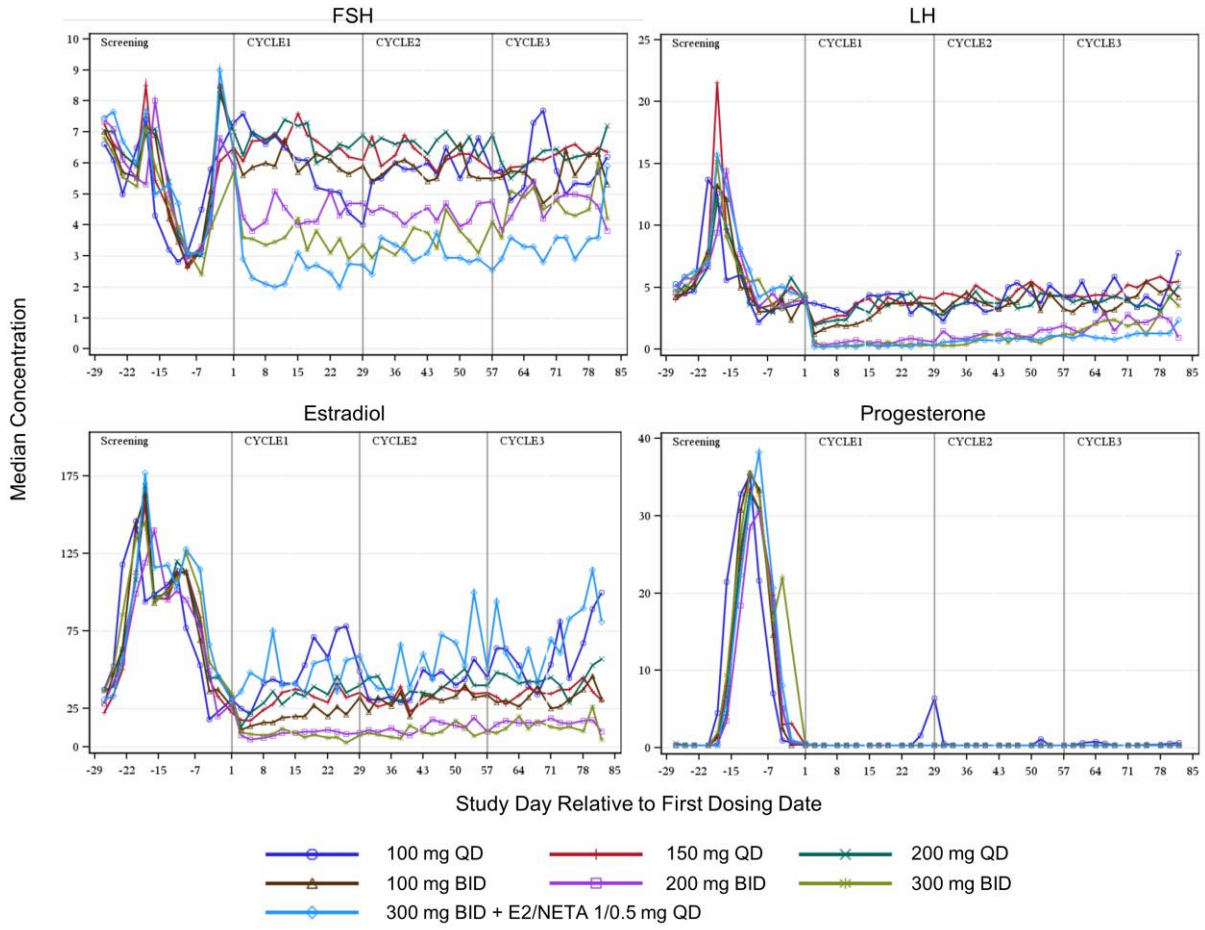

Figure 4